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

005100

MAY 5 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 53218-EUP-1,2. Cyhalothrin (Grenade™). Application for Experimental Use Permit and Temporary Tolerance to Support Use on Cattle. No. 53218-EUP-1,2.

Tox. Chem. No. 271F

TO: George LaRocca (PM Team #15)
Registration Division (TS-767c)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

THRU: Edwin P. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

Background:

Coopers Animal Health, Inc. is requesting an Experimental Use Permit (EUP) for efficacy and residue testing of Grenade™ (Cyhalothrin active ingredient) insecticide on cattle. The proposal is for a two-year period over which the quantity of active ingredient to be shipped and used in the program will be 21.3 pounds. Testing is proposed on 3680 head of cattle. The following Temporary Tolerances for Cyhalothrin residues are requested with this EUP:

Commodity	Parts per Million
Meat and Meat By-Products of Cattle	0.01 ppm
Fat of Cattle	0.05 ppm
Milk Fat	0.1 ppm

No other specific details on the EUP program were submitted. Supporting toxicologic data were submitted for the technical product, the 20% EC formulation and the 5% EC formulation.

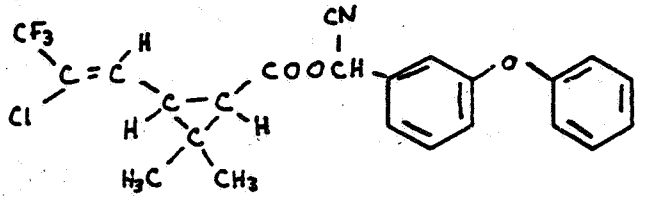
Substance Identification:

This is a new chemical not previously reviewed by the Toxicology Branch. The active ingredient is a synthetic pyrethroid, similar in structure to other pyrethroids already reviewed by the Agency.

1. Chemical name: (RS)-alpha-cyano-3-phenoxybenzyl (1RS)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethyl-cyclopropanecarboxylate

2. Synonyms: Cyhalothrin, Grenade

3. Structure:



Cyhalothrin consists of two pairs of diastereoisomers:
1R cis R alpha-cyano and 1S cis S alpha-cyano
1R cis S alpha-cyano and 1S cis R alpha-cyano
Small amounts of other isomers (i.e. trans, E)

Technical Data - Technical Product

1. Molecular weight: 449.9
2. Purity of technical material: not <83.79% w/w cyhalothrin
3. Physical state: yellow to dark brown viscous liquid at room temperature
4. Freezing point: becomes rigid/glass-like solid below 10°C
5. Boiling point: Decomposes on boiling at 227°C at 1 mm Hg
6. Octanol/water partition coefficient at 20°C: Log P_{ow}=6.86
7. Density: 1.25g/cm^3 at 25°C
8. Vapor pressure: $4x10^{-6}$K Pa at 80°C*
   $3x10^{-7}$K Pa at 60°C
   $2x10^{-8}$K Pa at 40°C
   $1x10^{-9}$K Pa at 20°C**
   $2x10^{-10}$K Pa at 10°C**

   * K Pa not defined in text.
   ** By extrapolation
9. Dissociation constant: N/A
10. Solubility:
    Water (buffered (pH 5.0), purified (pH 6.5) or buffered (pH 9.2) at 20°C: virtually insoluble (<5 ug/L)
    Acetone: freely soluble (>500g/L)
    Dichloromethane: freely soluble (>500g/L)
    Ethyl Acetate: freely soluble (>500g/L)
    Hexane: freely soluble (>500g/L)

Methanol: freely soluble (>500g/L)
Toluene: freely soluble (>500g/L)
Diethyl ether: freely soluble (>500g/L)

11. pH: N/A
12. Stability: No detectable decomposition when stored in the dark at temperatures up to 50°C for 4 years. Very slow photodegradation when stored in the light for prolonged periods (average loss <10% total pyrethroid in 20 months).
13. Oxidizing or reducing action: No known hazard
14. Flammability: Not below 80°C
15. Explodability: Not known to be explosive
16. Viscosity: Viscous
17. Corrosion characteristics: slowly corrodes mild steel

Technical Data - Unless otherwise stated, the following characteristics apply to both the 5% and the 20% EC Formulations

1. Color: Amber to brown mobile liquid
2. Weight/ml at 20°C: 0.955g (20%); 0.925g (5%)
3. Cyhalothrin content: 18.0-22.0% w/v (20%); 4.5-5.5% (w/w) (5%)
4. Odor: Hydrocarbon solvents
5. pH of 5% v/v solution in distilled water: 4.2 (20%); 4.6 (5%)
6. Oxidizing/reducing action: no known hazard
7. Flammability
   Flashpoint: 52°C (Abel closed cup) (5%)
   Flame extension: 43°C (Abel closed cup) (20%)
   Both support combustion.
8. Explodability: No known hazard
9. Storage stability: No physical or chemical changes were noted in samples stored in glass in the dark at ambient temperature, 37°C and 50°C for 2 years other than a slight darkening of the 50°C sample. The emulsifying character of all samples remained satisfactory throughout the storage period. Similar stable characteristics were observed for samples stored in tin plate and aluminum containers at ambient temperature, 30°C and 40°C for periods up to 24 months (12 months in the case of 40°C samples).

   Some solvent loss was noted for samples stored in aluminum containers but this was attributed to faulty container seals. No signs of corrosion were noted in either pack throughout the storage period.
10. Viscosity at 25°C: 33.8 Redwood seconds (5%)
    33.5 Redwood seconds (20%)
11. Miscibility: Intended for emulsification in water not petroleum solvents
12. Corrosion characteristics: no corrosive action on aluminum and tin plate

Comments:

Part A. Comments Related to the EUP and Temporary Tolerance

1. The following toxicity studies are recommended to be submitted in support of the proposed EUP (ref. EPA Pesticide Assessment Guidelines Subdivision I - Experimental Use Permits, October, 1982). Those recommendations that have been satisfied are indicated:

	Required	Satisfied
Technical Product		
Acute Inhalation LD_{50}	Yes*	No
90-Day Subchronic oral (rodent)	Yes	Yes
Subchronic oral (nonrodent)	Yes	Yes
Teratology	Yes	Yes
Gene Mutation	Yes	Partial
Chromosomal Aberration	Yes	Partial
Primary DNA Damage	Yes	Partial
End-Use Product (20% Formulation)		
Acute Oral LD_{50}	Yes	Yes
Acute Dermal LD_{50}	Yes	Yes
Primary Dermal Irritation	Yes	Yes
Primary Eye Irritation	Yes	No
Acute Inhalation LD_{50}	Yes*	Yes
Dermal Sensitization	Yes*	No
End-Use Product (5% Formulation)		
Acute Oral LD_{50}	Yes	Yes
Acute Dermal LD_{50}	Yes	Yes
Primary Dermal Irritation	Yes	Yes
Primary Eye Irritation	Yes	No
Acute Inhalation	Yes*	No
Dermal Sensitization	Yes*	No

*The EUP program was not submitted. Therefore, the mode of exposure is unknown. It is possible that these studies would not be required if the program indicates no exposure via either inhalation or repeated dermal contact.

2. An 8-point review based on these data and other data is attached.

3. Toxicology Branch (TB) has the following comments related to the 20% and 5% formulations to be used in the EUP program.

a. The labels (draft labels dated 11/84 for the 20% and 5% formulations) need to be rewritten. For the 20% formulation, the word WARNING should be changed to DANGER because the acute inhalation study in rats was classified as toxicity category I. In addition, the word POISON should appear in red on a background of distinctly contrasting color with a skull and cross-bones in immediate proximity to the word "poison". The precautionary statements for both the labels should be changed to reflect the toxicity category I classification for skin irritation, which has been classified as corrosive.

Since the technical material was shown to be a sensitizer, the label should also contain the statement, "may cause sensitization skin reactions in some individuals - avoid contact with skin". This precaution must be on the label until the potential (if any) for cyhalothrin and its products to cause sensitization is resolved (see d below).

b. Primary eye irritation studies with both the 20% and 5% EC formulations are required to support labelling.

c. An acute inhalation LC_{50} study with the 5% formulation is required (if use of this product results in exposure by the inhalation route). Based on the high toxicity level of the 20% formulation (Toxicity Category I), it is expected that this product may also represent an inhalation hazard under some conditions.

d. The potential for dermal sensitization by cyhalothrin is unresolved. The technical material resulted in a mild positive response which may or may not have been definitive. The dermal sensitization studies with the formulations were determined by TB to be uninterpretable because of the primary irritation due to the formulated test material. In order to resolve this problem, additional dermal sensitization studies with cyhalothrin technical and each of the formulated products must be submitted. It is recommended that the formulation be diluted to minimize primary irritation and the solvents (formulation minus cyhalothrin) be included as a negative control.

e. TB has classified the dermal irritation studies on both the 20% and 5% EC formulations as Toxicity Category I (corrosive).

f. The inert ingredients in both the 20% and the 5% EC formulations have not all been cleared for use under 180.1001. TB has no information on either [redacted] The registrant is required to have these cleared before the formulations can be used in agricultural applications.

4. Mutagenicity - For various technical reasons, the mutagenicity studies do not meet current state of the art criteria. The tests, however, do not indicate that technical cyhalothrin is a mutagen under the conditions of the assays conducted. Thus, for the purposes of an EUP program with limited use and taking into consideration that no evidence of mutation was evident in the other toxicity studies with cyhalothrin, mutagenicity testing should not alone be the basis for denying an EUP program.

5. TB must defer to Registration Division the acceptability of the toxicity data base for this EUP program because the details of this program were not submitted to TB. In any case, the comments above regarding labelling the products and the inerts identification must be addressed before initiating the program.

Part B. Comments on the Toxicity Data Base for Cyhalothrin

1. Many of the studies were determined to be CORE MINIMUM and others were found to be SUPPLEMENTARY for various reasons. The Registrant should refer to the individual reviews for justification of the CORE classification.

2. The 21-day rabbit dermal toxicity study was classified as SUPPLEMENTARY. The study as presented does not allow TB to determine if certain lesions of the liver (bile duct proliferation and portal tract inflammation) and heart (myocardial fibrosis) are induced by the test material. An increase in this liver lesion is noted in both males and females (although the males do not show a dose-response relationship). The test report ascribes this lesion to the possibility that the rabbits were infected with the coccidiosis protozoan Emeria stiedae. TB cannot at this time readily accept this explanation although the infection could account for the lesion in the liver. The infection alone would not account for the apparent dose-response relationship. The heart also shows evidence of a test chemical effect. In order to attempt to resolve this problem, TB requests 3 additional slides of the bile duct and heart from each rabbit. The slides should be made at 3 mm intervals and should be from identical areas.

3. Rat and rabbit teratology studies were reviewed by EPA's Contractor and were assigned SUPPLEMENTARY classification. TB, however, has upgraded these studies to CORE MINIMUM.

   The SUPPLEMENTARY classification for these studies was based on either high incidences of maternal deaths (rabbit study), high incidences of dilated ureters (rat study) and the method of sacrificing the rat pups by intracardiac injection.

   TB has determined that although there were high incidences of maternal deaths in the rabbit study due to pulmonary disorders,

the final number of dams per dose group was still within acceptable limits for a CORE MINIMUM study.

TB assessment of the problem of higher incidences of dilated ureters (which is not a teratogenic response in itself) was not demonstrated to be a response to the test material. This assessment is based on comparison of the test results with historical control information. For example, the control values for this study had much lower incidences than the historical controls, and although the treated animals had higher incidences than the concurrent controls, the incidences in these groups were still within the historical control limits. The nature of the lesion in question (dilated ureters) is considered by TB to be a fetotoxic response only when the response is very pronounced, and a teratogenic response only if there is a frank malformation of the ureter. It is the experience of TB that dilated ureters are often a function of when the fetuses were sacrificed. These presumed abnormalities tend to disappear when the pups are allowed to be born naturally or allowed to develop to weaning.

According to the Contractor, the use of the intracardiac injection method to sacrifice the fetuses may lead to a distortion of the cardiac tissue and compromise the study. Although TB agrees with the Contractor reviewer in principle, TB does not consider that the use of this procedure will so seriously compromise the study to justify the SUPPLEMENTARY classification. The procedure is a standard practice in European laboratories and there were no indications of malformations in the hearts of the pups in these studies with cyhalothrin.

TB has determined that both the rat and rabbit teratology studies are CORE MINIMUM.

4. The registrant is requested to provide verification that the test material was technical grade cyhalothrin and to submit the percent active ingredient for the test material used in the mouse oncogenicity and the dog (26 week) chronic study.

5. Mutagenicity testing - The following deficiencies in the mutagenicity studies were indicated by Dr. I. Mauer, TB geneticist.

   a. The <u>cell transformation study</u> is inconclusive because the results were erratic, a more detailed description of the protocol should have been submitted and the test should have been repeated, especially in light of the erratic results.

   b. The <u>Ames test</u> was unacceptable because the chemical should have been either tested at a higher dose level or justification for not doing so should have been given, and the activity of the S-9 mix should have been verified.

c. The dominant lethal study was inconclusive because there were insufficient data presented to determine whether or not the highest dose levels were appropriately selected or the chemical reached the target tissue. In addition, the route of administration for the positive control was inappropriate.

d. The cytogenetics study was also deemed to be inconclusive because of insufficient data presented to determine if the highest dose levels were appropriate or if the test material reached the target tissue. Also, for this study the data should have been presented as numerical counts of chromosomal aberrations per cell as opposed to percentage of aberrant cells.

6. TB reclassified the primary eye irritation study with technical cyhalothrin to Toxicity Category II rather than Toxicity Category III as classified by the contract reviewer.

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Draft Label GRENADE 20%
EUP/TT
November, 1984

GRENADE™ Insecticide
Emulsifiable Concentrate
For Experimental Use Only

Active Ingredient: Cyhalothrin -

α-cyano-3-phenoxybenzyl 3(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate*.....20.9%

Inert ingredient:.....79.1%

TOTAL 100.0%

*Cis/trans ratio: Min 95% cis and max 5% trans.
Contains 200 grams active ingredient per liter.

KEEP OUT OF REACH OF CHILDREN
WARNING

See Side Panel for Additional Precautionary Statements and Statement of Practical Treatment.

Not for sale to any person other than a participant or cooperator of the EPA approved Experimental Use Permit Program.

Net Contents: _____
EPA Est. No. _____ EPA Experimental Use Permit No. _____

Coopers Animal Health Inc.
Kansas City, MO 64108, U.S.A.

DIRECTIONS FOR USE

It is a violation of federal law to use this product in a manner inconsistent with its labeling.

Apply GRENADE according to the following chart:

LACTATING AND NONLACTATING DAIRY CATTLE AND BEEF CATTLE

Target Species	Method of Application	Dilute	Application Rate
Horn Flies, Face Flies, Stable Flies, House Flies, Black Flies, Ticks, Lice, Mites	Sprayer	Dilute product in accordance with EPA approved experimental program.	1-2 quarts of spray per animal. Retreat as needed but not more often than once every two weeks.

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS
AND DOMESTIC ANIMALS

WARNING

Causes Eye Irritation: Do not get in eyes. Wear goggles or face shield when handling.

MAY BE FATAL IF SWALLOWED, INHALED OR ABSORBED THROUGH SKIN: Do not get in eyes, on skin, or on clothing. Wear protective clothing and rubber gloves. Wash thoroughly with soap and water after handling and before eating, drinking or using tobacco. Remove contaminated clothing and wash before reuse. Do not breathe spray mist. Wear a mask or pesticide respirator jointly approved by the Mine Safety and Health Administration and the National Institute for Occupational Safety and Health.

MAY CAUSE ALLERGIC SKIN REACTIONS.

FIRST AID:

IF SWALLOWED: Call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. Do not induce vomiting or give anything by mouth to an unconscious person.

IF ON SKIN: Wash with plenty of soap and water. Get medical attention.

IF INHALED: Remove victim to fresh air. If not breathing, give artificial respiration, preferably mouth-to-mouth. Get medical attention.

IF IN EYES: Flush eyes with plenty of water. Call a physician if irritation persists.

ENVIRONMENTAL HAZARDS: Do not contaminate water by cleaning of equipment or disposal of wastes. This product is toxic to fish. Keep out of lakes, streams or ponds.

PHYSICAL OR CHEMICAL HAZARDS: Do not use or store near heat or open flame.

STORAGE AND DISPOSAL:

PROHIBITIONS: Do not contaminate water, food or feed by storage or disposal. Open dumping is prohibited. Do not reuse empty container.

STORAGE: Store in a cool place and protect from freezing. Keep container closed when not in use.

PESTICIDE DISPOSAL: Pesticide wastes are toxic. Improper disposal of excess pesticide, spray mixture, or rinsate is a violation of federal law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance.

CONTAINER DISPOSAL: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

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Draft Label GRENADE 5%
EUP/TT
November, 1984 005100

GRENADE™ Insecticide
Emulsifiable Concentrate
For Experimental Use Only

Active Ingredient: Cyhalothrin -

α-cyano-3-phenoxybenzyl 3(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate*.....5.4%

Inert ingredient:.....94.6%

TOTAL 100.0%

*Cis/trans ratio: Min 95% cis and max 5% trans.
Contains 50 grams active ingredient per liter.

KEEP OUT OF REACH OF CHILDREN
WARNING

See Side Panel for Additional Precautionary Statements and Statement of Practical Treatment.

Not for sale to any person other than a participant or cooperator of the EPA approved Experimental Use Permit Program.

Net Contents: _____
EPA Est. No. _____ EPA Experimental Use Permit No. _____

Coopers Animal Health Inc.
Kansas City, MO 64108, U.S.A.

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DIRECTIONS FOR USE

It is a violation of federal law to use this product in a manner inconsistent with its labeling.

Apply GRENADE according to the following chart:

LACTATING AND NONLACTATING DAIRY CATTLE AND BEEF CATTLE

Target Species	Method of Application	Dilute	Application Rate
Horn Flies, Face Flies, Stable Flies, House Flies, Black Flies, Ticks, Lice, Mites	Sprayer	Dilute product in accordance with EPA approved experimental program.	1-2 quarts of spray per animal. Retreat as needed but not more often than once every two weeks.

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PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS
AND DOMESTIC ANIMALS

WARNING

Causes Eye Irritation: Do not get in eyes. Wear goggles or face shield when handling.

MAY BE FATAL IF SWALLOWED, INHALED OR ABSORBED THROUGH SKIN: Do not get in eyes, on skin, or on clothing. Wear protective clothing and rubber gloves. Wash thoroughly with soap and water after handling and before eating, drinking or using tobacco. Remove contaminated clothing and wash before reuse. Do not breathe spray mist. Wear a mask or pesticide respirator jointly approved by the Mine Safety and Health Administration and the National Institute for Occupational Safety and Health.

MAY CAUSE ALLERGIC SKIN REACTIONS.

FIRST AID:

IF SWALLOWED: Call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. Do not induce vomiting or give anything by mouth to an unconscious person.

IF ON SKIN: Wash with plenty of soap and water. Get medical attention.

IF INHALED: Remove victim to fresh air. If not breathing, give artificial respiration, preferably mouth-to-mouth. Get medical attention.

IF IN EYES: Flush eyes with plenty of water. Call a physician if irritation persists.

ENVIRONMENTAL HAZARDS: Do not contaminate water by cleaning of equipment or disposal of wastes. This product is toxic to fish. Keep out of lakes, streams or ponds.

PHYSICAL OR CHEMICAL HAZARDS: Do not use or store near heat or open flame.

STORAGE AND DISPOSAL:

PROHIBITIONS: Do not contaminate water, food or feed by storage or disposal. Open dumping is prohibited. Do not reuse empty container.

STORAGE: Store in a cool place and protect from freezing. Keep container closed when not in use.

PESTICIDE DISPOSAL: Pesticide wastes are toxic. Improper disposal of excess pesticide, spray mixture, or rinsate is a violation of federal law. If these wastes cannot be disposed of by use according to label instructions, contact your State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA Regional Office for guidance.

CONTAINER DISPOSAL: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities.

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Studies Reviewed

....Technical....

Study	Results	Core Classification
Acute Oral LD_{50} - rat	LD_{50}:243(183-312) mg/kg for males & 144(100-320) mg/kg for females	Minimum
Acute Oral LD_{50} - mice	LD_{50}:36.7(17.4-58.1) mg/kg for males & 62.3(40.1-80.4) mg/kg for females	Minimum
Acute Oral LD_{50} - guinea pigs	LD_{50}>5000 mg/kg for males Females not tested	Supplementary
Acute Oral, acute delayed neurotox. - hen	LD_{50}>10 g/kg. No signs of clinical or histopath. neurotoxicity	Minimum
Acute Dermal - rat	LD_{50}>1000 mg/kg for both sexes	Minimum
Acute Dermal - Rabbit	LD_{50}>2 ml/kg for both sexes	Minimum
Acute i.p. - rat	LD_{50}:694(460-999) mg/kg for males. Females not tested	Acceptable
Dermal Irritation - rat	No irritation or sensitization at 0.1 ml/rat Only females tested.	Minimum
Dermal Irritation - rabbit	Mild irritant in females. Males not tested. 0.5 ml tested	Minimum
Eye Irritation - rabbit	Moderate eye irritant at dose of 0.1 ml/eye	Minimum
Skin Sensitization - guinea pig	Is a sensitizer to males	Minimum
Subacute Dermal - rabbit	10-1000 mg/kg/day, 6 hr/day 5d/wk, 15 applications. No effects noted. Animals may have had coccidiosis	Supplementary unless proven animals not diseased

Studies Reviewed

Technical (cont.)

Study	Results	Core Classification
28-day feeding - rat	NOEL 10 ppm and LOEL 20 ppm in females. NOEL 20 ppm and LOEL 250 ppm in males.	Acceptable
90-day feeding - rat	NOEL 50 ppm & LOEL 250 ppm based on body wt. gain	Guideline
26-wk oral - dog	NOEL 1 mg/kg/day, LOEL 2.5 mg/kg/day	Guideline
Chronic Feeding - rat	NOEL 50 ppm & LOEL 250 ppm based on reduced body wt. gain.	Guideline
Chronic/Onco. - mice	Not oncogenic (20-500ppm tested). NOEL 100 ppm & LOEL 500 ppm based on body wt. gain. Uncertain whether MTD used.	Minimum
Teratology - rabbit	NOEL maternal tox. 10 mg/kg/d, LOEL 30 mg/kg/d based on body wt gain. High incid. maternal deaths-pulmonary dis. NOEL fetotox. 30 mg/kg/d. No Malformations.	Minimum
Mutagenicity - Ames	Negative, but dose not high enough	Unacceptable
Cell Transform.	Results erratic.	Inconclusive
Muta.-Cytogenetics - rat	Doses may not have been high enough. Uncertain if chemical reached target.	Inconclusive
Muta. - Dom. Lethal - male mice	Unknown if MTD appropriately selected. Uncertain if chem. reached target. Inappropriate route of admin. for pos. controls.	Inconclusive

Studies Reviewed

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Technical (cont.)

Study	Results	Core Classification
Metabolism - rat	3 studies. 55% oral absorp. Metab. inclu. cleavage of ester to cyclopropylcarboxylic acid & phenoxybenzyl deriv. Accum. in fat upon chronic admin. Otherwise, rapidly metab. & excreted.	Guideline
Metabolism - dog	Extensive cleavage of ester. Excretion in urine & feces rapid. Absorption of radioact. cmpd. 48% & 80% of each side of ester respectively.	Minimum
Teratology - rat	NOEL maternal tox. 10 mg/kg/d. LOEL 15 mg/kg/d. based on reduced body wts. NOEL embryoleth. & fetotox. 15 mg/kg/d.	Minimum
Reproduction - rat	NOEL parental tox. 10 ppm. LOEL 30 ppm based on reduced body wt. Offspring: NOEL 10 ppm, LOEL 30 ppm based on decr. body wt. gain during weaning.	Guideline

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 22 through 23 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

X INFORMATION ON A PRODUCT THAT IS NOT REGISTERED

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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8-Point Review

[Prepared for 5G3204, cyhalothrin on meat and meat by-products of cattle, fat of cattle and milk fat, January, 1986]

1. Toxicity data with technical grade cyhalothrin considered in support of these tolerances (selected studies).

Acute Oral LD_{50}, rats	243 mg/kg in males 144 mg/kg in females
90-day feeding, rats	NOEL:50ppm, LOEL:250 ppm based on body wt gain
26-week oral, dogs	NOEL 1 mg/kg/day LOEL 2.5 mg/kg/day (liquid feces)
Chronic feeding, rat	NOEL 50 ppm, LOEL 250 ppm (reduced body wt gain. No oncogenic effects)
Chronic/Onco, mouse	NOEL 100 ppm, LOEL 500 ppm (decreased body wt gain. No oncogenic effects)
Teratology, rabbit	NOEL maternal tox. 10 mg/kg/d, LOEL 30 mg/kg/d (decreased body wt gain). NOEL fetotox. 30 mg/kg/d Not teratogenic.
Teratology, rat	NOEL maternal tox. 10 mg/kg/d, LOEL 15 mg/kg/d (reduced body wt). NOEL embryo-leth. & fetotox. 15 mg/kg/d. Not teratogenic.
Reproduction - 3 gen., rat	NOEL parental tox. 10 ppm, LOEL 30 ppm (decreased body wt gain). Offspring: NOEL 10 ppm, LOEL 30 ppm (decreased body wt gain).

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Metabolism, rats	55% oral absorption. Extensively metabolized when absorbed; cleavage of ester to cyclopropylcarboxylic acid & phenoxybenzyl derivatives. Accumulation of unchanged cmpd. in fat upon chronic administration.

Mutagenicity Studies

Reverse Mutation Assay (Ames), Cytogenetics in rats, Dominant Lethal in mice either unacceptable or inconclusive due to insufficient data on whether or not the highest dose levels were appropriately chosen.

2. Additional toxicity data considered desirable:

   a. Gene mutation study
   b. Chromosomal aberration study
   c. Primary DNA damage and repair study

3. The above studies have been requested to be performed in the TB review of the proposed EUP for Grenade (January, 1986)

4. This is a new pesticide. No other tolerances have been granted.

5. Establishing these tolerances will theoretically contribute 0.0071 mg/day to the diet (1.5 kg) and will result in 2.37% of the MPI being used up (see computer printout, next page).

6. The 3-generation reproduction study in the rat with a safety factor of 100 was used to calculate the ADI. The NOEL was 0.5 mg/kg/day (10 ppm). The ADI is calculated to be 0.0050 mg/kg/day and the MPI is 0.3000 mg/day (60 kg).

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

8. None.

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DRAFT

NCEL
Recorded

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EPA: 68-01-6561
TASK: 107
July 22, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Acute Oral Toxicity Study in Rats

STUDY IDENTIFICATION: Nixon, J., and Jackson, S. J. Cyhalothrin: acute toxicity. (Unpublished study No. AR0329 and report No. CTL/T/1555 by Imperial Chemical Industries Limited, Central Toxicology Laboratory, Cheshire, UK for ICI Limited, Plant Protection Division, Berkshire, UK; dated June 22, 1981.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 7-22-85

1. CHEMICAL: Cyhalothrin; a synthetic pyrethroid insecticide; (R,S)α-cyano-3-phenoxybenzyl (±)-cis-3, 3(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2 dimethylcyclopropanecarboxylate.

2. TEST MATERIAL: Dark brown, viscous liquid. The sample (94% pyrethroid of which approximately 97% is the cis-isomer) was given the CTL reference No. Y00102/006/001.

3. STUDY/ACTION TYPE: Acute oral toxicity study in the rat.

4. STUDY IDENTIFICATION: Nixon, J., and Jackson, S. J. Cyhalothrin: acute toxicity. (Unpublished study No. ARO329 and report No. CTL/T/1555 by Imperial Chemical Industries Limited, Central Toxicology Laboratory, Cheshire, UK for ICI Limited, Plant Protection Division, Berkshire, UK; dated June 22, 1981.) Accession No. 073203.

5. REVIEWED BY:

Brian R. Browne, M.S.
Principal Author
Dynamac Corporation

Signature: James R. Plaunty for
Date: July 22, 1985

Sharon M. Ambrose, B.S.
Independent Reviewer
Dynamac Corporation

Signature: Sharon M. Ambrose
Date: July 22, 1985

6. APPROVED BY:

Finis Cavender, Ph.D.
Acute Toxicology
Technical Quality Control
Dynamac Corporation

Signature: for
Date: 7-22-85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela M. Hurley
Date: 1/23/86

Edwin Budd
EPA Section Head

Signature:
Date: 4/21/86

7. SUMMARY:

Groups of 5 male and 5 female rats per dose level were reported used. Alderley Park, SPF-derived, albino strain rats were obtained from the Animal Breeding Unit (ICI Limited, Cheshire, UK) with an initial body weight range of 119 to 220 g. A solution of cyhalothrin in corn oil was used for doses of 50, 100, 160, 200, 250, 320, 400, or 500 mg/kg body weight for males; 50, 100, 126, 140, 160, 200, or 320 mg/kg body weight for females. Standard volume of 10 ml/kg of test compound was administered once to fasted animals by oral gavage. Animals were observed at least once daily for mortality and signs of toxicity for 14 days.

Mortality data and the symptoms observed at each dose level are shown in Appendix A. The acute oral LD_{50} was calculated to be 243 (183-312) mg/kg for male rats and 144 (range estimated 100-320) mg/kg for female rats which corresponds to Toxicity Category II.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

There were some discrepancies and deviations from the EPA Guidelines noted in review of this report.

The Experimental Procedures section of the report listed the doses as 50, 100, 160, 200, 250, 320, 400, and 500 mg/kg; however, the results section indicates that females were dosed at 50, 100, 126, 140, 160, 200, or 320 mg/kg. This resulted in 5 of the dose groups containing only 5 males or 5 females. Apparently, the additional dose groups were added because of the sex difference in response to the test compound. This deviation improved the validity of the study since the intermediate dose levels resulted in doses that did not result in complete mortality of the test group. In addition, necropsies are required by the Guidelines but were not reported.

A signed and dated quality assurance statement was included with this report.

9. CBI APPENDIX:

Appendix A, CBI pp. 13, 54, 55.

10. CLASSIFICATION:

Core Classification: Core minimum.

Toxicity Category: II.

LD_{50} Male rats: 243 (183-312) mg/kg.
Female rats: 144 (range estimated 100-320) mg/kg.

APPENDIX A

Results

CYHALOTHRIN: ACUTE ORAL TOXICITY TO MALE RATS

005100

Time after dosing	Dose (mg cyhalothrin/kg) and cumulative mortality							
	50	100	160	200	250	320	400	500
0-3 hours	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
4 hours	0/5	0/5	0/5	0/5	0/5	0/5	2/5	1/5
Day 1	0/5	0/5	0/5	1/5	0/5	3/5	4/5	3/5
Day 2	0/5	0/5	1/5	2/5	2/5	4/5	4/5	5/5
Day 7	0/5	0/5	1/5	2/5	2/5	4/5	4/5	5/5
Day 14	0/5	0/5	1/5	2/5	2/5	4/5	4/5	5/5

CYHALOTHRIN: ACUTE ORAL TOXICITY TO FEMALE RATS

Time after dosing	Dose (mg cyhalothrin/kg) and cumulative mortality						
	50	100	126	140	160	200	320
3-5 hours	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Day 1	0/5	0/5	2/5	0/5	3/5	2/5	4/5
Day 2	0/5	0/5	3/5	0/5	5/5	3/5	5/5
Day 3	0/5	0/5	3/5	0/5	5/5	4/5	5/5
Day 7	0/5	0/5	3/5	0/5	5/5	4/5	5/5
Day 14	0/5	0/5	3/5	0/5	5/5	4/5	5/5

005100

TABLE 14

ACUTE ORAL TOXICITY (RAT): CLINICAL SIGNS OF TOXICITY OBSERVED AND THE NUMBER OF ANIMALS AFFECTED AT EACH DOSE LEVEL

Test Substance: Cyhalothrin
No of Animals: 5 per dose level
Species: Rat
Sex: Male

Clinical Observation	Dose level (mg/kg)							
	50	100	160	200	250	320	400	500
Salivation	0	3	5	5	5	5	5	4
Scouring	0	4	1	3	1	2	1	0
Incontinence	0	0	5	4	2	5	2	4
Piloerection	1	3	5	5	5	5	3	4
Ataxia	0	0	4	2	3	5	2	4
Ungroomed appearance	0	1	5	3	3	2	1	0
Subdued behaviour	0	4	5	5	5	5	3	4
Unsteady gait	0	0	3	2	5	0	2	1
Chromodacryorrhoea	0	0	5	2	2	5	1	0
Respiratory difficulties	0	0	0	0	0	0	0	2
Hunched attitude	0	1	0	1	0	0	0	0
Tiptoe gait	0	1	0	2	0	0	0	0
Flaccid appearance	0	0	0	3	0	0	0	1
Ptosis	0	0	0	0	0	0	0	1
Blood stains around snout	0	0	0	0	1	0	2	3
Ventral surface fur stained	0	0	0	0	1	0	0	0
Right hind limb trapped in cage	0	0	0	0	0	0	0	1

005100

TABLE 15

ACUTE ORAL TOXICITY (RAT): CLINICAL SIGNS OF TOXICITY OBSERVED AND THE NUMBER OF ANIMALS AFFECTED AT EACH DOSE LEVEL

Test Substance: Cyhalothrin
No of Animals: 5 per dose level
Species: Rat
Sex: Female

Clinical Observation	Dose level (mg/kg)						
	50	100	126	140	160	200	320
Salivation	0	3	4	5	5	5	5
Scouring	0	0	0	0	0	1	2
Incontinence	0	0	3	4	4	4	4
Piloerection	0	5	4	5	5	5	5
Ataxia	0	0	2	2	3	2	3
Ungroomed appearance	0	4	1	4	0	3	0
Subdued behaviour	0	5	4	5	5	5	5
Unsteady gait	0	0	2	4	1	2	3
Chromodacryorrhoea	0	2	1	1	3	1	3
Hunched attitude	0	0	0	0	0	1	0
Tiptoe gait	0	0	0	0	0	2	0
Flaccid appearance	0	0	0	0	0	1	0
Blood stains around snout	0	0	1	1	1	0	1

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 33 through 44 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

_____ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

X INFORMATION ON A PRODUCT THAT IS NOT REGISTERED

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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EPA: 68-01-6561
TASK: 107
July 22, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Acute Oral Toxicity Study in Mice

STUDY IDENTIFICATION: Nixon, J., and Jackson, S.J. Cyhalothrin: acute toxicity. (Unpublished study No. AM1859 and report No. CTL/T/1555 by Imperial Chemical Industries Limited, Central Toxicology Laboratory, Cheshire, UK for their Pharmaceuticals Division; dated June 22, 1981.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I Cecil Felkner

Date: 7-22-85

005100

1. CHEMICAL: Cyhalothrin; a synthetic pyrethroid insecticide; (R,S)α-cyano-3-phenoxybenzyl (±)-cis-3, 3(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2 dimethylcyclopropanecarboxylate.

2. TEST MATERIAL: Dark brown, viscous liquid. The sample (being 90.8% pyrethroid of which 98% is the cis-isomer) was given the CTL reference No. Y00102/010/004.

3. STUDY/ACTION TYPE: Acute oral toxicity study in mice.

4. STUDY IDENTIFICATION: Nixon, J., and Jackson, S.J. Cyhalothrin: acute toxicity. (Unpublished study No. AM1859 and report No. CTL/T/1555 by Imperial Chemical Industries Limited, Central Toxicology Laboratory, Cheshire, UK for their Pharmaceuticals Division; dated June 22, 1981.) Accession No. 073203.

5. REVIEWED BY:

Brian R. Browne, M.S.
Principal Author
Dynamac Corporation

Signature: James R Blaney for
Date: 7-22-85

Sharon M. Ambrose, B.S.
Independent Reviewer
Dynamac Corporation

Signature: Sharon M Ambrose
Date: July 22, 1985

6. APPROVED BY:

Finis Cavender, Ph.D.
Acute Toxicology
Technical Quality Control
Dynamac Corporation

Signature: Ina Cavender for
Date: 7-22-85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela M. Hurley
Date: 4/23/86

Edwin Budd
EPA Section Head

Signature: Edwin Budd
Date: 4/21/86

7. SUMMARY:

Groups of 5 male and 5 female mice per dose level were reportedly used in the study. Alderley Park, SPF-derived albino strain mice were obtained from the Animal Breeding Unit (ICI Limited, Cheshire, UK) with an initial body weight range of 20-31 g. A solution of cyhalothrin in corn oil was used for doses of 10, 25, 50, 80, or 100 mg/kg body weight for males; 25, 50, 80, or 100 mg/kg body weight for females. A standard volume of 10 ml/kg of the test compound was administered once to fasted animals by oral gavage. The animals were observed at least once daily for signs of mortality and systemic toxicity over a 14-day period.

Mortality data and the symptoms observed at each dose level are shown in Appendix A. The acute oral LD_{50} was calculated to be 36.7 (17.4-58.1) mg/kg for male mice and 62.3 (40.1-80.4) mg/kg for female mice.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

There were some discrepancies and deviations from the EPA Guidelines noted in review of this report.

The Experimental Procedures section of the report listed the doses as 25, 50, 80, and 100 mg/kg; however, the results section indicates that males were also dosed at 10 mg/kg. This resulted in one of the dose groups containing only 5 males. This deviation strengthened the validity of the study since the 10 mg/kg dose level was not lethal to male mice, and no deaths occurred in the females at the 25 mg/kg. The study had one minor deficiency; necropsies are required by the Guidelines but were not reported.

A signed and dated Quality Assurance Statement was included with the report.

9. CBI APPENDIX: Appendix A, Results, CBI pp. 17, 18, 74, 75.

10. CLASSIFICATION:

Core Classification: Core minimum.

Toxicity Category: I.

LD_{50} Male mice: 36.7 (17.4 - 58.1) mg/kg.
Female mice: 62.3 (40.1 - 80.4) mg/kg.

APPENDIX A

Results

CYHALOTHRIN: ACUTE ORAL TOXICITY TO MALE MICE

Time after dosing	Dose (mg cyhalothrin/kg) and cumulative mortality				
	10	25	50	80	100
Day 1	0/5	0/5	3/5	4/5	5/5
Day 2	0/5	1/5	3/5	4/5	5/5
Day 3	0/5	1/5	3/5	4/5	5/5
Day 5	0/5	2/5	3/5	4/5	5/5
Day 7	0/5	2/5	3/5	4/5	5/5
Day 10	0/5	2/5	3/5	4/5	5/5
Day 15	0/5	2/5	3/5	4/5	5/5

CYHALOTHRIN: ACUTE ORAL TOXICITY TO FEMALE MICE 005100

Time after dosing	Dose (mg cyhalothrin/kg) and cumulative mortality			
	25	50	80	100
Day 1	0/5	1/5	3/5	4/5
Day 2	0/5	1/5	4/5	5/5
Day 3	0/5	1/5	4/5	5/5
Day 5	0/5	1/5	4/5	5/5
Day 7	0/5	1/5	4/5	5/5
Day 10	0/5	1/5	4/5	5/5
Day 15	0/5	1/5	4/5	5/5

CYHALOTHRIN: ACUTE TOXICITY

005100

TABLE 25

ACUTE ORAL TOXICITY (MOUSE): CLINICAL SIGNS OF TOXICITY OBSERVED AND THE NUMBER OF ANIMALS AFFECTED AT EACH DOSE LEVEL

Test Substance: Cyhalothrin
No of Animals: 5 per dose level
Species: Mouse
Sex: Male

Clinical Observation	Dose level (mg/kg)				
	10	25	50	80	100
Salivation	0	0	1	0	0
Scouring	2	1	1	0	0
Incontinence	0	0	2	0	0
Piloerection	4	2	2	1	0
Dehydration	0	0	1	0	0
Ataxia	0	1	2	0	0
Subdued behaviour	2	3	3	2	5
Unsteady gait	0	0	0	1	0
Upward curvature of spine	0	1	1	1	0
Eyes closed	0	1	0	0	0
Respiratory difficulities	0	1	0	0	0
Ventral surface stained	0	0	1	0	0
Damp fur on back	0	0	1	0	0

NB Observations recorded prior to, or at the time of dosing are not included in the above table.

CYHALOTHRIN: ACUTE TOXICITY

TABLE 26

ACUTE ORAL TOXICITY (MOUSE): CLINICAL SIGNS OF TOXICITY OBSERVED AND THE NUMBER OF ANIMALS AFFECTED AT EACH DOSE LEVEL

005100

:t Substance: Cyhalothrin
of Animals: 5 per dose level
:cies: Mouse
:: Female

:linical Observation	Dose level (mg/kg)			
	25	50	80	100
:alivation	1	3	2	0
:couring	0	1	1	0
:ncontinence	1	3	2	1
?iloerection	1	2	1	0
)ehydration	0	0	1	1
\taxia	1	3	1	1
:ubdued behaviour	2	3	2	1
:nsteady gait	0	0	0	0
:pward curvature of spine	0	0	2	1
?tosis	1	1	0	0

IB Observations recorded prior to, or at the time of dosing are not included in the above table.

EPA: 68-01-6561
TASK: 107
July 22, 1985

005100

DATA EVALUATION RECORD

CYHALOTHRIN

Acute Oral Toxicity Study in Guinea Pigs

STUDY IDENTIFICATION: Nixon, J., and Jackson, S.J. Cyhalothrin: acute toxicity. (Unpublished study No. AG1860 and report No. CTL/T/1555 by Imperial Chemical Industries Limited, Central Toxicology Laboratory, Cheshire, UK for their Pharmaceuticals Division; dated February 22, 1981.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 7-22-85

1. CHEMICAL: Cyhalothrin; a synthetic pyrethroid insecticide; (R,S)α-cyano-3-phenoxybenzyl (±)-cis-3, 3(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2 dimethylcyclopropanecarboxylate.

2. TEST MATERIAL: Dark brown, viscous liquid. The sample (90.8% pyrethroid of which 98% is the cis-isomer) was given the CTL reference no. Y00102/010/004.

3. STUDY/ACTION TYPE: Acute oral toxicity study in guinea pigs.

4. STUDY IDENTIFICATION: Nixon, J., and Jackson, S.J. Cyhalothrin: acute toxicity. (Unpublished study No. AG1860 and report No. CTL/T/1555 by Imperial Chemical Industries Limited, Central Toxicology Laboratory, Cheshire, UK for their Pharmaceuticals Division; dated February 22, 1981.) Accession No. 073203.

5. REVIEWED BY:

Brian R. Browne, M.S.
Principal Author
Dynamac Corporation

Signature: James R. Plautz for
Date: 7-22-85

Sharon M. Ambrose, B.S.
Independent Reviewer
Dynamac Corporation

Signature: Sharon M. Ambrose
Date: July 27, 1985

6. APPROVED BY:

Finis Cavender, Ph.D.
Acute Toxicology
Technical Quality Control
Dynamac Corporation

Signature: Ina Cavender
Date: 7-22-85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela M. Hurley
Date: 1/23/86

Edwin Budd
EPA Section Head

Signature: Edwin Budd
Date: 4/21/86

7. SUMMARY:

Groups of 5 male animals per dose level were used. Alderley Park, SPF-derived albino strain guinea pigs were obtained from the Animal Breeding Unit (ICI Limited, Cheshire, UK) with an initial body weight range of 321-479 g. A solution of cyhalothrin in corn oil was used for doses of 50, 100, 500, 2000, and 5000 mg/kg body weight. A standard volume of 10 ml/kg of the test compound was administered once to fasted animals by oral gavage. The animals were observed for signs of systemic toxicity and mortality over a 14-day period.

Following the various doses, test animals showed signs of toxicity including incontinence, salivation, staining of the ventral surface and/or face, and subdued behavior. These toxic signs increased in severity with increased doses of cyhalothrin. Recovery rates for doses of 50, 100, 500, 2000, and 5000 mg/kg were 6, 8, 9, 6, and 11 days after dosing, respectively. One animal was found dead on day 3, and had prolapse of the rectum following a dose of 2000 mg/kg, but was not considered to be a compound-related effect. One animal dosed with 5000 mg/kg appeared thin and had a large scab on its left hind limb and had not fully recovered by the end of the study period. The acute oral LD_{50} to male guinea pigs was greater than 5000 mg/kg which corresponds to Toxicity Category IV.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

The results of this study could not be verified due to the absence of individual animal data. In addition, necropsies are required by the Guidelines, but were not reported. The study does, however, provide useful information.

A signed and dated quality assurance statement was included in the report.

9. CLASSIFICATION:

Core classification: Supplementary.

Toxicity category: IV.

LD_{50} male and female guinea pigs: greater than 5000 mg/kg.

005100

EPA: 68-02-4225
DYNAMAC No. 29-F6
November 22, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Acute Oral and Acute Delayed Neurotoxicity Study in Hens

STUDY IDENTIFICATION: Roberts, N. L., Fairley, C., et al. The acute oral toxicity (LD_{50}) and neurotoxic effects of cyhalothrin to the domestic hen. (Unpublished study No. JX0081 and report No. ICI/374NT/81742 prepared by Huntingdon Research Centre for Imperial Chemical Industries PLC, Nr. Macclesfield, Cheshire, England; dated February 1, 1982.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 11-21-85

1. CHEMICAL: Cyhalothrin (Grenade).

2. TEST MATERIAL: Described as a brown viscous liquid, designated as material no. YO0102/010/003 from batch no. ADM46110/80; the purity was reported as 91.3% pyrethroid of which 97.7% was cyhalothrin.

   Tri-ortho-cresyl phosphate (TOCP), the positive control compound, was supplied by Coalite and Chemical Products Limited (Ref. No. S16848).

3. STUDY/ACTION TYPE: Acute oral toxicity and acute delayed (21-day) neurotoxicity study in hens.

4. STUDY IDENTIFICATION: Roberts, N. L., Fairley, C., et al. The acute oral toxicity (LD_{50}) and neurotoxic effects of cyhalothrin to the domestic hen. (Unpublished study No. JX0081 and report No. ICI/374NT/81742 prepared by Huntingdon Research Centre for Imperial Chemical Industries PLC, Nr. Macclesfield, Cheshire, England; dated February 1, 1982.) Accession No. 073203.

5. REVIEWED BY:

   James R. Plautz, M.S.
   Principal Reviewer
   Dynamac Corporation

   Signature: James R. Plautz
   Date: November 21, 1985

   Paul Wennerberg, D.V.M., M.S.
   Independent Reviewer
   Dynamac Corporation

   Signature: [illegible]
   Date: 1-2-85

6. APPROVED BY:

   Finis Cavender, Ph.D.
   Acute Toxicity
   Technical Quality Control
   Dynamac Corporation

   Signature: Finis Cavender
   Date: 11/21/85

   Pamela Hurley, Ph.D.
   EPA Reviewer

   Signature: Pamela Hurley
   Date: 1/23/86

   Edwin Budd
   EPA Section Head

   Signature: John Schaefer
   Date: 4/21/86

7. SUMMARY:

Adult (> 14 months of age) domestic hens were obtained from Graygable Poultry Services, Bury St. Edmonds, Suffolk, and were allowed a 14-day "settling-in" period before dosing began. The birds were group-housed in pens of wire and wood with wood shavings on the concrete floors. During the studies, the room temperature ranged from 12-36° C and the relative humidity from 59-96 percent; 17 hours of artificial light was provided daily. Food and water were available ad libitum except on the night before dosing, at which time the hens were fasted.

Acute oral toxicity

Six groups of five hens each received by gavage a single oral dose of a 70 percent (w/v) suspension of the test material in corn oil at 0, 2000, 4000, 6000, 8000, or 10,000 mg/kg. The control hens received corn oil at 29.9 ml/bird, which approximated the largest dose volume used.

No signs of toxicity were observed (individual animal data not present) and no mortalities occurred during the 14-day observation period. No compound-related effects on body weight were observed.

Neurotoxicity study

Six groups of ten hens each were used. Four groups were administered a single oral dose of cyhalothrin (70% (w/v) in corn oil) by gavage at 2500, 5000, or 10,000 (two groups) mg/kg; a positive control group received a single dose of tri-ortho-cresyl phosphate (TOCP) in corn oil at 500 mg/kg (5.2 ml/bird), and a negative control group received corn oil at 30.7 ml/bird.

The birds were examined daily for mortality and signs of toxicity including ataxia scored according to Cavanagh (1961).[1] Body weight and food consumption were measured twice weekly during the study. Twenty-one days after dosing, all birds were examined at necropsy. The spinal cord (cervical, thoracic, and lumbar) and the sciatic nerve from all birds were fixed both in situ by systemic perfusion, and after removal, fixed in 10 percent neutral buffered formalin. These tissues were stained with hematoxylin and eosin, with luxol fast blue for myelin, or with Glees-Marsland for axons; multiple, longitudinal, and cross sections of each tissue were evaluated for histopathological changes.

No signs of neurotoxicity were observed in the corn oil-treated group (negative control) or in any of the cyhalothrin dosed groups. Nine of 10 hens in the TOCP group showed signs of ataxia beginning at day 10 after dosing; one was sacrificed at day 16 after showing severe (grade 8) ataxia.

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[1] Cavanagh et al., Brit. J. Pharmacol. 17 (1961): 21.

One negative control bird was found dead on day 2; two birds in the highest group were found dead, at 21 hours and nine days after dosing, respectively. For study days 0-21, the group mean body weight change (g/bird) was +132 in the negative control group compared with +7, -143, -235, and -211 in the 2500, 5000, 10,000, and 10,000 mg/kg cyhalothrin groups, respectively. Statistical analyses of the body weight changes, conducted by the reviewers using ANOVA and Duncan's Test for Multiple Comparisons, showed the change in the 5000 and both 10,000 mg/kg groups to be significantly ($p < 0.05$) less than the negative control group. Food consumption for the cyhalothrin-dosed groups during this period was comparable to or exceeded the negative control group.

Examination of each bird at death or final sacrifice showed grossly visible changes in the livers and ovaries or oviducts of the hens in the cyhalothrin-dosed groups (see Appendix A: Post Mortem Results).

Results of the histopathologic examinations indicated no compound-related effects in the hens dosed with cyhalothrin when compared to the negative controls; all of the hens in the TOCP group showed "morphological evidence of neurotoxicity, maximal in the cervical cord."

The authors concluded that the LD_{50} for cyhalothrin exceeded 10,000 mg/kg and that under the conditions of this study (doses up to 10,000 mg/kg), cyhalothrin was not associated with clinical or histopathologic signs of neurotoxicity.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

The hens should be dosed at the LD_{50} value; however, since the LD_{50} is greater than 5,000 mg/kg, higher doses are not required. Therefore, this was an adequate study for assessing both the median lethal dose and the acute (21-day) delayed neurotoxicity of cyhalothrin in hens. It should be noted that sections of the medulla oblongata were not reported to have been taken or examined histologically as suggested by the EPA Guidelines (1982). However, this was not a significant omission because of the absence of clinical signs of neurotoxicity during the study and the absence of histopathological changes in the examined sections of the sciatic nerve and spinal cord. Both the conduct of the study and the final report were inspected by the Quality Assurance Unit of the testing laboratory; the director of the Unit signed the report on January 19, 1982.

9. CBI APPENDIX: Appendix A, Results of Gross Examinations, CBI pp. 13, 14.

10. CLASSIFICATION:

Toxicity Category: IV

Core Classification: Minimum.

Neurotoxicity: Cyhalothrin did not cause acute (21-day) delayed neurotoxic changes.

APPENDIX A
Results of Gross Examinations
CBI, pp. 13, 14

APPENDIX A

Results of Gross Examinations

CBI, pp. 13, 14

NEUROTOXIC SIGNS

005100

No neurotoxic signs were observed in the negative control group or any of the groups dosed with cyhalothrin. Nine of the ten birds dosed with TOCP developed signs of ataxia following dosing, and it was necessary to sacrifice Bird No. 18 as it had developed severe (Grade 8) ataxia.

Detailed results of the ataxia gradings in Group 2 (TOCP 500 mg/kg) are shown in Table 5 below:

TABLE 5*

Ataxia assessment of birds dosed with TOCP at 500 mg/kg using a score system based on daily examination of all birds (see Appendix 1 for key to scoring system)

Group	Treatment	Bird No.	Days of study																				
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22++
2	TOCP 500 mg/kg	11				1										1	1	2	3	3	3	3	3	3
		12											1	1	2	2	2	3	3	4	4	4	4	4
		13											1	2	3	4	5	6	7	7	7	7	7	-
		14																						
		15											1	2	3	4	6	6	7	7	7	7	7	-
		16											1	1	1	1	1	2	2	2	3	3	3	3
		17										1	1	2	4	5	6	7	7	7	7	7	7	-
		18				1	1	1	1	1	1	2	2	3	4	6	7	8+	-	-	-	-	-	-
		19										1	2	2	3	4	4	5	6	6	7	7	7	-
		20																1	1	1	2	2	2	3

* Scores of 0 recorded in the study day book have been omitted from the table to aid clarity
\+ Bird sacrificed
++ Because it was not possible to sacrifice all birds on Day 21, ataxia scoring was carried out until the bird was sacrificed.

POST MORTEM RESULTS

The following observations were made during macroscopic post mortem examination of the birds at death or at termination of the study:

Group	Treatment	Bird No.	Observation
1	Corn oil	7	Spinal cord asymmetric in sacral region.
2	TOCP (500 mg/kg)	14	Several green subcapsular areas up to 4 x 4 mm on all surfaces of liver.
		17	Moderate wasting of muscle.
		18	Remnants of imperfectly formed eggs in lower oviduct.

Group	Treatment	Bird No.	Observation
2	TOCP (continued)	19	Gross wasting of muscle. Ovaries appeared underdeveloped.
		20	Minute, diffuse, pale speckling on liver.
3	Cyhalothrin (2500 mg/kg)	29	Haemorrhagic raised areas up to 3 x 1 mm on peritoneal surface of left ventral lobe of liver.
		30	Multiple, firm, white nodules up to 4 mm diameter arising from mesenteric fat. Firm, light grey mass (26 x 28 x 22 mm) on oviduct with prominent surface vascularisation. (Light grey whorled appearance in cross-section.) Liver yellow-tinted.
4	Cyhalothrin (5000 mg/kg)	33	Liver pale brown. Dark, blotchy areas on visceral surface of left lobe up to 6 x 10 mm. Areas soft and slightly raised, and appeared haemorrhagic in cross-section.
		36	Firm, light grey mass (21 x 23 x 26 mm) on oviduct with prominent surface vascularisation. (Whorled arrangement of fibrous tissue in cross-section.) Serosal surface of oviduct: area (46 x 26 mm) of raised, white nodules up to 5 mm in diameter; surface firm with prominent vascularisation. Mucosal surface of oviduct: many pink nodules up to 2 mm diameter.
		38	Dark indentations up to 3 x 0.5 mm on peritoneal surface of left ventral lobe of liver.
		39	Ovaries appeared underdeveloped.
		40	Dark indentations up to 3 x 0.5 mm on peritoneal surface of ventral lobes of liver.
5	Cyhalothrin (10000 mg/kg)	45	Inflammation with a purulent exudate present in abdominal cavity. Pericardial surface of heart covered by a thin, white, plaque-like material.
		48	Ovaries appeared underdeveloped.
6	Cyhalothrin (10000 mg/kg)	51	Firm, light grey mass (26 x 27 x 22 mm) with prominent vascularisation, attached to visceral surface of peritoneal fat (homogeneous in cross-section). Oviduct cystic and distended with cloudy, watery fluid.
		52	Liver dark with pale, subcapsular foci (1 mm diameter) over all surfaces. Surface tinted dark green.
		55	Firm, white nodule (3 x 4 x 3 mm) attached to pancreas. Faint, pale subcapsular foci up to 1 mm diameter on all surfaces of liver.

No abnormalities were observed in any of the other birds examined.

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CONFIDENTIAL
NATIONAL SECURITY INFORMATION

005100

EPA: 68-01-6561
TASK: 107
July 22, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Acute Dermal Toxicity Study in Rats

STUDY IDENTIFICATION: Nixon, J., and Jackson, S. J. Cyhalothrin: acute toxicity. (Unpublished study No. CR0353 and report No. CTL/T/1555 by Imperial Chemical Industries, Limited, Central Toxicology Laboratory, Cheshire, UK for their Pharmaceuticals Division; dated June 22, 1981.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 7-22-85

005100

1. CHEMICAL: Cyhalothrin; a synthetic pyrethroid insecticide; (R,S)α-cyano-3-phenoxybenzyl(±)-cis-3,3(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2-dimethylcyclopropanecarboxylate.

2. TEST MATERIAL: Dark brown, viscous liquid. The sample (being 90.8% pyrethroid of which 98% was the cis-isomer) was given the CTL reference No. Y00102/010/004.

3. STUDY/ACTION TYPE: Acute dermal toxicity in rats.

4. STUDY IDENTIFICATION: Nixon, J., and Jackson, S. J. Cyhalothrin: acute toxicity. (Unpublished study No. CR0353 and report No. CTL/T/1555 by Imperial Chemical Industries, Limited, Central Toxicology Laboratory, Cheshire, UK for their Pharmaceuticals Division; dated June 22, 1981.) Accession No. 073203.

5. REVIEWED BY:

Brian R. Browne, M.S.
Principal Author
Dynamac Corporation

Signature: James R. Plaut for
Date: 7-22-85

Sharon M. Ambrose, B.S.
Independent Reviewer
Dynamac Corporation

Signature: Sharon M Ambrose
Date: July 22, 1985

6. APPROVED BY:

Finis Cavender, Ph.D.
Acute Toxicology
Technical Quality Control
Dynamac Corporation

Signature: Ina Carol Blumpfor
Date: 7-22-85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela M Hurley
Date: 1/23/86

Edwin Budd
EPA Section Head

Signature: John Schaeffer
Date: 4/21/86

7. SUMMARY:

Groups of 5 male and 5 female rats were used. Alderly Park, SPF-derived albino strain rats were obtained from the Animal Breeding Unit (ICI Limited, Cheshire, UK) with an initial body weight range of 119 to 220 g. A solution of cyhalothrin in propylene glycol for doses of 200 (10% w/v) and 1000 (50% w/v) mg/kg body weight was used. Cyhalothrin was also applied neat for a dose of 2 ml/kg (approximately 2000 mg/kg). A standard volume of 2 ml/kg of test material was applied to a shaved area of each animal, and an occlusive dressing of aluminum foil and impermeable tape kept the test material in contact with the skin for 24 hours. The animals were observed daily for any signs of systemic toxicity and for mortality over a 14-day period. All animals given 2 ml/kg died by day 7. No other males died. Two females given 1000 mg/kg died on day 3 of the study. Symptoms observed at each dose level are shown in Appendix A. The acute dermal LD_{50} for cyhalothrin in rats is greater than 1000 mg/kg.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

There were some deviations from the EPA guidelines noted in review of this report.

The method of occlusion was an unconventional one; the guidelines suggest gauze, tape, and an additional covering to ensure that animals cannot ingest the test material. Terminal body weights and gross necropsy findings were not reported and the size of the animals was smaller than that recommended by the guidelines for ease of conduct of the test.

The acute dermal LD_{50} for cyhalothrin in rats is greater than 1000 mg/kg which corresponds to Toxicity Category II.

A signed and dated Quality Assurance Statement was included with the report.

9. C8I APPENDIX: Appendix A, Results, C8I pp. 23, 76.

10. CLASSIFICATION:

Core Classification: Core minimum.

Toxicity Category: II.

LD_{50} greater than 1000 mg/kg.

APPENDIX A

Results

CYHALOTHRIN: ACUTE DERMAL TOXICITY TO MALE RATS

005100

Time after dosing	Dose (mg cyhalothrin/kg) and cumulative mortality		
	200	1000	2ml
Day 1	0/5	0/5	0/5
Day 2	0/5	0/5	0/5
Day 3	0/5	0/5	0/5
Day 4	0/5	0/5	2/5
Day 5	0/5	0/5	4/5
Day 7	0/5	0/5	5/5
Day 15	0/5	0/5	5/5

CYHALOTHRIN: ACUTE DERMAL TOXICITY TO FEMALE RATS

Time after dosing	Dose (mg cyhalothrin/kg) and cumulative mortality		
	200	1000	2ml
Day 1	0/5	0/5	0/5
Day 2	0/5	0/5	0/5
Day 3	0/5	2/5	0/5
Day 4	0/5	2/5	1/5
Day 5	0/5	2/5	3/5
Day 7	0/5	2/5	5/5
Day 15	0/5	2/5	5/5

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CYHALOTHRIN: ACUTE TOXICITY

TABLE 27

ACUTE DERMAL TOXICITY (RAT): CLINICAL SIGNS OF TOXICITY OBSERVED AND THE NUMBER OF ANIMALS AFFECTED AT EACH DOSE LEVEL

Test Substance: Cyhalothrin
No of Animals: 10 per dose level
Species: Rat
Sex: Male and Female

Clinical Observation	200mg/kg		1000mg/kg		2ml/kg	
	Male	Female	Male	Female	Male	Female
Salivation	0	0	0	1	5	4
Scouring	3	1	2	0	3	0
Incontinence	5	5	5	5	5	5
Piloerection	1	2	5	3	2	0
Dehydration	5	4	5	5	5	5
Subdued behaviour	5	5	5	5	5	5
Hypothermia	0	0	0	0	0	1
Partially closed eye(s)	0	0	0	0	1	0
Staining on ventral surface	3	1	0	0	4	5
Staining around eye(s)	1	1	2	1	2	2
Staining around snout	0	0	0	2	2	0
Ataxia	0	0	0	0	4	4
Downward curvature of spine	3	3	4	5	1	4
Upward curvature of spine	2	0	3	3	4	4
Slow righting reflex	0	0	0	0	1	1
Abnormal gait (including splayed, unco-ordinated and/ or unsteady gait; walking high on hind limbs; partial paralysis of hind limbs)	3	0	5	2	2	3
Tremors in fore-limbs	0	0	0	0	1	1
'Nervous' appearance	2	0	1	2	0	0
Increased vocalisation when handled	0	2	0	1	0	2
Flaccid appearance	0	0	0	1	0	0
Nose-bleed	0	0	0	0	0	1
Noise hypersensitivity	0	0	0	0	1	0
'Pinched in' abdomen	0	0	0	0	0	1
Scab on back	1	0	0	0	0	0
Red area on back	1	1	0	0	0	0
Shallow respiration	0	0	0	0	1	0

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CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 71 through 79 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

X INFORMATION ON A PRODUCT THAT IS NOT REGISTERED

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

005100

EPA: 68-01-6561
TASK: 107
July 22, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Acute Dermal Toxicity Study in Rabbits

STUDY IDENTIFICATION: Nixon, J., and Jackson, S. J. Cyhalothrin: acute toxicity. (Unpublished study No. CB0354 and report No. CTL/T/1555 submitted and prepared by Imperial Chemical Industries, Limited, Central Toxicology Laboratory, Cheshire, UK for their Pharmaceuticals Division; dated June 22, 1981.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 7-19-85

005100

1. CHEMICAL: Cyhalothrin; a synthetic pyrethroid insecticide; (R,S)α-cyano-3-phenoxybenzyl (±)-cis-3,3(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2 dimethylcyclopropanecarboxylate.

2. TEST MATERIAL: Dark brown, viscous liquid. The sample (90.8% pyrethroid of which 98% was the cis-isomer) was given the CTL reference no. Y00102/010/004.

3. STUDY/ACTION TYPE: Acute dermal toxicity study in rabbits.

4. STUDY IDENTIFICATION: Nixon, J., and Jackson, S. J. Cyhalothrin: acute toxicity. (Unpublished study No. CB0354 and report No. CTL/T/1555 submitted and prepared by Imperial Chemical Industries Limited, Central Toxicology Laboratory, Cheshire, UK for their Pharmaceuticals Division; dated June 22, 1981.) Accession No. 073203.

5. REVIEWED BY:

Brian R. Browne, M.S.
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Date: 7-22-85

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Date: July 22, 1985

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Date: 7-19-85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela Hurley
Date: 1/23/86

Edwin Budd
EPA Section Head

Signature: Edwin Budd
Date: 4/21/86

7. SUMMARY:

One group of 5 male and 5 female test rabbits and one group of 2 male and 2 female control rabbits were used in the study. The animals were New Zealand white rabbits (Hacking and Churchill, Cambridgeshire, UK), with an initial body weight range of 2.24 to 2.85 kg. Cyhalothrin was applied neat (2 ml/kg) to the shaved and abraded backs of the 10 test animals. The backs were then covered with a surgical gauze patch held in place with a piece of rubber sheeting and a stretched crepe bandage. Animals were observed for signs of systemic toxicity once or twice daily for up to 14 days after dosing. No animals died on study. Scarring occurred in one female rabbit. Individual animal data showing signs of toxicity and duration are given in Appendix A. Histopathological data for individual animals are given in Appendix A. The acute dermal LD_{50} for cyhalothrin in both male and female rabbits was greater than 2 ml/kg (approximately 2 g/kg).

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

There were some deficiencies and deviations from the EPA guidelines noted in review of this report. Terminal body weights and gross necropsy findings were not reported. EPA guidelines require intact skin for dermal irritation studies, these animals were treated on abraded skin only; however, since minimal effects were observed in abraded skin, we would expect a lesser or equal reaction in intact skin.

The acute dermal LD_{50} for cyhalothrin in rabbits is greater than 2 ml/kg (approximately 2 g/kg) which corresponds to Toxicity Category III.

A signed and dated quality assurance statement accompanied the report.

9. CBI APPENDIX:

Appendix A, Results, CBI pp. 77-80.

10. CLASSIFICATION:

Core Classification: Core minimum.

Toxicity Category: III.

LD_{50} male and female rabbits: "in excess of 2 ml/kg" (approximately 2 g/kg).

APPENDIX A

Results

TABLE 28

005100

ACUTE DERMAL TOXICITY (RABBIT):
DURATION OF THE CLINICAL SIGNS OF TOXICITY
(INDIVIDUAL ANIMAL DATA)

Test Substance: Cyhalothrin
Dose: 2ml/kg as supplied

Species: Rabbit
Sex: Male
Number of animals:5

Animal Number	Clinical Sign	Day										
		1	2	3	4	5	6	7	8	9	10	11
1	Incontinence	-	-	-	-	-	-	-	-	-	-	-
	Subdued behaviour	-	-	-	+	-	-	-	-	-	-	-
	Scar/scab on left flank	-	-	-	-	-	-	-	-	-	-	-
	Scouring	-	-	+	+	-	-	-	-	-	-	-
	Splayed hind legs	-	-	-	-	-	-	-	-	-	-	-
2	Incontinence	-	-	-	-	-	-	-	-	-	-	-
	Subdued behaviour	-	-	-	-	-	-	-	-	-	-	-
	Scar/scab on left flank	-	-	-	-	-	-	-	-	-	-	-
	Scouring	-	-	-	-	-	-	-	-	-	-	-
	Splayed hind legs	-	-	-	-	-	-	-	-	-	-	-
3	Incontinence	-	-	-	-	-	-	-	-	-	-	-
	Subdued behaviour	-	-	+	-	-	+	-	-	-	-	-
	Scar/scab on left flank	-	-	-	-	-	-	-	-	-	-	-
	Scouring	-	-	-	-	-	-	-	-	-	-	-
	Splayed hind legs	-	-	+	-	-	-	-	-	-	-	-
4	Incontinence	-	-	+	-	-	-	-	-	-	-	-
	Subdued behaviour	-	-	+	-	-	-	-	-	-	-	-
	Scar/scab on left flank	-	-	-	-	-	-	-	-	-	-	-
	Scouring	-	-	-	-	-	-	-	-	-	-	-
	Splayed hind legs	-	-	-	-	-	-	-	-	-	-	-
5	Incontinence	-	-	-	-	-	-	-	-	-	-	-
	Subdued behaviour	-	-	-	-	-	-	-	-	-	-	-
	Scar/scab on left flank	-	-	-	-	-	-	-	-	-	-	-
	Scouring	-	-	-	-	-	-	-	-	-	-	-
	Splayed hind legs	-	-	-	-	-	-	-	-	-	-	-

Key + slight
- not present

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TABLE 29

ACUTE DERMAL TOXICITY (RABBIT):
DURATION OF THE CLINICAL SIGNS OF TOXICITY
(INDIVIDUAL ANIMAL DATA)

Test Substance: Cyhalothrin
Dose: 2ml/kg as supplied

Species: Rabbit
Sex: Female
Number of animals:5

Animal Number	Clinical Sign	Day										
		1	2	3	4	5	6	7	8	9	10	11
11	Incontinence	-	-	+	-	-	-	-	-	-	-	-
	Subdued behaviour	-	-	-	-	-	-	-	-	-	-	-
	Scar/scab on left flank	-	-	-	-	-	-	-	-	-	-	-
	Scouring	-	-	-	-	-	-	-	-	-	-	-
	Splayed hind legs	-	-	-	-	-	-	-	-	-	-	-
12	Incontinence	-	-	-	-	-	-	-	-	-	-	-
	Subdued behaviour	-	-	-	-	-	-	-	-	-	-	-
	Scar/scab on left flank	-	-	-	-	-	-	-	-	-	-	-
	Scouring	-	-	-	-	-	-	-	-	-	-	-
	Splayed hind legs	-	-	-	-	-	-	-	-	-	-	-
13	Incontinence	-	-	-	-	-	-	-	-	-	-	-
	Subdued behaviour	-	-	-	-	-	-	-	-	-	-	-
	Scar/scab on left flank	-	-	-	-	-	-	-	-	-	-	-
	Scouring	-	-	-	-	-	-	-	-	-	-	-
	Splayed hind legs	-	-	-	-	-	-	-	-	-	-	-
14	Incontinence	-	-	-	-	-	-	-	-	-	-	-
	Subdued behaviour	-	-	-	-	-	-	-	-	-	-	-
	Scar/scab on left flank	-	-	-	-	-	-	+	+	+	+	-
	Scouring	-	-	-	-	-	-	-	-	-	-	-
	Splayed hind legs	-	-	-	-	-	-	-	-	-	-	-
15	Incontinence	-	-	-	-	-	-	-	-	-	-	-
	Subdued behaviour	-	-	+	-	-	-	-	-	-	-	-
	Scar/scab on left flank	-	-	-	-	-	-	-	-	-	-	-
	Scouring	-	-	-	-	-	-	-	-	-	-	-
	Splayed hind legs	-	-	-	-	-	-	-	-	-	-	-

Key + slight
- not present

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TABLE 30

HISTOPATHOLOGICAL EVALUATION OF PRIMARY DERMAL TOXICITY IN THE RABBIT
(INDIVIDUAL ANIMAL DATA)

Test Substance: Cyhalothrin
Doses: Untreated (control)
2ml/kg as supplied

Species: Rabbit
Sex: Male
Number of Animals: 7

	Animal Number	Skin Site	Histopathological Response at 14 days						
			Parakeratosis/ surface debris	Acanthosis	Inflammation		Oedema	Necrosis	Fibrosis
					Epidermis	Dermis			
Test animals	1	abraded	1	0	0	0	0	0	0
	2	abraded	0	0	0	1	0	0	0
	3	abraded	1	0	0	1	0	0	0
	4	abraded	1	0	0	0	0	0	0
	5	abraded	1	0	0	0	0	0	0
Control animals	6	abraded	0	0	0	0	0	0	0
		intact	0	0	0	0	0	0	0
	7	abraded	0	0	0	0	0	0	0
		intact	0	0	0	0	0	0	0

0 - no reaction
1 - slight reaction

CYHALOTHRIN: ACUTE TOXICITY

TABLE 31

HISTOPATHOLOGICAL EVALUATION OF PRIMARY DERMAL TOXICITY IN THE RABBIT
(INDIVIDUAL ANIMAL DATA)

Test Substance: Cyhalothrin
Dose: Untreated (control)
2ml/kg as supplied

Species: Rabbit
Sex: Female
Number of Animals: 7

	Animal Number	Skin Site	Histopathological Response at 14 days						
			Parakeratosis/ surface debris	Acanthosis	Inflammation		Oedema	Necrosis	Fibrosis
					Epidermis	Dermis			
Test animals	11	abraded	1	0	0	1	0	0	0
	12	abraded	1	0	0	1	0	0	0
	13	abraded	1	0	0	1	0	0	0
	14	abraded	1	0	0	1	0	0	0
	15	abraded	1	0	0	0	0	0	0
Control animals	16	abraded	0	0	0	0	0	0	0
		intact	0	0	0	0	0	0	0
	17	abraded	0	0	0	0	0	0	0
		intact	0	0	0	0	0	0	0

0 - no reaction.
1 - slight reaction

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 88 through 96 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

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____ The product confidential statement of formula.

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005100

EPA: 68-01-6561
TASK: 107
July 22, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Acute Intraperitoneal Toxicity Study in Rats

STUDY IDENTIFICATION: Nixon, J., and Jackson, S. J. Cyhalothrin: acute toxicity. (Unpublished study No. JR0097 and report No. CTL/T/1555 by Imperial Chemical Industries, Limited, Central Toxicology Laboratory, Chesire, UK for their Pharmaceuticals Division; dated June 22, 1981.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 7-22-85

005100

1. CHEMICAL: Cyhalothrin; a synthetic pyrethroid insecticide; (R,S)α-cyano-3-phenoxybenzyl(±)-cis-3,3(z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2 dimethylcyclopropanecarboxylate.

2. TEST MATERIAL: Dark brown, viscous liquid. The sample (90.8% pyrethroid of which 98% was the cis-isomer) was given the CTL reference no. Y00102/010/004.

3. STUDY/ACTION TYPE: Acute intraperitoneal toxicity study in rats.

4. STUDY IDENTIFICATION: Nixon, J., and Jackson, S. J. Cyhalothrin: acute toxicity. (Unpublished study No. JR0097 and report No. CTL/T/1555 by Imperial Chemical Industries, Limited, Central Toxicology Laboratory, Chesire, UK for their Pharmaceuticals Division; dated June 22, 1981.) Accession No. 073203.

5. REVIEWED BY:

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Date: 7-22-85

Sharon M. Ambrose, B.S.
Independent Reviewer
Dynamac Corporation

Signature: Sharon M. Ambrose
Date: July 22, 1985

6. APPROVED BY:

Finis Cavender, Ph.D.
Acute Toxicology
Technical Quality Control
Dynamac Corporation

Signature: Ina Cavender for
Date: 7-22-85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela Hurley
Date: 1/23/86

Edwin Budd
EPA Section Head

Signature: John Peheet
Date: 4/21/86

7. SUMMARY:

Groups of 5 male rats per dose level were used. Alderley Park, SPF-derived albino strain rats were obtained from the Animal Breeding Unit (ICI Limited, Cheshire, UK) with initial body weight range of 119 to 220 g per rat. A solution of cyhalothrin in corn oil was used for doses of 50, 250, 500, 750, and 1000 mg/kg body weight. A standard volume of 10 ml/kg of test compound was administered by intraperitoneal injection to each test animal and the animals were observed for signs of systemic toxicity and for mortality over a 14-day period.

All animals were found dead by day 2 following a dose of 1000 mg/kg. Two animals were found dead and the remaining animals were sacrificed due to the severity of reactions by day 4, following a dose of 750 mg/kg. Toxic signs included piloerection, damp fur, salivation, lachrymation, dehydration, ataxia, labored respiration, signs of hypothermia, chromodacryorrhea, and convulsions. One animal was found dead on day 2, following a dose of 500 mg/kg. Surviving animals recovered by day 10. Following a dose of 250 mg/kg, toxic signs were less severe than those described above. All animals recovered by day 6. Following a dose of 50 mg/kg, all animals showed slight signs of toxicity and all animals recovered by day 6. The authors reported that the acute ip LD_{50} was "between 250 and 750 mg/kg." Our reviewers calculated the ip LD_{50} for cyhalothrin in rats to be 694 (460-999) mg/kg using the probit analysis method.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

Acute intraperitoneal toxicity studies are not required for registration. This study was acceptable as a special study; however, some reporting discrepancies and deficiencies were noted. The Experimental Procedures section of the report listed the doses as 250, 500, 750, and 1000 mg/kg; however, the Results section indicated that animals were also dosed at 50 mg/kg.

The acute ip LD_{50} for cyhalothrin in rats is 694 (460-999) mg/kg.

A signed and dated quality assurance statement was included in the report.

9. CLASSIFICATION: Acceptable.

Toxicity Category: Not applicable.

LD_{50} male rats: 694 (460-999) mg/kg.

005100

EPA: 68-01-6561
TASK: 107
July 22, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Skin Irritation Study in Rats

STUDY IDENTIFICATION: Jackson, S. J. and Nixon, J. Skin Irritation Studies in the Rat. (Unpublished study No. ER1604 and report No. CTL/T/1504 prepared and submitted by Central Toxicology Laboratory, ICI limited, Alderley Park, Macclesfield, Cheshire, U.K. for Pharmaceuticals Division, ICI Limited, Alderley Park, Macclesfiled, Cheshire, U.K.; dated May 13, 1981.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 7-22-85

005100

1. CHEMICAL: Cyhalothrin; PP563, ICI 146,814; (R,S)-α-cyano-3-phenoxybenzyl(±)-cis-3,3(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2-dimethylcyclopropane carboxylate.

2. TEST MATERIAL: Synthetic pyrethroid insecticide; dark-brown liquid; 90.8% pyrethroid of which 98% was in the cis-isomer.

3. STUDY/ACTION TYPE: Skin irritation study in rats.

4. STUDY IDENTIFICATION: Jackson, S. J. and Nixon, J. Skin Irritation Studies in the Rat. (Unpublished study No. ER1604 and report No. CTL/T/1504 prepared and submitted by Central Toxicology Laboratory, ICI limited, Alderley Park, Macclesfield, Cheshire, U.K. for Pharmaceuticals Division, ICI Limited, Alderley Park, Macclesfiled, Cheshire, U.K.; dated May 13, 1981.) Accession No. 073203.

5. REVIEWED BY:

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Signature: Brian Browne for
Date: July 22 1985

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Date: 7-19-85

6. APPROVED BY:

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Date: 7/22/85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela Hurley
Date: 4/23/86

Edwin Budd
EPA Section Head

Signature: Edwin Budd
Date: 4/21/86

7. SUMMARY

Two groups, each consisting of 6 female Alderley Park rats, SPF-derived, with an initial body weight range of 153-178 g were used in this study. One group of rats was used for single dermal application of the test compound and the other group was used for the repeated application of test compound. Undiluted cyhalothrin was applied to shorn backs (0.1 ml/rat) and the treated area was covered for 24 hours. After 1-2 hours, skin reactions were noted. In the case of the repeated-application group, the material was re-applied 24 hours later. No abnormalities, except for dark-brown stains, were seen following the first and second applications. However, in the single-application group, one animal showed toxic signs including ataxia, moderate salivation, red-stained saliva, and gasping at day 3. All animals in the group were showing these toxic signs by day 4. In the repeated application group, one animal was found dead on day 5 and all others were sacrificed because of the severity of the toxic signs. In conclusion, undiluted cyhalothrin is not a skin irritant in the rat, but produces toxicity following dermal application. Individual animal data are given in Appendix A.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

This study appears to be valid and includes a signed and dated Quality Assurance statement.

Cyhalothrin did not produce dermal irritation or sensitization in this study. This corresponds to Toxicity Category IV.

9. CBI APPENDIX:

Appendix A, Results, CBI pp. 9 and 10.

10. CLASSIFICATION:

Core Classification: Core Minimum.

Toxicity Category: IV.

Dermal Response: Not a dermal irritant.

APPENDIX A
RESULTS

CYHALOTHRIN

SKIN IRRITATION STUDIES IN THE RABBIT AND RAT

TABLE 1a

INDIVIDUAL ANIMAL DATA : SINGLE APPLICATION TO RAT SKIN

Observation Time (Days)	Animal Number					
	37	38	39	40	41	42
1 (Application)	-	-	-	-	-	-
2 (Decontamination)	B	B	B	B	B	B.
3	/	/	A_4S_3bGK	/	/	/
4	$A_4S_3bGI_3$ WK	$A_4S_3bGI_3$ WK		$A_4S_3bGI_3$ WK	$A_4S_3bGI_3$ WK	$A_4S_3bGI_3$ WK

Key: B - brown staining of the skin
W - weakness
G - laboured respiration (gasping)
/ - no reaction
K - killed in extremis due to severity of systemic effects
A - ataxia)
S - salivation) 1 - slight 3 - moderate
I - incontinence) 2 - mild 4 - marked
- - no observations made
b - blood-stained saliva

CYHALOTHRIN

005100

SKIN IRRITATION STUDIES IN THE RABBIT AND RAT

TABLE 1b

INDIVIDUAL ANIMAL DATA : REPEATED APPLICATION TO RAT SKIN

Observation Time (Days)	Animal Number					
	49	50	51	52	53	54
1 (Application)	-	-	-	-	-	-
2 (Decontamination)	B	B	B	B	B	B
3 (Application)	/	/	/	/	/	/
4 (Decontamination)	B	B	B	B	B	B
5 (Application)	BA_4S_3b GWK	BA_4S_3b GWK	D	BA_4S_3b GWK	BA_4S_3b GWK	BA_4S_3b GWK

Key: B - brown staining of the skin
W - weakness
G - laboured respiration (gasping)
/ - no reaction
K - killed in extremis due to severity of systemic effects
A - ataxia) 1 - slight 3 - moderate
S - salivation) 2 - mild 4 - marked
D - found dead
b - blood-stained saliva
- - no observations made

005100

EPA: 68-01-6561
TASK: 107
July 22, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Skin Irritation Study in Rabbits

STUDY IDENTIFICATION: Jackson, S. J. and Nixon, J. Skin Irritation Studies in the Rabbit. (Unpublished study No. EB1602 and report No. CTL/T/1504 prepared and submitted by Central Toxicology Laboratory, ICI limited, Alderley Park, Macclesfield, Cheshire, U.K. for Pharmaceuticals Division, ICI Limited, Alderley Park, Macclesfiled, Cheshire, U.K.; dated May 13, 1981.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 7-22-85

005100

1. CHEMICAL: Cyhalothrin; PP563, ICI 146,814; (R,S)-α-cyano-3-phenoxybenzyl(±)-cis-3,3(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2-dimethyl cyclopropanecarboxylate).

2. TEST MATERIAL: Cyhalothrin, Synthetic pyrethroid insecticide; dark-brown liquid; 90.8% pyrethroid of which 98% was in the cis-isomer.

3. STUDY/ACTION TYPE: Skin irritation study in rabbits.

4. STUDY IDENTIFICATION: Jackson, S. J. and Nixon, J. Skin Irritation Studies in the Rabbit. (Unpublished study No. EB1602 and report No. CTL/T/1504 prepared and submitted by Central Toxicology Laboratory, ICI limited, Alderley Park, Macclesfield, Cheshire, U.K. for Pharmaceuticals Division, ICI Limited, Alderley Park, Macclesfiled, Cheshire, U.K.; dated May 13, 1981.) Accession No. 073203.

5. REVIEWED BY:

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Signature: Brian R. Browne for
Date: July 22 1985

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Signature: William M Butler Jr.
Date: 7-19-85

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Pamela Hurley, Ph.D.
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Signature: Pamela Hurley
Date: 1/23/86

Edwin Budd
EPA Section Head

Signature:
Date: 1/24/86

7. SUMMARY

Six female white New Zealand rabbits with an initial body weight range of 2.5-3.0 kg were used in this study. Hair on the flanks of the rabbits was removed and the right flank of each rabbit was further prepared by making epidermal abrasions. Four areas on the flanks of the rabbits (two areas on the right and left flank each) were treated with 0.5 ml of undiluted cyhalothrin and covered for 24 hours. Assessment of irritation was made immediately after the removal of the gauze covering and at 72 hours. One application of undiluted cyhalothrin to rabbit skin caused brown staining which obscured erythema in 3 animals. The other 3 animals produced only very slight or no erythema in both intact and abraded skin. At 24 hours, edema was slight in most animals, but disappeared by 72 hours. One rabbit showed severe signs of toxicity, which included a subdued appearance, piloerection, severe ataxia, and labored respiration, and was therefore sacrificed at 18 hours. The other 5 rabbits showed toxic signs at 24 and 72 hours; these included slight ataxia, labored respiration, a subdued appearance, and increased abdominal tone. In conclusion, undiluted cyhalothrin is a mild dermal irritant in rabbits and produces severe systemic toxicity following dermal application. Individual animal data are given in Appendix A, Table 2, pg. 11.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

It was mentioned in the conclusion section of the report that restraining collars were not used and it was possible that some oral administration of cyhalothrin occurred; this would likely increase the intensity of toxicity. A signed and dated Quality Assurance Statement was included.

Cyhalothrin is a mild dermal irritant which corresponds to Toxicity Category IV.

9. CBI APPENDIX:

Appendix A, Results, CBI pp. 11.

10. CLASSIFICATION:

Core Classification: Core Minimum.

Toxicity Category: IV.

Mild dermal irritant.

APPENDIX A

RESULTS

CYHALOTHRIN
SKIN IRRITATION STUDIES IN THE RABBIT AND RAT

TABLE 2

INDIVIDUAL ANIMAL DATA : RABBIT SKIN IRRITATION STUDY

	Skin Condition / Skin Site	Erythema				Oedema			
		24 hrs		72 hrs		24 hrs		72 hrs	
		Top	Bottom	Top	Bottom	Top	Bottom	Top	Bottom
Rabbit 1	Intact	*	*	0	0	2	2	0	0
	Abraded	*	*	0	0	2	2	0	0
Rabbit 2	Intact	animal killed in extremis at 18 hrs due to severity of systemic effects.							
	Abraded								
Rabbit 3	Intact	0	0	0	0	2	2	0	0
	Abraded	0	0	0	0	2	2	0	0
Rabbit 4	Intact	*	*	0	0	2	2	0	0
	Abraded	*	*	0	0	2	2	0	0
Rabbit 5	Intact	1	1	1	0	1	1	0	0
	Abraded	1	0	0	0	1	1	0	0
Rabbit 6	Intact	*	*	0	0	0	0	0	0
	Abraded	*	*	0	0	1	1	0	0
	Totals	2	1	1	0	15	15	0	0

Sum Total = 34+ Primary Irritation Index = $\frac{34+}{40}$ = 0.85+

* Skin stained brown and hence evaluation of degree of erythema difficult

CTL/T/1504

98

110

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CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 111 through 125 are not included.

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EPA: 68-01-6561
TASK: 107
July 22, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Eye Irritation Study in Rabbits

STUDY IDENTIFICATION: Jackson, S. J. Cyhalothrin: Eye irritation study in the rabbit. (Unpublished study No. FB 1835 and report No. CTL/T/1502 prepared and submitted by Central Toxicology Laboratory, ICI Limited, Alderley Park, Macclesfield, Cheshire, U.K. for Pharmaceuticals Division, ICI Limited, Alderley Park, Macclesfield, Cheshire, U.K.; dated February 19, 1981.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I Cecil Felkner

Date: 7-22-85

005100

1. CHEMICAL: Cyhalothrin; PP 563, ICI 146,814; (R,S)-α-cyano-3-phenoxybenzyl(±)-cis-3,3(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2-dimethylcyclopropanecarboxylate.

2. TEST MATERIAL: Synthetic pyrethroid insecticide; dark-brown, viscous liquid; pH 4.35; 90.8% was pyrethroid and of this 98% was cyhalothrin.

3. STUDY/ACTION TYPE: Eye irritation study in rabbits.

4. STUDY IDENTIFICATION: Jackson, S. J. Cyhalothrin: Eye irritation study in the rabbit. (Unpublished study No. FB 1835 and report No.. CTL/T/1502 prepared and submitted by Central Toxicology Laboratory, ICI Limited, Alderley Park, Macclesfield, Cheshire, U.K. for Pharmaceuticals Division, ICI Limited, Alderley Park, Macclesfield, Cheshire, U.K.; dated February 19, 1981.) Accession No. 073203.

5. REVIEWED BY:

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Date: July 22, 1985

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Signature: William M. Butler Jr.
Date: 7-19-85

6. APPROVED BY:

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Date: 7/22/85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela Hurley
Date: 4/23/86

Edwin Budd
EPA Section Head

Signature: Edwin Budd
Date: 5/5/86

7. SUMMARY:

Nine female New Zealand White rabbits with an initial weight range between 2.0 and 3.5 kg from Hacking and Churchill, Cambridgeshire, U.K.) were used in this study. Cyhalothrin was instilled into the conjunctival sac of the left eye of all nine animals in a volume of 0.1 ml/test eye. Three of the animals' eyes were irrigated for one minute with 175 ml of clean, lukewarm water 20-30 seconds post-cyhalothrin instillation. Ocular lesions during a 7-day observation period were scored. Instillation of cyhalothrin into the rabbit eye caused very little initial pain in seven animals and slight-to-moderate initial pain in the other two. Corneal opacity and iritis was noted in all animals, but was less prominent in rabbits receiving irrigation with water; in all cases the cornea and iris were normal by day 7. Conjunctivitis was noted in all animals, being less prominent in the water-irrigated group, and by day 7 the conjunctivas in all animals were normal. The animals had convoluted and crusting eyelids early in the experiment, but were normal by day 7. Cyhalothrin is a moderate irritant to the rabbit eye without water irrigation and a mild irritant when instillation is followed by irrigation with water.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

This appears to be a valid experiment with a "recommendation for handling" statement and "probable effects in man" statement included which follow the results of this test. Details on the method of clinical examinations were not given. A signed and dated quality assurance statement was included in the report. Cyhalothrin is a moderate eye irritant which corresponds to Toxicity Category III.

9. CBI APPENDIX:

Appendix A, Results, pp. 5, 8-10, 12-14.

10. CORE CLASSIFICATION: Core Minimum .

Toxicity Category: ~~IV~~ II .

Eye Irritation Results: Cyhalothrin is a moderate eye irritant.

APPENDIX A

Results

TABLE 1a

005100

CYHALOTHRIN: MEAN UNWASHED EYE IRRITATION SCORES*

	Group Mean Score					
	1-2hr	Day 1	Day 2	Day 3	Day 4	Day 7
Cornea (max 80)	8	10	5	5	2	0
Iris (max 10)	4	3	2	1	1	0
Conjunctiva (max 20)	14	11	4	3	1	0
Total (max 110)	26	24	11	9	4	0

*Means based on six animals and scores rounded to the nearest whole number.

TABLE 1b

CYHALOTHRIN: MEAN WASHED EYE IRRITATION SCORES*

	Group Mean Score					
	1-2hr	Day 1	Day 2	Day 3	Day 4	Day 7
Cornea (max 80)	10	7	0	0	0	0
Iris (max 10)	5	3	0	0	0	0
Conjunctiva (max 20)	14	9	3	0	0	0
Total (max 110)	29	19	3	0	0	0

*Means based on three animals and scores rounded to the nearest whole number.

CYHALOTHRIN: EYE IRRRITATION STUDY IN THE RABBIT

TABLE 2a

INSTILLATION OF CYHALOTHRIN INTO THE RABBIT EYE WITHOUT IRRIGATION

	Rabbit 63						Rabbit 64						Rabbit 65					
Initial Pain	Slight/Moderate						Practically none						Practically none					
	1-2 hr	Day 1	Day 2	Day 3	Day 4	Day 7	1-2 hr	Day 1	Day 2	Day 3	Day 4	Day 7	1-2 hr	Day 1	Day 2	Day 3	Day 4	Day 7
CORNEA																		
opacity	1	1	1	1	1	0	1	0	0	0	0	0	1	0	0	0	0	0
area	2	4	4	4	2	0	2	0	0	0	0	0	2	0	0	0	0	0
SCORE	10	20	20	20	10	0	10	0	0	0	0	0	10	0	0	0	0	0
IRIS	0	0	1	1	1	0	1	0	0	0	0	0	1	0	0	0	0	0
SCORE	0	0	5	5	5	0	5	0	0	0	0	0	5	0	0	0	0	0
CONJUNCTIVA																		
redness	2	2	2	2	2	0	2	1	0	0	0	0	2	1	1	1	0	0
chemosis	2	2	2	2	1	0	2	1	0	0	0	0	2	0	0	0	0	0
discharge	3	3	3	3	1	0	3	2	0	0	0	0	3	2	0	0	0	0
SCORE	14	14	14	14	8	0	14	8	0	0	0	0	14	6	2	2	0	0
TOTAL SCORE	24	34	39	39	23	0	29	8	0	0	0	0	29	6	2	2	0	0

CYHALOTHRIN: EYE IRRRITATION STUDY IN THE RABBIT

TABLE 2a - continued

INSTILLATION OF CYHALOTHRIN INTO THE RABBIT EYE WITHOUT IRRIGATION

	Rabbit 66						Rabbit 67						Rabbit 68					
Initial Pain	Practically none						Practically none						Practically none					
	1-2 hr	Day 1	Day 2	Day 3	Day 4	Day 7	1-2 hr	Day 1	Day 2	Day 3	Day 4	Day 7	1-2 hr	Day 1	Day 2	Day 3	Day 4	Day 7
CORNEA																		
opacity	0	0	0	0	0	0	0	1	1	1	0	0	1	1	0	0	0	0
area	0	0	0	0	0	0	0	4	2	2	0	0	4	4	0	0	0	0
SCORE	0	0	0	0	0	0	0	20	10	10	0	0	20	20	0	0	0	0
IRIS	1	1	0	0	0	0	1	1	1	0	0	0	1	1	0	0	0	0
SCORE	5	5	0	0	0	0	5	5	5	0	0	0	5	5	0	0	0	0
CONJUNCTIVA																		
redness	2	2	0	0	0	0	2	2	0	0	0	0	2	2	1	0	0	0
chemosis	2	1	0	0	0	0	2	2	0	1	0	0	2	2	1	0	0	0
discharge	3	2	0	0	0	0	3	2	0	1	0	0	3	3	1	1	0	0
SCORE	14	10	0	0	0	0	14	12	0	4	0	0	14	14	6	2	0	0
TOTAL SCORE	19	15	0	0	0	0	19	37	15	14	0	0	39	39	6	2	0	0

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CYHALOTHRIN: EYE IRRRITATION STUDY IN THE RABBIT

TABLE 2b

INSTILLATION OF CYHALOTHRIN INTO THE RABBIT EYE WITH IRRIGATION

	Rabbit 69						Rabbit 70						Rabbit 71					
Initial Pain	Practically none						Practically none						Slight					
	1-2 hr	Day 1	Day 2	Day 3	Day 4	Day 7	1-2 hr	Day 1	Day 2	Day 3	Day 4	Day 7	1-2 hr	Day 1	Day 2	Day 3	Day 4	Day 7
CORNEA																		
opacity	0	0	0	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0
area	0	0	0	0	0	0	2	0	0	0	0	0	4	4	0	0	0	0
SCORE	0	0	0	0	0	0	10	0	0	0	0	0	20	20	0	0	0	0
IRIS	1	1	0	0	0	0	1	0	0	0	0	0	1	1	0	0	0	0
SCORE	5	5	0	0	0	0	5	0	0	0	0	0	5	5	0	0	0	0
CONJUNCTIVA																		
redness	2	2	1	0	0	0	2	1	0	0	0	0	2	2	1	0	0	0
chemosis	2	1	0	0	0	0	2	0	0	0	0	0	2	2	1	0	0	0
discharge	3	3	1	0	0	0	3	1	0	0	0	0	3	2	0	0	0	0
SCORE	14	12	4	0	0	0	14	4	0	0	0	0	14	12	4	0	0	0
TOTAL SCORE	19	17	4	0	0	0	29	4	0	0	0	0	39	37	4	0	0	0

005100

CYHALOTHRIN:
EYE IRRITATION STUDY IN THE RABBIT

APPENDIX 2

PAIN EVALUATION

When the material is instilled in the eye there may or may not be an initial pain reaction. The reaction should be graded as follows:

Class	Reactions by animal	Descriptive rating
0	No response	No initial pain
1	A few blinks only; normal within one or two minutes	Practically no initial pain
2	Rabbit blinks and tries to open eye, but the reflexes close it	Slight initial pain
3	Rabbit holds eye shut aand puts pressure on lids; may rub eye with paw	Moderate initial pain
4	Rabbit holds eye shut vigcrously; may squeal	Severe initial pain
5	Rabbit holds eye shut vigorously; may squeal, claw at eye, jump and try to escape	Very severe initial pain

There is often no correlation between the initial pain and the subsequent eye irritation.

CYHALOTHRIN:

005100

EYE IRRITATION STUDY IN THE RABBIT

APPENDIX 3

FROM: The Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics, FDA 1959 p 51.

Scale for Scoring Ocular Lesions

(1) Cornea

(A) Opacity-degree of density (area most dense taken for reading)

No opacity	0
Scattered or diffuse area, details of iris clearly visible	1
Easily discernible translucent areas, details of iris slightly obscured	2
Opalescent areas, no details or iris visible, size of pupil barely discernible	3
Opaque, iris invisible	4

(B) Area of cornea involved

One quarter (or less) but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4

A X B X 5 Total maximum = 80

(2) Iris

(A) Values

Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)	1
No reaction to light, hemorrhage, gross destruction (any or all of these)	2

A X 5 Total maximum = 10

(3) Conjunctivae

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal	0
Vessels definitely injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2
Diffuse beefy red	3

(B) Chemosis

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids about half closed to completely closed	4

(C) Discharge

No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs, and considerable area around the eye	3

Sum (A+B+C) X 2 Total maximum = 20

135

ITL/T/1502 - 13

CYHALOTHRIN :

EYE IRRITATION STUDY IN THE RABBIT

095100

APPENDIX 4

KAY AND CALANDRA INTERPRETATION OF EYE IRRITATION TEST

Maximum mean total score during first 4 days	Persistance of score	Descriptive rating (and class)
0.0 to 0.5	Mean total score at 1 day = 0	Non-irritating (1)
	Mean total score at 1 day greater than 0	Practically non-irritating (2)
0.5 to 2.5	Mean total score at 1 day = 0	Non-irritating (1)
	Mean total score at 1 day greater than 0	Practically non-irritating (2)
2.5 to 15	Mean total score at 2 days = 0	Slight irritant (3)
	Mean total score at 2 days greater than 0	Mild irritant (4)
15 to 25	Mean total score at 3 days = 0	Mild irritant (4)
	Mean total score at 3 days greater than 0	Moderate irritant (5)
25 to 50	Mean total score at 7 days 20 or less: More than half of the individual total scores at 7 days 10 or less.	Moderate irritant (5)
	Mean total score at 7 days 20 or less: More than half of the individual total scores at 7 days greater than 10 but no individual total score at 7 days greater than 20.	Moderate irritant (5)
	Mean total score at 7 days 20 or less: More than half of the individual total scores at 7 days greater than 10 and any individual total score at 7 days greater than 20.	Severe irritant (6)
	Mean total score at 7 days greater than 20	Severe irritant (6)
50 to 80	Mean total score at 7 days 40 or less: More than half of the individual total scores at 7 days 20 or less.	Severe irritant (6)
	Mean total score at 7 days 40 or less: More than half of the individual total scores at 7 days greater than 20 but no individual total score at 7 days greater than 60.	Severe irritant (6)
	Mean total score at 7 days 40 or less: More than half of the individual total scores at 7 days greater than 20 and any individual total score at 7 days greater than 60.	Very severe irritant (7)
	Mean total score at 7 days greater than 40	Very severe irritant (7)
80 to 100	Mean total score at 7 days 60 or less: More than half of the individual total scores at 7 days 60 or less.	Very severe irritant (7)
	Mean total score at 7 days 60 or less: More than half of the individual total scores at 7 days greater than 60 but no individual total score at 7 days greater than 100.	Very severe irritant (7)
	Mean total score at 7 days 60 or less: More than half of the individual total scores at 7 days greater than 60 and any individual total score at 7 days greater than 100.	Extremely severe irritant (8)
	Mean total score at 7 days greater than 60	Extremely severe irritant (8)
100 to 110	Mean total score at 7 days 80 or less	Very severe irritant (7)
	Mean total score at 7 days greater than 80	Extremely severe irritant (8)

EPA: 68-01-6561
TASK: 107
July 22, 1985

005100

DATA EVALUATION RECORD

CYHALOTHRIN

Skin Sensitization Study in Guinea Pigs

STUDY IDENTIFICATION: Nixon, J., and Jackson, S. J. Cyhalothrin: Skin sensitization study in the guinea pig. (Unpublished study No. GG 1881 and report No. CTL/T/1552 by Central Toxicology Lab., Alderley Park, Macclesfield, Cheshire, UK for ICI Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, UK; dated June 5, 1981.) Accession No. 073203.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 7-22-85

112

[redacted]

137

1. CHEMICAL: Cyhalothrin; [PP563, ICI 145,814: (R,S)α-cyano-3-phenoxybenzyl(±)-cis-3,3(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2-dimethylcyclopropanecarboxylate].

2. TEST MATERIAL: Synthetic pyrethroid insecticide; dark-brown viscous liquid; pH 4.35; 90.8% was pyrethroid and of this 98% was the cis-isomer.

3. STUDY/ACTION TYPE: Skin sensitization study in guinea pigs.

4. STUDY IDENTIFICATION: Nixon, J., and Jackson, S. J. Cyhalothrin: skin sensitization study in the guinea pig. (Unpublished study No. GG 1881 and report No. CTL/T/1552 by Central Toxicology Lab., Alderley Park, Macclesfield, Cheshire, UK for ICI Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, UK; dated June 5, 1981.) Accession No. 073203.

5. REVIEWED BY:

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Pamela Hurley, Ph.D.
EPA Reviewer

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Date: 4/23/86

Edwin Budd
EPA Section Head

Signature: John Schaefer
Date: 5/15/86

7. SUMMARY:

Two groups of ten male Alderley Park, SPF-derived, albino strain guinea pigs with an initial body weight range of 300-400 g were used in this study. In the induction phase, cyhalothrin was applied neat in a volume of 0.4 ml on the scapular region of each animal. The test material was covered and held in place for 6 hours/day. This procedure was repeated on alternate days for a total of 10 times over a 3-week period. The animals were left untreated for an additional 2 weeks. The challenge phase consisted of the application of cyhalothrin at 75% and 50% (w/v) in corn oil (one dose on each flank) and corn oil control at a third (unspecified) site, other than the site used for the induction period.

The results showed that during the induction phase of the study, a very slight, transient erythema occurred in all control animals and a slight to moderate erythema was observed in all test animals. Signs of faint erythema at challenge sites prompted the conclusion that cyhalothrin is a sensitizer to guinea pig skin under the test conditions employed in this study.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

The test appears to be valid. A signed and dated quality assurance statement was included in the report.

9. CBI APPENDIX:

Appendix A, Results, CBI pg. 9.

10. CLASSIFICATION:

Core Classification: Core Minimum.

Sensitization Results: Cyhalothrin is a sensitizer.

APPENDIX A

Results

CYHALOTHRIN:

SKIN SENSITISATION STUDY IN THE GUINEA PIG

TABLE 1

SKIN RESPONSES IN THE SKIN SENSITISATION STUDY

	Animal No	Erythematous Response at Challenge					
		75% solution		50% solution		Vehicle only	
		24hr	48hr	24hr	48hr	24hr	48hr
Test Animals	35	0	0	0	0	0	0
	36	1	1	1	1	1	1
	37	0	0	1	0	0	0
	38	0	0	0	0	0	0
	39	0	0	1	0	0	0
	40	0	0	1	0	0	0
	41	1	0	1	0	0	0
	42	0	0	0	0	0	0
	43	0	0	0	0	0	0
	44	0	0	0	0	0	0
Control Animals	45	0	0	0	0	0	0
	46	0	0	0	0	0	0
	47	0	0	0	0	0	0
	48	0	0	0	0	0	0
	49	0	0	0	0	0	0
	50	0	0	0	0	0	0
	51	0	0	0	0	0	0
	52	0	0	0	0	0	0
	53	0	0	0	0	0	0
	54	0	0	0	0	0	0

0 = no reaction

1 = faint erythema

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 142 through 157 are not included.

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____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

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00510[illegible]

EPA: 68-01-6561
TASK: 107
September 13, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Subacute Dermal Toxicity Study in Rabbits

STUDY IDENTIFICATION: Henderson, C. and Jackson, S.J. Cyhalothrin: Subacute dermal toxicity study in rabbits. (Unpublished study No. LB 0023 and report No. CTL/P/680 prepared and submitted by Control Toxicology Laboratory, ICI Limited, Alderley Park, Macclesfield, Cheshire, U.K. for Pharmaceuticals Division, ICI Limited, Alderley Park, Macclesfield, Cheshire, U.K.; dated March 16, 1982.) Accession No. 073203.

APPPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I Cecil Felkner

Date: 9-13-85

005100

1. CHEMICAL: Cyhalothrin; PP563, ICI 146, 814; (R,5)-α-cyano-3-phenoxybenzyl (±)-cis-3, 3(z-2-chloro-3,3,3-trifluoroprop-1-(-en)-2,2 dimethylcyclopropanecarboxylate.

2. TEST MATERIAL: Synthetic pyrethroid insecticide; pale-yellow liquid; sample contains 90.2% (w/v) cyhalothrin with 97.1% of that being the cis-isomer and 2.9% being the trans-isomer; CTL reference no. Y00102/010/006. The diluent was polyethylene glycol, average M.Wt. 300 (PEG 300) obtained from Ex BDH Chemicals, Poole, England and was given the CTL reference numbers Y01012/004/005 and Y01012/004/006.

3. STUDY/ACTION TYPE: Subacute dermal toxicity study in rabbits.

4. STUDY IDENTIFICATION: Henderson, C. and Jackson, S. J. Cyhalothrin: Subacute dermal toxicity study in rabbits. (Unpublished study No. LB 0023 and report No. CTL/P/680 prepared and submitted by Control Toxicology Laboratory, ICI Limited, Alderley Park, Macclesfield, Cheshire, U.K. for Pharmaceu- ticals Division, ICI Limited, Alderley Park, Macclesfield, Cheshire, U.K.; dated March 16, 1982.) Accession No. 073203.

5. REVIEWED BY:

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Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela Hurley
Date: 4/23/86

Edwin Budd
EPA Section Head

Signature: John Budd
Date: 4/21/86

7. SUMMARY:

Groups of 10 male and 10 female rabbits per dose level were used in this study. Half of each group was used for testing with abraded skin. New Zealand Albino rabbits were obtained from Hacking and Churchill Limited, Abbots Ripton Road, Wyton, Huntingdon, Cambridgeshire, U.K., with initial body weights ranging from 2.25-3.05 kg (males) and 2.10-3.15 kg (females). Three dose levels of 10, 100, and 1000 mg/kg/day were used. A control group of 28 rabbits (14 males and 14 females) was treated with 2 ml/kg/day of polyethylene glycol 300 (PEG 300). The extra 8 animals served as replacements or as control animals for early sacrifices.

The test material was diluted with PEG 300 and applied dermally to rabbits in a dosage volume of 2 ml/kg of body weight. The test material was applied to the rabbit skin for 6 hours/day, 5 days/week for a total of 15 applications. A two day rest period was observed after each fifth application. An occlusive dressing consisting of a sterilized gauze patch covered by a piece of rubber sheeting and elastic net bandaging was used to hold material in contact with the skin. At the end of each six-hour exposure, the occlusive dressing was removed and discarded, and the skin was washed with wool-cotton swabs and warm water. In the high-dose group, the skin was washed with wool-cotton swabs and methylated spirits followed by warm water. For the remaining 18 hours, each rabbit was wrapped with a surgical tubular stockinette to prevent oral contamination during grooming. Approximately one week prior to the start of the study, each animal was fitted with a collar to prevent chewing on the occlusive dressing.

The animals were observed daily, prior to each application, for gross signs of toxicity, skin irritation, and individual body weights. Food consumption was measured over a 24-hour period on six separate occasions. Biochemical and hematology analyses were done 2-3 days prior to dosing and approximately 18 hours following the final application. The animals were sacrificed after terminal blood samples were taken. Gross necropsy and microscopic pathology examinations were performed.

There appeared to be no difference in the incidence of signs of systemic toxicity between the abraded and non-abraded animals. The systemic effects observed did not appear to be test material related. Both the test material, in its various dilutions, and the vehicle control, PEG 300, caused slight to severe skin irritation with repeated application. The highest dose level, 1000 mg/kg/day, showed an increase in the incidence of erythema and edema. Very little difference was found in the intensity of skin reactions when the control and treated groups were compared. Most of the animals showed no clinical signs of systemic toxicity. Only non-abraded males which received 10 mg/kg/day showed an increase in body weight; all other groups showed a decrease in body weight. Concomitantly, there was an increase in mean food consumption in this male non-abraded group. In all other groups, abraded and non-abraded, there was a decrease in food consumption. Hematology, clinical chemistry, and histopathological findings showed no effects that could be attributed to the repeated administration of cyhalothrin.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES:

The design and report of the experiment appear to be valid. A series of toxic signs were observed, only in one animal, in the 10 mg/kg/day dosage group (see Appendix A, Table 2), appearing to show a toxic effect. However, most of these signs were observed in one animal (No. 35) whose collar was stuck in his mouth, putting pressure on eyes, nictitating membrane, and sclera. Animal No. 38 injured a front limb and displayed a subdued appearance for the remainder of the study. The remaining systemic toxic signs were respiratory and splayed gait in different animals. These findings were not those of significant systemic toxicity, but were the result of physical injury. A similar observation can be made of data reported at the 1000 mg/ kg/day dose in the non-abraded male rabbits. Four of the toxic signs; downward curvature of spine, clonic convulsions, labored respiration, and cyanosed mucous membranes and eyes, were found in one animal that was killed in extremus. There was not significant systemic toxicity at the high dose level of cyhalothrin.

The assessment of skin irritation (Draize scale) in male and female animals appeared to range from none to very slight (barely perceptible) to a slight (well defined) erythema and essentially no signs of edema. The mid- and high-dose males showed some grading of moderate to severe for erythema (3,4) and slight to moderate edema. The authors reported that these irritant levels were due to the occlusive dressing being too tight. This appears along with Draize scores of slight, moderate, and severe in Tables 12 and 13 (mid- and high-dose males) and Tables 16 and 17 (mid- and high-dose females). The assessment of skin irritation for erythema and edema appears to range from very slight (barely perceptible) to a slight erythema and edema through all dose levels when the mechanical irritation is considered. Another observation of toxicity was a decrease in mean body weight and mean body weight gain in the control group (PEG 300), and in all but one of the dosage groups. The non-abraded male rabbits in the 10 mg/kg/day dosage group showed a gain in body weight, and in the later exposure period statistically significant gains in body weight. In the 1000 mg/kg/day dosage group, male and female rabbits, abraded and non-abraded, a statistically significant decrease in mean body weight gain was observed. Concomitantly with the decrease in body weight gain there appears to be a decrease in food consumption. Since this decrease is observed in the control groups, the effect in all groups may be due to the PEG 300 and not cyhalothrin.

A signed and dated quality assurance statement was included in the report.

9. CBI APPENDIX:

Appendix A, Results, CBI pp. 18-51, 58; Individual Animal Data, pp. 10-18.

10. CLASSIFICATION:

In the conduct of the study the occlusive dressing and the stockinette, worn between applications of the test material, were reported to have produced the irritation observed in the control and the dosed groups. The reported decrease in body weight gain could have been due to the effects of the PEG solvent and not to the test material. The authors explained a proliferation of the bile duct along with a lymphocytic infiltration as being suggestive of coccidiosis infection, Emeria stiedae. If the animals were sick due to coccidiosis, this could be the reason for the weight loss, decrease in weight gain, and food consumption throughout the study. Evidence must be presented that the animals were not sick from an infection of coccidiosis.

Core Classification: Core supplemental until data are presented to validate whether or not some of the effects seen were due to disease in the animals.

APPENDIX A

Results

CYHALOTHRIN 128567

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Pages 164 through 208 are not included.

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005100

EPA: 68-01-6561
TASK: 107
September 3, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

28-Day Feeding Study in the Rat

STUDY IDENTIFICATION: Moyes, A., Godley, M. J., Hall, M., Pratt, I., Stonard, R. D., Tinston, D. J., and Forbes, D. 28-Day feeding study in the rat. (Unpublished study No. PR 0397 and report No. CTL/P/1013 by Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K., for Imperial Chemicals Industries, Alderley Park, Macclesfield, Cheshire, U.K., dated May 15, 1984) Accession No. 073204.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I Cecil Felkner

Date: 9-3-85

005100

1. CHEMICAL: Cyhalothrin [(RS)α-cyano-3-phenoxybenzyl(z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-carboxylate].

2. TEST MATERIAL: Viscous dark brown liquid with a 89.2% (w/w) cyhalothrin content. Unspecified as to technical grade or formulation. The CTL reference number was Y00102/010/001.

3. STUDY/ACTION TYPE: Subchronic (28-day) feeding study in rats.

4. STUDY IDENTIFICATION: Moyes, A., Godley, M. J., Hall, M., Pratt, I., Stonard, R. D., Tinston, D. J., and Forbes, D. 28-Day feeding study in the rat. (Unpublished study No. PR 0397 and report No. CTL/P/1013 by Imperial Chemical Industries PLC, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K., for Imperial Chemicals Industries, Alderley Park, Macclesfield, Cheshire, U.K., dated May 15, 1984) Accession No. 073204.

5. REVIEWED BY:

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Date: 1/23/86

Edwin Budd
EPA Section Head

Signature: Edwin Budd
Date: 4/21/86

7. CONCLUSIONS.

Feeding cyhalothrin to rats caused a significant decrease in mean body weight gain during the first week of the study in males receiving 250 ppm ($p \leq .05$) and in females receiving 10, 20 ($p \leq .05$), or 250 ($p \leq .01$) ppm. In addition, there was a significant reduction in mean weight gain over the 4 weeks of the study in males receiving 250 ppm ($p \leq .05$) and females receiving 20 or 250 ($p \leq .05$) ppm. Hepatic aminopyrine demethylase activity (HADA) was increased, and smooth endoplasmic reticulum (SER) was proliferated in the livers of rats of both sexes receiving the high dose of cyhalothrin. Liver weights were not significantly affected by the test substance, but liver-to-body weight ratios were higher ($p \leq .01$) in the male 250 ppm group. As defined within the scope of this study, the NOEL for cyhalothrin in female rats is 10 ppm and the LOEL is 20 ppm; and the NOEL in male rats is 20 ppm and the LOEL 250 ppm.

Item 8 - see footnote 1.

9. BACKGROUND:

In a previous 28-day feeding study in rats (Faupel, P. F., et al., 1980), male rats fed 20 ppm cyhalothrin showed a trend towards elevated hepatic aminopyrine-N-demethylase activity at termination. At dietary levels of 20 ppm and above, there was proliferation of hepatic smooth endoplasmic reticulum (SER) in male rats and in the female rats fed 250 ppm cyhalothrin. The present study was designed to establish a no effect level (NOEL) to be used in setting levels for a long-term study.

Item 10 - see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

1. The cyhalothrin used in the study was supplied by ICI, Ltd. pharmaceutical division. It was a dark brown viscous liquid with a cyhalothrin content of 89.2% (w/w).

2. The test animals were Wistar derived Alderley Park rats, bred as SPF animals. Dosing started when the animals were 5 weeks old.

---

[1] Only items appropriate to the OER have been included.

3. The basal diet was Porton Combined Diet (PCD) manufactured by Special Diets Service. The test substance was applied to the diet as an acetone solution. Pellets were made and air dried in a furnace at 50°C. The dietary dosages of cyhalothrin were control, 1, 5, 10, 20, and 250 ppm.

4. Animals were randomly distributed to experimental groups using a shuffle card method. Body weights, body weight gains, liver weights, ratios, hepatic APDM, and quantified E.M. results were compared, test to control, using a two-sided Student's t-test.

5. Test and control diets were prepared for analysis of cyhalothrin by Soxhlet extraction, cleaned up through Florisil columns and the eluate analyzed by gas-liquid chromatography using an electron capture detector.

B. Protocol:

See Materials and Methods in Appendix A.

12. REPORTED RESULTS:

A. The cyhalothrin content of all but one of the test diets was found to be within ± 10% of the target cyhalothrin content; the 1 ppm diet was 81% of the target cyhalothrin content.

B. No deaths occurred. No signs of toxicity or clinical observations related to the test substance were seen at any dose level throughout the study. Mean body weights and mean body weight gains are presented in Table 1 and Table 2, respectively. There were statistically significant reductions in body weight gains during the first week of study for males and females receiving 250 ppm ($p \leq .01$) cyhalothrin and for the females receiving 10 and 20 ppm ($p \leq .05$). Also, there was a significant reduction ($p \leq .05$) in body weight gain from the start to completion of the study for males and females receiving 250 ppm cyhalothrin and for the females receiving 20 ppm. Mean body weight was significantly reduced ($p \leq .05$) at the 250 ppm level in weeks 1 and 2 of the study. In the males receiving 250 ppm cyhalothrin, liver-to-body weight ratios were increased ($p \leq .01$) while liver weight was lower than the control but not significantly reduced. There was a significant reduction ($p \leq .05$) in liver weight in females receiving 20 ppm cyhalothrin; the liver-to-body weight ratio was not affected. HADA activity was increased ($p \leq .01$) in both sexes receiving 250 ppm cyhalothrin. Mild but statistically significant ($p \leq .01$) pro- liferation of smooth endoplasmic reticulum (SER) in hepatocytes was seen in male and female rats receiving 250 ppm cyhalothrin. A few males in the 20 ppm group also showed SER proliferation but this was not statistically different from control values.

C. Table 3 presents the results of mean liver weights, mean liver-to-body weight ratios, hepatic aminopyrine-N-demethylase activity (HADA), and smooth endoplasmic reticulum measurements (SER).

TABLE 1. Mean Body Weights for Rats Fed Cyhalothrin for 4 Weeks

Week	Dietary Concentration (ppm) 0	1	5	10	20	250
Males						
0	124.9	111.9	118.6	120.0	116.5	117.5
1	181.0	166.5	176.0	176.1	175.4	152.1*
2	233.0	215.4	230.4	228.4	230.8	204.4*
3	278.9	263.0	276.0	273.9	280.9	251.0
4	319.4	296.1 (93)[a]	319.9 (100)	314.4 (98)	323.0 (101)	286.0 (90)
Females						
0	94.6	96.8	106.9	109.6	107.9	104.5
1	142.3	140.8	145.4	142.8	141.0	131.0
2	167.8	164.3	171.8	167.4	163.1	160.1
3	190.0	185.3	196.5	186.6	185.0	182.1
4	210.4	201.9 (96)	215.8 (102)	203.8 (100)	197.9 (94)	197.0 (94)

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

[a]Percent of control.

TABLE 2. Mean Body Weight Gain for Rats Fed Cyhalothrin for 4 Weeks

Week	Dietary Concentration (ppm) 0	1	5	10	20	250
Males						
0 - 1	56.1	54.6	57.4	56.1	58.9	34.6**
1 - 2	52.1	48.9	54.4	52.3	55.4	52.3
2 - 3	45.8	47.6	45.6	45.5	50.1	46.6
3 - 4	40.5	33.1	43.9	40.5	42.1	35.0
0 - 4	194.5	184.3	201.3	194.4	206.5	168.5*
Females						
0 - 1	47.6	44.0	38.5	33.1*	33.1*	26.5**
1 - 2	25.5	23.5	26.4	24.6	22.1	29.1
2 - 3	22.3	21.0	24.8	19.3	21.9	22.0
3 - 4	20.4	16.6	19.3	17.1	12.9	14.9
0 - 4	115.8	105.1	108.9	94.1	90.0*	92.5*

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

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

TABLE 3. Selected Liver Data for Rats Fed Cyhalothrin for 4 Weeks

Effect Measured	Dietary Concentration (ppm) 0.0	1.0	5.0	10	20	250
Males						
Liver Weight (g)	15.581	14.364	15.723	15.703	16.323	14.926
Liver/Body Wt. Ratio	4.871	4.852	4.913	4.977	5.049	5.212**
HADA[a]	30.9	30.2	29.5	32.5	30.5	43.9**
SER[b]	134.3	--	--	131.8	146.3	169.7**
Females						
Liver Weight (g)	9.923	9.551	9.988	9.553	8.925*	9.076
Liver/Body Wt. Ratio	4.720	4.727	4.632	4.690	4.508	4.608
HADA	12.6	12.4	12.0	14.1	13.6	17.7**
SER	109.4	--	--	--	105.8	130.9**

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

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

[a] Hepatic Aminopyrine Demethylase Activity expressed as µmol formaldehyde/hour/g tissue.

[b] Smooth Endoplasmic Reticulum.

005100

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. "In conclusion, cyhalothrin produced definite toxicological effects at a dietary level of 250 ppm. This level is recommended as the maximum level for a long-term feeding study. The no effect level achieved in this study is 10 ppm cyhalothrin." Principal toxic effects included weight gain suppression and liver toxicity consisting of increased SER proliferation and increased HADA activity.

B. The draft and final reports were audited for good laboratory practice and the methods and results given in the report were felt to reflect the data produced during the study.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. This specific study design was based on results obtained from a prior study in which liver alterations were found. There was no effect on survival at any dosage level. No judgment can be made on signs of toxicity as no data were included. Body weight was statistically decreased ($p \leq .05$) in male rats at 250 ppm for the first 2 weeks. The male 250 ppm group's weight gain was decreased at week one only, while the females' weight gains were decreased at 10, 20, and 250 ppm for week one. When weight gains were examined over the entire study, there was a decrease for the males at 250 ppm and for the females at 20 and 250 ppm. Although no food consumption measurements were taken, it appears that body weight and body weight gains were compound affected early in the study, with accommodation taking place.

The liver is clearly affected due to dietary exposure to cyhalothrin. The significantly reduced liver weight for the female 20 ppm group appears not to follow a dose-effect relationship and does not appear to be compound related. The male rats at 250 ppm showed an increased liver weight-to-body weight ratio, increased HADA, and proliferation of the SER. The female rats at the 250 ppm level showed increased HADA and proliferation of the SER. The SER proliferation occurred without a concomitant increase in liver weight.

B. There are no substantive differences between conclusions reported by the study authors and those of the reviewer.

C. The study was not designed as a core study but as a follow-up to set the NOEL and LOEL for cyhalothrin in rats. As defined within the scope of this study, the NOEL for cyhalothrin in rats is 10 ppm and the LOEL is 20 ppm based on body weight and liver effects.

Item 15 - see footnote 1.

16. CBI APPENDIX:

Appendix A (CBI pp. 2-7) Materials and Methods.

Core Classification: Core supplemental because the design and conduct of the study were so limited.

APPENDIX A

Materials and Methods

(CBI pp. 2-7)

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 219 through 224 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

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____ The document is not responsive to the request.

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EPA: 68-01-6561
TASK: 107
September 3, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

90-Day Feeding Study in Rats

STUDY IDENTIFICATION: Lindsay, S., Chart, I. S., Godley, N. J., Gore, C. W., Hall, M., Pratt, I., Robinson, M., and Stonard, M. Cyhalothrin: 90-day feeding study in rats. (Unpublished study No. PR 0405 and report No. CTL/P/629 by Central Toxicology Laboratory, Imperial Chemical Industries, Ltd., Alderley Park, Macclesfield, Cheshire, U.K. for Imperial Chemical Industries, Ltd., PLC, Alderley Park, Macclesfield, Cheshire, U.K., date of issue: July 24, 1981.) Accession No. 073204.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner
Date: 9-3-85

005100

1. CHEMICAL: Cyhalothrin (Grenade): [(RS)α cyano-3-phenoxybenzyl (Z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate].

2. TEST MATERIAL: The test material had a pyrethroid content of 92.2% w/w of which 96.8% w/w was cyhalothrin. The batch number was ADM/46156/80. The CTL reference number was Y00102/010/005.

3. STUDY/ACTION TYPE: Subchronic (90-day) feeding study in rats.

4. STUDY IDENTIFICATION: Lindsay, S., Chart, I. S., Godley, N. J., Gore, C. W., Hall, M., Pratt, I., Robinson, M., and Stonard, M. Cyhalothrin: 90-day feeding study in rats. (Unpublished study No. PR0405 and report No. CTL/P/629 by Central Toxicology Laboratory, Imperial Chemical Industries, Ltd., Alderley Park, Macclesfield, Cheshire, U.K. for Imperial Chemical Industries, Ltd., PLC, Alderley Park, Macclesfield, Cheshire, U.K., date of issue: July 24, 1981.) Accession No. 073204.

5. REVIEWED BY:

Robert Weir, Ph.D.
Principal Author
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Signature: Robert Weir
Date: 9/3/85

Finis Cavender, Ph.D.
Independent Reviewer
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Date: 9/3/85

6. APPROVED BY:

William L. McLellan, Ph.D.
Subchronic Toxicity
Technical Quality Control
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Signature: William L. McLellan
Date: 9/3/85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pam Hurley
Date: 1/23/85

Edwin Budd
EPA Section Head

Signature: _____
Date: _____

7. CONCLUSIONS:

Groups of 20 male and 20 female Wistar-derived rats were fed diets containing 0, 10, 50, or 250 ppm for 90 days.

Body weight gain was significantly reduced in males fed cyhalothrin at 250 ppm. Body weight gain was also significantly reduced in females at this level, but only during the first week. Body weight gain was not significantly affected at lower dosages. Therefore, the LOEL is 250 ppm and the NOEL is 50 ppm for cyhalothrin in rats.

9. CLASSIFICATION: Core Guideline.

Items 8 and 10--See footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A copy of the study author's materials and methods section is appended (Appendix A). A synopsis of the materials and methods follows:

A. Materials and Methods:

1. The test material was technical grade containing 92.2% w/w pyrethroids of which 96.8% was cyhalothrin. One batch (AOM/46156/80) was used for the entire study.

2. The test animals were Wistar-derived rats of the Alderley Park Strain (Specific Pathogen Free). They were acclimated, randomized, uniquely identified, and started on the test diet at approximately 5 weeks of age. Rats were housed 4 per cage by sex and according to dosage group, in stainless steel cages elevated above the droppings.

3. The diets were prepared from Porton Combined Diet supplied by B.P. Nutrition Ltd., Witham, Essex, U.K. The test diets were prepared by mixing appropriate quantities of cyhalothrin with the feed and forming pellets. Control diet was also in pellet form. The dietary concentrations were 0, 10, 50, or 250 ppm cyhalothrin.

4. Dietary homogeneity and stability in pelleted diets were determined. Batches of diets were analyzed for cyhalothrin concentration. Diets were acetone extracted in a Soxhlet apparatus. Following Florisil column clean-up, the extract was analyzed by gas chromatography using an electron capture detection.

---

[1]Only items appropriate to this DER have been included.

5. Statistical methods used consisted of analysis of variance, analysis of covariance, Student's t-test, or a one degree of freedom comparison (f-test, equivalent to a t-test). Adjustment for missing values or transformations were used as required.

B. Protocol: (See appended Materials & Methods).

No protocol was included in the report.

12. REPORTED RESULTS:

A. Test Material: Most of the diets analyzed for cyhalothrin content were within 8% of the nominal levels. One premix was incorrectly calculated in correcting for purity and all dosage groups were as much as 26% low for 9 days when the analytical results were reported. Homogeneity was shown to be within ±7% of the overall mean concentration in the diet. The cyhalothrin in the pellets was stable for at least 11 weeks.

B. Survival and Clinical Health: Two female rats from the control group died, one in week 1 and the other in the final week of study. No other deaths occurred. Aside from a scaly tail condition which occurred from approximately the 9th week of treatment to termination, no other effect was noted. The incidence of rats with this finding was similar among groups.

C. Body Weight: There was a reduction in body weight gain in the males at all three dosages throughout the study which was statistically significant only at the 250 ppm level. Females showed lower body weight gains at the 250 ppm level but this effect was only statistically significant in the first week of dosing as shown in Table 1.

D. Food Consumption and Utilization: Males fed cyhalothrin generally consumed less food than control rats. This was only statistically different (lower) than the control group in the 50 ppm group at weeks 6 and 8 and in the 250 ppm group at weeks 1 and 8. In the females, food consumption was reduced in the 250 ppm group during week 1 only. There were no effects on food utilization in either sex at any dosage level.

E. Food Wastage: Food wastage was greater in males fed 50 and 250 ppm cyhalothrin, than the controls, for the first 8 weeks of the study. From week 10 on, there was no compound-related effect on food wastage. Food wastage for the entire 13-week study was greater in the 50 and 250 ppm groups, when compared to the controls, but was statistically significant only in the 50 ppm group. In the females, food wastage did not occur during the first eight weeks of the study and from week 8 to termination lower wastage was seen in the 50 and 250 ppm groups. In the 50 and 250 ppm groups, food wastage was reduced for the entire 13-week study as compared to the controls.

TABLE 1. Selected Body Weight Data for Rats Fed Cyhalothrin for 90 Days

Dietary Concentration (ppm)	Mean Body Weight (g) at Week 0	1	2	7	13	Total Weight gained (g)
Males						
0	136	186	245	414	507	371
10	133	180	236	402	483	350
50	137	182	237	404	495	359
250	134	156**	213**	383**	456**	322**
(Percent of Control)	(99)	(84)	(87)	(93)	(90)	(87)
Females						
0	114	149	176	252	275	161
10	116	150	177	251	274	158
50	113	149	177	248	274	161
250	106	135*	167	235	258	252
(Percent of Control)	(93)	(91)	(95)	(93)	(94)	(94)

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

F. Hematology: The mean red blood cell volume was reduced in all treated groups at week 13. There was also evidence of compensatory increases in red cell counts of all treated groups although they had normal hematocrit and hemoglobin level. At week 4, the mean hemoglobin of female rats fed 250 ppm was reduced slightly; it was also reduced in the 10 ppm group females and the 250 ppm males fed 250 ppm cyhalothrin at week 13. The female 250 ppm group had increased hemoglobin at week 13. No other compound-related hematologic effects were evident. These results are summarized in Table 2.

G. Clinical Chemistry: No changes were found in plasma glucose, albumin, and total protein, levels or in alkaline phosphatase activity. Plasma alanine transaminase, asparatate transaminase activities, and cholesterol levels were statistically significantly increased in the males fed 10 and 50 ppm cyhalothrin after 4 weeks. Plasma alanine transaminase activity was increased in the female 10 ppm group after 4 weeks. Males fed 10 ppm cyhalothrin showed increased plasma urea after 4 weeks, while the 50 ppm male group showed decreased plasma urea levels after 13 weeks. There was a reduction in plasma triglyceride levels at 4 weeks for males fed 250 ppm; at 13 weeks triglyceride levels were decreased in rats fed 50 and 250 ppm cyhalothrin. These results are summarized in Table 3.

H. Urinalysis: There were no differences seen in urine volume, pH, specific gravity, proteins, ketones, or urobilinogen in cyhalothrin-treated groups when compared to the control group. There were small, but statistically significant, differences in male glucose values in the 50 and 250 ppm groups at 13 weeks. Values were as follows:

Urinary Glucose Level for Male Rats at Week 13

	Dietary Concentration (ppm)			
	0	10	50	250
mg/18 hours	0.550	0.650	0.820*	0.930**

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

I. Hepatic Aminopyrine-N-Demethylase Activity (APDM)

At 13 weeks, a dose-related increase (46-68%) in mean APDM activity (μmol HCHO formed g liver/hour) was noted in both sexes at 250 ppm and the males at 50 ppm (34.1%) as compared to the mean control values. Based on log transformation of the data, these increases were significantly different from control mean values at a p of 0.01 using a two-sided t-test (Table 4).

TABLE 2. Selected Hematology Data for Rats Fed Cyhalothrin for 90 Days[a]

Weeks	Dietary Concentration (ppm)															
	0				10				50				250			
	Hb[b] (g/dl)	Hcrit (%)	RBC count ($\times 10^{12}$/l)	Cell vol (fl)	Hb (g/dl)	Hcrit (%)	RBC count ($\times 10^{12}$/l)	Cell vol (fl)	Hb (g/dl)	Hcrit (%)	RBC count ($\times 10^{12}$/l)	Cell vol (fl)	Hb (g/dl)	Hcrit (%)	RBC Count ($\times 10^{12}$/l)	Cell vol (fl)
	MALES															
0	15.42	36.5	6.00	60.9	13.34	36.7	6.09	60.5	12.98	35.4	5.86	60.7	13.24	36.5	6.03	60.8
	15.55	42.3	7.66	55.8	15.74	42.9	7.82	55.5	15.48	42.2	7.70	55.5	15.44	41.9	7.66	55.0
13	15.69	44.0	8.58	52.7	15.91	44.3	8.98*	50.6**	15.46	42.9	8.68	50.9*	15.39	42.5	8.74	49.8**
	FEMALES															
0	13.04	36.6	6.05	60.6	12.86	35.9	5.98	59.9	13.21	36.9	6.04	61.1	14.22	39.5	6.53	60.4
	15.49	43.0	7.40	59.2	15.16	42.3	7.38	59.1	15.44	42.8	7.30	59.8	15.23	41.9	7.25	58.8
13	15.45	43.2	7.79	56.8	15.28	42.7	8.01	55.0	15.54	42.9	7.92	54.6*	15.76	43.5	8.11	55.0*

[a] Statistical analyses of the data used Analyses of Covariance to adjust for differences in pre-exposure values.

[b] Hb = hemoglobin; Hcrit = hematocrit; RBC count = red blood cell count; cell vol = mean cell volume.

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

TABLE 3. Selected Clinical Chemistry Data for Rats Fed Cyhalothrin for 90 Days[a]

Weeks	Dietary Concentration (ppm)																			
	0					10					50					250				
	Alan trans[b] (mU/ml)	Aspart trans (mU/ml)	Chol (mg/dl)	TriG (mg/dl)	P Urea (mg/dl)	Alan trans (mU/ml)	Aspart trans (mU/ml)	Chol (mg/dl)	TriG (mg/dl)	P Urea (mg/dl)	Alan trans (mU/ml)	Aspart trans (mU/ml)	Chol (mg/dl)	TriG (mg/dl)	P Urea (mg/dl)	Alan trans (mU/ml)	Aspart trans (mU/ml)	Chol (mg/dl)	TriG (mg/dl)	P Urea (mg/dl)
MALES																				
0	16.4	50.2	47.6	114	28.7	16.2	47.6	47.7	94	31.8	15.1	43.2	49.6	95	31.2	13.3	42.7	48.3	81	31.8
4	14.6	35.7	42.4	144	38.4	16.6*	40.7*	47.8**	148	47.1**	17.6**	42.5**	47.1**	167	42.3	15.3	35.5	44.6	112	42.8
13	14.6	45.6	47.2	203	40.8	14.2	45.7	48.6	189	39.7	16.6	48.5	48.3	117**	34.8*	14.7	40.3	44.7	83**	37.8
FEMALES																				
0	12.6	38.7	44.5	77	35.6	13.1	41.7	50.8	80	31.4	14.0	40.7	51.3	68	30.7	11.3	37.6	59.2	91	45.5
4	11.3	35.8	41.3	77	59.0	13.4*	34.2	40.9	74	51.9	12.1	34.8	41.0	96	53.5	12.5	34.9	40.5	61	47.9
13	11.9	38.0	40.0	82	46.8	10.9	45.8	39.3	73	44.8	11.7	34.0	40.0	94	43.8	11.5	36.6	37.7	80	44.8

[a]Statistical analyses of the data used Analyses of Covariance to adjust for differences in pre-exposure values.
[b]Alan trans = plasma alanine transaminase; Aspart trans = plasma aspartate transaminase; Chol = cholesterol; TriG = triglycerides; P Urea = Plasma urea.

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

TABLE 4. Group Mean Hepatic Aminopyrine-N-Demethylase (Week 13)

	µmol HCHO/g liver/hr at a dietary level (ppm) of			
	0	10	50	250
Males	22.6	25.2	30.3**	38.0**
Females	16.9	16.5	17.4	24.7**

**Significantly different from control value ($p < 0.01$) when log transformed data were analyzed.

J. Ophthalmoscopy: Feeding cyhalothrin to rats at 0, 10, 50, or 250 ppm produced no evidence of effect on the eyes of the rats examined.

K. Organ Weights: Organ-weight data are reported in Table 5 for organs where statistically significant results were found. Data are presented as organ weights and organ weights corrected for body weight. A decrease in mean liver weight was seen in the 250 ppm male group. The mean lung weights were slightly, but significantly, decreased for the male and female 250 ppm groups ($p < 0.05$). However, they were not significantly different from control mean values when the mean values were adjusted for body weight. The authors did not explain how the organ weights were adjusted; their statistical analysis used body weights in analyses of covariance with organ weights. When individual liver-to-body weight ratios were calculated (by our reviewers) and analyzed statistically, no significant differences were noted (Table 5). The mean heart weight (adjusted for body weight) was increased in males fed 50 and 250 ppm cyhalothrin. This finding was only statistically significant in the male 50 ppm group. Mean brain weights were slightly decreased in both sexes at the 250 ppm level and in the 10 ppm male group. These differences were partly explained by differences in body weight between the control and treated groups. There was no effect on the kidney, adrenal, gonad, or pituitary weights in either sex.

L. Histopathology: Two female rats from the control group died or were killed moribund during the study. The rat killed during week 1 and the one which died during the 13th week of treatment had pyelonephritis or urolithiasis. The tissues of rats killed at termination had a variety of background histopathologic changes, none of which appeared to be compound related.

M. Electron Microscopy: Mild proliferation of smooth endoplasmic reticulum (SER) was seen in three male rats receiving 50 ppm and three males receiving 250 ppm cyhalothrin; however, the quantitated group means were slightly higher, but not significantly different, from the control group.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Cyhalothrin showed a definite toxicological effect, as judged by a reduction in body weight gain in males receiving 250 ppm as compared to their controls. At 10 and 50 ppm cyhalothrin, the changes "which were accompanied by lower food consumption but no effects on food utilization" were considered to have "resulted from a reduced diet palatability due to addition of cyhalothrin" and to be of no toxicological significance. Therefore, the no-effect level achieved in this study was 50 ppm cyhalothrin.

TABLE 5. Selected Organ Weight Data for Rats Fed Cyhalothrin for 90 Days

	Males Dietary Concentration (ppm)				Females Dietary Concentration (ppm)			
	0	10	50	250	0	10	50	250
Liver (g)	18.3	17.6	17.6	17.0*	9.7	9.7	9.8	9.6
Adj. Bd. wt.[a]	17.7	17.7	17.3	17.9	9.5	9.6	9.7	10.1
Liver/body wt. ratio(%)[b]	3.65	3.65	3.54	3.73	3.55	3.53	3.58	3.74
Lung (g)	1.69	1.65	1.69	1.60*	1.25	1.25	1.25	1.19**
Adj. Bd. wt.	1.64	1.66	1.67	1.66	1.23	1.24	1.23	1.24
Heart (g)	1.320	1.289	1.365	1.286	0.842	0.869	0.854	0.843
Adj. Bd. wt.	1.288	1.293	1.350*	1.328	0.831	0.862	0.846	0.866
Brain (g)	2.164	2.125*	2.145	2.128*	2.000	1.994	1.984	1.964*
Adj. Bd. wt.	2.153	2.127	2.146	2.143	1.900	1.988	1.977	1.983

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

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

[a]Mean adjusted for body weight.

[b]Analysis by our reviewers.

B. The protocol was audited at study initiation; there were 14 procedural audits during the conduct of the study. The draft and final reports were audited against the protocol and recorded results.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. The following parameters were not affected by the inclusion of cyhalothrin in the diet of rats: survival; signs of toxicity; hemoglobin, hematocrit, platelet counts, white blood cell counts, differential white cell counts, and prothrombin time; kaoline-cephalin time, plasma alkaline phosphatase, total protein, albumin, and glucose; urine volume, pH, specific gravity (2 hr. sample), protein, ketones and urobilinogens; spleen, gonad, kidney, adrenal, and pituitary weights; ophthalmoscopy; histopathology viewed with light microscopy, and the condition of the SER in the liver viewed with the electron microscope.

A scaly tail condition was the only sign observed frequently. This is not considered compound related. There was a significant reduction in body weight gain in the males at the 250 ppm level. This correlated with food consumption, as males fed cyhalothrin generally consumed less food than the controls; however, this was only statistically significant at the 50 and 250 ppm level. There was no effect on food utilization in any group. Food consumption was reduced in the 250 ppm female group for the first week only. This was accompanied by a significantly lower body weight in the females for the first week. Dietary palatability and food refusal with concurrent reduced body weight seem to be indicated. Reduced mean red cell volume values in both sexes in all three dosages at 13 weeks followed a dose-effect relationship; however, a downward trend was also observed in the controls. Hemoglobin, hematocrit, and red blood cell counts were elevated indicating an opposite trend or an accommodation. Small isolated differences in plasma alanine transaminase, asparatate transaminase, urea, cholesterol, triglycerides, and urinary glucose were not dose related or recurring on a time basis, or they were not supported by histological alterations. Hence, these changes are not considered compound related.

The hepatic aminopyrine-N-demethylase activity was increased in both sexes at the 250 ppm level and in the males at 50 ppm. This is a reversible, compensatory change usually considered to be adaptive rather than toxicological.

B. There are no substantive differences between the authors' and the reviewers' conclusions.

C. The study design and reporting are representative of 90-day subchronic studies conducted in most toxicology laboratories today. During the 9 days when the compound doses in the diets were as much as 26% below nominal, an effect on body weight at lower

levels could have been produced; this effect might not be apparent from the way the study was conducted. When young (weanling) animals are placed on a feeding study, the quantity of food eaten is greater than later in life. Therefore, the dose on a mg/kg of body weight basis would be higher in young animals. In the current study, the initial miscalculated dietary concentration may have affected dietary intake. Nervertheless, the group mean intake of cyhalothrin for the first week of the study was nearly equal in mg/kg/week to that of the second week. The occurrence of the reduced compound intake in the study probably did not adversely affect the study's validity.

Item 15 - see footnote 1.

16. APPENDIX: Appendix A, Material and Methods, CBI pp 2-11.

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APPENDIX A

MATERIALS AND METHODS

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 239 through 248 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

005100

DATA EVALUATION REPORT

STUDY TYPE: Chronic Toxicity (Dog)

ACCESSION NUMBER: 073205

TEST MATERIAL: Cyhalothrin

SYNONYMS: (R,S)alpha-cyano-3-phenoxybenzyl (+)-cis-3-(Z-2-chloro-3,3,3-trifluoropropyl-enyl)-2,2-dimethylcyclopropane carboxylate, batches Y 00102/010/001 and Y 00102/010/002

STUDY NUMBER(S): Central Toxicology Lab (CTL) CTL No. PDO 395

REPORT NUMBER: CTL/C/1093; Huntingdon Research Centre No. ICI/326/8162

SPONSOR: Imperial Chemical Industries Ltd.

TESTING FACILITY: Huntingdon Research Centre

TITLE OF REPORT: Cyhalothrin Oral Toxicity Study in Beagle Dogs (Repeated Daily Dosing for 26 Weeks)

AUTHOR(S): Harold Chesterman, Ralph Heywood, Thomas R. Allen, Alan E. Street, Donald F. Kelly, Chirukandath Gopinath, David E. Prentice

REPORT ISSUED: August 6, 1981

IDENTIFYING VOLUME: Volume II, Book 3 of 16 (Tab Reference 9C)

CONCLUSION: This study is classified as CORE GUIDELINE. Although a slight increase in passage of liquid feces was seen in the lowest dose group (7% over controls), this effect at this dose level is not considered to have any particular toxicological significance. Therefore, the NOEL is set at 1 mg/kg/day and the LEL is 2.5 mg/kg/day. Since this study was performed prior to publication of the Subpart F Guidelines, it is accepted as fulfilling the requirement for a chronic dog study.

Toxicity Category: N/A

Classification: CORE GUIDELINE

COMMENTS AND QUESTIONS: The registrant should verify that the test material was technical grade. The registrant should also address the presence of a small amount of cyhalothrin detected in the control solutions during analysis. In addition, a statement should be made as to how soon after collection of the samples were the analyses conducted.

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MATERIALS AND METHODS:

005100

Test Compound

Two batches of cyhalothrin were used for the study. Solutions for dosing were prepared at weekly intervals and stored. Concentrations of the chemical in corn oil solutions were measured at weeks 1, 2, 4, 9, 11, 13, 17, 21 and 25 of the study. Stability of cyhalothrin in corn oil was analyzed after 0, 5 and 10 days storage. The stability of cyhalothrin itself was measured at four and six months of dosing.

Animals

Forty-eight pure-bred beagle dogs (24 males and 24 females supplied from the Animal Breeding Unit of ICI Ltd., Alderly Park) were selected for the study. The animals were between four and five months of age and weighed between 7.9 and 12.5 kg.

Administration of Test Compound

The dogs were divided into groups of six males and six females per dose group. Cyhalothrin was administered orally, as a solution in corn oil in gelatin capsules at the following levels for 26 weeks: 0, 1.0, 2.5 and 10.0 mg/kg/day. A constant dosage volume was set at 0.1 ml/kg bodyweight. Individual dosage levels were calculated each week on the basis of bodyweight.

Observations

All animals were checked regularly throughout the working day and up to midday on weekends. Body weights were determined weekly. Food consumption was recorded daily and water consumption was recorded on weekdays during the four weeks prior to commencement of dosing and during weeks 1-3, 5-7, 9-11, 13-15, 17-19 and 21-24 of the dosing period. Eye examinations by means of a Keeler indirect ophthalmoscope were conducted on each animal once before commencement of dosing and again during weeks 6, 12 and 24. Before commencement of treatment and during week six, a neurological examination was performed on all high level and control animals.

Laboratory Examinations

A sample of venous blood was taken from each animal prior to the commencement of dosing and again during weeks 4, 8, 12, 16, 20 and 25. Urine samples were taken prior to commencement of dosing and again during weeks 8, 16 and 25. The urine samples were collected over a 16-hour period, water having been removed from the kennels five hours prior to the start of the collection. The following estimations were performed:

Hematology: erythrocyte sedimentation rate, packed cell volume, hemoglobin, red cell count, MCHC, MCV, WBC, differential blood count, platelet count, prothrombin index, activated partial thromboplastin time.

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Biochemistry: BUN, plasma glucose, serum total protein, serum albumin, SAP, SGPT, SGOT, serum bilirubin, Na, K, Cl, Ca, P, serum cholesterol, serum creatinine, LDH, alpha-hydroxy-butyric dehydrogenase, creatinine phosphokinase.

Urinalysis: volume, specific gravity, pH, protein, reducing substances, glucose, ketones, bile pigments, urobilinogen and hemoglobin. Microscopic examinations of the urine sediments were also performed.

Terminal Studies

Bone Marrow

On the day before the first day of autopsy, bone marrow was obtained from each animal by sternal puncture. A smear was prepared and examined.

Gross Pathology

The following organs were examined macroscopically and weighed: brain, pituitary, thyroids, spleen, heart, liver, kidneys, lungs, adrenals, pancreas, testes or ovaries, uterus or prostate and thymus.

Histopathology

The following organs were preserved together with any tissues showing macroscopic abnormalities and were examined microscopically: aorta, trachea, heart, lungs, thymus, lymph nodes, liver, gall bladder, spleen, pancreas, kidneys, spinal cord, ureter, urinary bladder, uterus, prostate, testes, ovaries, epididymides, cervix, thyroids, parathyroids, adrenals, salivary gland, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, skin, skeletal muscle, mammary gland, tongue, eyes and optic nerves, brain (cerebral cortex, thalamic nuclei, midbrain, medulla, cerebellum), pituitary, sciatic nerve, posterior tibial nerve, bronchi. Bone (sternum) was preserved but not processed.

Statistical Analyses

Statistical analyses were conducted using either the Student's 't' test, Bartlett's test, Williams' test, or the Chi^2 test where appropriate.

Results

No animals died during the course of the study. A dose-related increase in the passage of liquid feces was observed for all test groups throughout the study. This was coupled with the fact that in the highest dose group (10.0 mg/kg/day) there was a statistically significant increase in water consumption during the first four weeks of the study. This continued through week 15, although statistical significance disappeared. Vomiting,

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usually within a few hours following dose administration occurred occasionally in the controls and the two lower dose groups and more often in the highest dose group. Occasional disturbances of the nervous system (unsteadiness and/or muscular trembling) were recorded for dogs receiving 10 mg/kg/day. During week two, head shaking and excessive salivation were recorded for several animals at this dose level. These signs were observed only occasionally at this dose level during subsequent test weeks. One male dog at the 10 mg/kg/day dose level exhibited more severe signs. During the second week this dog exhibited excessive salivation and head shaking. On day 14, three hours after dosing, he was found in a state of collapse stiff limbed and frothing at the mouth with the presence of vomitus. The recovery period was approximately six hours. During the following weeks there were periods of head shaking, salivation and loss of appetite, episodes of collapse, muscular spasms, marked incoordination and vocalization and one episode of convulsive behavior.

With the exception of the one dog discussed above, bodyweight gain for all treated groups was similar to controls. A slight, but significant reduction in food intake was observed for animals in the 10 mg/kg/day group.

No abnormalities of the eye were noted that could be related to administration of the test material. The neurological assessment did not reveal any treatment-related changes.

During the pre-dosing and dosing periods, there were isolated incidences of statistically significant intergroup differences in the laboratory examinations. Since there was no dose-related trend and no consistency in the results, these incidences are not considered to be biologically significant.

No treatment-related effects were noted in either the bone marrow, macroscopic or microscopic examinations for any of the dose groups. In addition, no intergroup differences were noted for organ weights.

Discussion

This study is classified as CORE GUIDELINE. It is a well-run study. There was a dose-related effect on the gastrointestinal tract which appeared immediately during the first week at all dose levels and continued to the end of the study. The clinical sign was the passage of liquid feces. The mean increase in the total number of passages of liquid feces over controls for the entire 26 weeks was approximately 7, 26 and 39 percent for 1.0, 2.5, and 10.0 mg/kg/day respectively. The increase was not due to treatment-related activity in only a few dogs. All of the treated animals exhibited the effect to a greater degree than the controls. However, although the effect was seen at the lowest dose level, since it was only a 7% increase over controls and since no other effects were observed at this dose level, the slight increase in passage of liquid feces in dogs dosed with 1 mg/kg/day is not considered to be of toxicological significance. Therefore, 1 mg/kg/day is considered to be the NOEL for dogs in this study. 2.5mg/kg/day is the LEL.

At selected times throughout the study, samples of the dosing solutions from each dose level were collected for analysis of concentration of cyhalothrin. At weeks one, four and nine, a small amount of cyhalothrin was detected in the control solutions. Although this probably did not affect the outcome of the study, an explanation for the presence of the chemical in the control solution was not addressed in the final report. In addition, a statement should have been made as to how soon after

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collection of the samples were the analyses conducted. The stability analyses of cyhalothrin in corn oil were only determined for a storage time of ten days. If the concentration analyses were conducted at a time much greater than ten days, then cyhalothrin degradation may have been an important factor in the concentration determinations.

005100

EPA: 68-01-6561
TASK: 107
September 3, 1985

DATA EVALUATION RECORD

CYHALOTHRIN (Grenade)

Chronic Toxicity Study in Rats

STUDY IDENTIFICATION: Pigott, G. H., Chart, I. S., Godley, M. J., Gore, C. W., Hollis, K. J., Robinson, M., Taylor, K., and Tinston, D. J. Cyhalothrin: Two-year feeding study in rats. (Unpublished report No. CTL/P/980 and study No. PR0414 prepared by Imperial Chemical Industries PLC (ICI), Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K. for Coopers Animal Health, Inc., Kansas City, MO; dated 6/27/84.) Accession No. 073210-073213.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 9-3-85

005100

1. CHEMICAL: Grenade insecticide (containing cyhalothrin) [(Rs)α-cyano-3-phenoxybenzyl(Z)-(1RS,3RS)-3-(2,chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate]. Total pyrethroid content 92.2% (w/w) of which 96.8% (w/w) was cyhalothrin.

2. TEST MATERIAL: Cyhalothrin as described above. A single batch (ADM/46156/80) was used for the chronic study. It was supplied by Imperial Chemical Industries PLC, Pharmaceutical Division. The CTL reference number was Y00102/010/005.

3. STUDY/ACTION TYPE: Chronic feeding study in rats.

4. STUDY IDENTIFICATION: Pigott, G. H., Chart, I. S., Godley, M. J., Gore, C. W., Hollis, K. J., Robinson, M., Taylor, K., and Tinston, D. J. Cyhalothrin: Two-year feeding study in rats. (Unpublished report No. CTL/P/980 and study No. PR0414 prepared by Imperial Chemical Industries PLC (ICI), Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K. for Coopers Animal Health, Inc., Kansas City, MO; dated 6/27/84.) Accession No. 073210-073213.

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7. CONCLUSIONS:

A. Groups of 52 male and 52 female Alpk/AP strain rats were fed 0, 10, 50, or 250 ppm cyhalothrin for two years. Additional groups of 20 males and females were added to each dose level as extras and for the purpose of interim sacrifice. Female rats fed 50 and 250 ppm cyhalothrin in the diet showed decreased adrenal weights (corrected for body weight). However, the control adrenal weights appeared high when compared to the males. Additional effects at 250 ppm cyhalothrin levels included reduced body weight gain and decreased feed consumption in both sexes. There were no neurological effects noted. The LOEL for chronic toxicity in rats is 250 ppm cyhalothrin in the diet and the NOEL is 50 ppm. There was no indication of oncogenic activity for this chemical.

B. This is a valid study with respect to study design, execution and reporting.

8. Classificantion: Core Guideline.

Items 9 through 10 - see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

The submitted Materials and Methods section for this study is appended in Appendix A.

A. Materials and Methods:

1. The test material was the insecticide Grenade; the active ingredient was cyhalothrin with a purity of 89.2%. The total pyrethroid content was 92.2%.

2. The test animal was a Specific Pathogen Free, Alderley Park, Alpk/AP strain rat. The rats were randomly distributed to dosage groups of 0, 10, 50, and 250 ppm, each containing 72 rats per sex.

3. The basal diet was Porton Combined Diet (PCD) supplied by Special Diet Services (SDS). It was formulated by adding cyhalothrin to acetone and the solution mixed with PCD. The air-dryed feed was fed as a pellet or as a powdered diet ad libitum.

4. Most of the measurement data was evaluated by analysis of variance or analysis of covariance on pre-experimental data. Group means were adjusted for missing values. Group means were compared to control means using Student's t-test

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[a]Only items appropriate to this DER have been included.

(two-sided). Mortality data were evaluated using Mantel (1966) logrank test. Neoplastic findings were analyzed with Fischer's exact test. One-sided significance tests were used according to Gart et al. (1979).

5. Test diet was analyzed for homogeneity and stability. Dietary cyhalothrin content was also analyzed at approximately monthly intervals. The treated feed was extracted with acetone in a Soxhlet apparatus and analyzed by gas-liquid chromatography using an electron capture detector after Florisil column cleanup.

B. Protocol: See Materials & Methods, Appendix A.

12. REPORTED RESULTS:

A. Feed and Chemical Analysis: Cyhalothrin was stable in the diet for at least 9 weeks. The mixing method produced homogeneous mixes both as pellets and powdered diet. Cyhalothrin concentrations found in treated diets were within ±10% of the nominal level.

B. Mortality: There were no statistically significant differences in mortality between the dosed and control rats. Survival at 18 months ranged from 83 to 94 percent and at 24 months survival among groups ranged from 34 to 48 percent.

C. Clinical Observations: There were no adverse clinical observations which could be related to the dietary exposure to cyhalothrin. Specifically, there were no signs of neurotoxicity in any treatment group.

D. Body Weight: Mean body weight was reduced in both sexes fed diets containing 250 ppm cyhalothrin. The body weight effect was significant for the females throughout the study, while in the males it was significant to week 84 as shown in Table 1.

E. Food Consumption and Food Efficiency: There was a consistently reduced food consumption in male rats fed 250 ppm cyhalothrin for the first twelve weeks of the study. This occurred as a trend in the high-level female rats, but rarely reached statistical significance.

Male rats fed 250 ppm showed statistically increased efficiency of food utilization during the first month of the study. Mean food utilization was significantly increased for the high-level females during weeks 9-12. Although the latter is related to the reduction in body weight, the effects in either sex is of little biological significance.

F. Ophthalmology: There were no compound-related eye changes noted following ophthalmoscopic examination.

TABLE 1. Selected Body Weight Data for Rats Fed Cyhalothrin for Two Years

Dietary Level (ppm)	Group Mean Body Weight at Week					
	0	1	13	27	79	105
Males						
0	137.2	191.7	506.7	608.7	647.0	549.0
10	136.8	191.5	506.5	609.1	653.5	577.9
50	135.8	189.5	508.7	605.1	636.1	538.5
250	135.9	171.4	469.2*	561.9*	596.4*	505.5
Females						
0	125.4	158.1	286.1	320.1	405.4	379.6
10	125.8	159.4	288.9	321.8	410.1	352.3
50	123.4	156.9	286.6	314.2	400.2	351.5
250	126.4	151.0*	270.4*	299.4*	371.3*	332.2*

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

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TABLE 2. Selected Hematology Data for Rats Fed Cyhalothrin for Two Years

Period (weeks) and Hematology Parameter	Dietary Concentrations (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
Pre-experimental	-	-	-	-	-	-	-	-
4								
M.C.Hb.Conc.	37.84	37.63	37.58	37.29*	36.49	36.32	36.33	36.32
M.W.B.C.	9.75	9.97	9.49	10.08	7.20	7.54	7.49	8.44*
M.E.C.	0.15	0.06	0.12	0.05*	0.08	0.23**	0.11	0.07
13	-	-	-	-	-	-	-	-
26								
M.RBC	8.79	8.66	8.95	9.15*	7.91	8.02	7.90	7.98
M.P.C.	570	560	578	505	529	488	561	395*
39								
M.RBC	8.77	8.83	8.80	8.94	7.69	8.01*	7.96	8.04*
M.C.V.	49.1	49.5	49.3	48.3	55.0	54.5	54.7	53.4*
M.WBC	8.43	7.69	8.48	8.09	5.03	5.49	6.37*	6.78**
M.L.C.	5.78	5.27	5.76	5.32	3.53	3.83	4.09	4.86*
52								
M.Hb	15.66	15.87	15.84	15.57	15.92	15.38*	15.39*	15.35*
M.H.crit	0.422	0.430	0.430	0.422	0.439	0.427	0.422**	0.422**
M.P.C.	948	660**	813	720**	679	730	636	608
65								
M.H.crit	0.412	0.429	0.426	0.415	0.424	0.430	0.423	0.402*
M.L.C.	5.29	5.32	5.14	5.43	3.90	3.91	4.62	6.54*
M.E.C.	0.30	0.26	0.23*	0.21*	0.14	0.10	0.12	0.10
78	-	-	-	-	-	-	-	-
91								
M.WBC	10.69	10.80	12.56	9.97	5.89	6.12	8.52*	7.38
MMC	0.27	0.29	0.48	0.52*	0.05	0.18	0.28*	0.17
104								
M.RBC	7.17	7.89*	7.14	7.40	7.72	7.39	7.26	7.76
MEC	0.09	0.12	0.09	0.08	0.06	0.04*	0.05*	0.01*

Key:

M.C.Hb.Conc. = mean cell hemoglobin concentration
M.W.B.C. = mean white cell count
M.E.C. = eosinophil count
M.WBC = mean white cell count
M.Hb = mean hemoglobin
MMC = mean monocyte count
M.RBC = mean red blood cell
M.P.C. = mean platelet count
M.C.V. = mean cell volume
M.L.C. = mean lymphocyte count
M.H.crit = mean hematocrit

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

G. Hematology: Selected results of hematology studies are presented in Table 2. There was a small but statistically significant decrease in hemoglobin at week 52 in female rats in all groups receiving cyhalothrin. The effect was not dose-related and may have been significant as a result of an unusually high control value.

H. Clinical Chemistry: Rats in the group that were fed 250 ppm cyhalothrin showed a tendency for reduced levels of plasma glucose, triglycerides, and alkaline phosphatase activity. The effect on triglycerides was most marked and was primarily evident in the female rats. Plasma urea levels were higher in the 250 ppm group with the females showing the effect more than the males.

There were occasionally other parameters that were significantly different from the controls, but in the absence of a consistent dose-effect relationship or time pattern the effects were considered unrelated to the treatment with cyhalothrin. Selected clinical chemical findings are summarized in Table 3.

I. Urinalysis: According to the study authors, there was a trend to a lower urine volume with an associated increase in urine specific gravity in the 250 ppm cyhalothrin group. These findings seldom were of statistical significance. The urinary glucose levels of the female test animals tended to be lower than the controls through the course of the study. This parameter reached statistical significance only twice during this study.

There were isolated statistically significant differences between other dosed and control animals for other parameters, but due to the lack of a dose-effect relationship or a pattern over time, none of these effects were considered to be test compound related.

J. Organ Weights: For the rats killed at 52 weeks, liver weights (when adjusted for body weights) were elevated for both sexes fed 250 ppm cyhalothrin. Brain weights of the female rats fed 10 or 50 ppm cyhalothrin were reduced, but this is not considered to be compound induced because of lack of dose-effect relationship.

In the animals killed at termination, adrenal weights (when corrected for body weight) were significantly decreased in female 50 or 250 ppm groups when compared to controls. No other organs showed treatment related effects. Table 4 presents selected organ weight data.

K. Gross Pathology: The majority of the gross lesions were similar to those expected in the rat strain used. A significant number of rats at all levels, including the controls, had unilateral or bilateral oro-nasal fistulation (erosion of the palate). Additionally, erosion of the gum (cavities) of the lower jaw occurred in a number of rats. The oro-nasal pathological lesions were not compound related.

TABLE 3. Selected Clinical Chemistry Data (Means) Rats Fed Cyhalothrin for Two Years

Period (weeks)	Dietary Concentration (ppm)															
	0				10				50				250			
	P.glucose*	P.urea	Alk.phos	Trigly.	P.glucose	P.urea	Alk.phos	Trigly.	P.glucose	P.urea	Alk.phos	Trigly.	P.glucose	P.urea	Alk.phos	Trigly.
Males																
Pre-experimental	143	34.3	422	88	145	32.7	445	93	141	35.8	486	95	138	35.6	458	116
4	150	48.5	263	133	154	51.0	279	146	149	52.2	268	125	145	47.7	267	123
13	150	50.6	149	167	151	51.5	147	172	145	53.4	150	139	142	54.9	144	118**
26	139	48.3	130	134	136	48.3	126	131	136	47.4	115*	126	127**	49.4	126	104*
39	135	42.5	115	152	133	40.8	123	137	135	42.3	133*	127*	131	45.0	115	140
52	138	39.8	130	198	138	38.4	128	123	133	41.4	152	145	126*	43.1	115	180
65	127	45.0	125	194	128	39.7	131	156	122	45.0	125	164	124	51.1	112	174
78	116	49.5	114	211	120	45.9	128	195	110	47.4	124	204	116	51.5	122	157
91	116	43.3	127	104	118	37.9	115	162	110	58.7	107	202	110	51.4	112	136
104	116	54.6	122	189	117	46.4	111	160	123	52.8	106	201	115	60.2	117	140
Females																
Pre-experimental	141	39.3	394	80	138	39.4	382	91	134	38.2	379	86	138	38.7	359	83
4	137	55.3	175	97	141	53.8	181	104	139	52.9	173	88	137	55.1	153	98
13	142	62.7	108	109	145	61.2	102	100	143	63.7	90*	107	140	63.8	82**	90
26	141	57.3	67	151	136	55.8	73	126	128**	62.3	59	126	131*	68.3**	54	110**
39	139	56.4	66	144	137	53.7	62	139	133	55.6	54	152	127**	64.8**	49*	105**
52	140	54.8	59	203	132	49.3	55	132*	134	53.4	50	176	131	58.6	48	125**
65	128	50.2	53	202	125	52.0	57	201	121	58.6	48	221	133	55.3	49	148
78	112	49.7	54	270	113	47.5	53	279	110	49.8	48	255	116	55.3	49	169*
91	111	46.8	52	272	107	45.3	45	177	115	44.5	50	205	114	47.2	41	139**
104	119	44.0	67	270	119	46.8	63	219	111	50.5	54	180	117	50.0	40	175

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

*P. glucose = plasma glucose.
P. urea = plasma urea.
Alk. phos. = plasma alkaline phosphotase.
Trigly = plasma triglycerides.

TABLE 4. Intergroup Comparison of Selected Organ Weights from Rats Fed Cyhalothrin for Two Years

Interval & Tissue	Dietary Concentration (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
52 Weeks								
Brain								
mean	2.283	2.313	2.369	2.328	2.140	2.085*	2.088*	2.110
mean adjusted for body weight	2.283	2.308	2.358	2.344	2.140	2.085*	2.088*	2.109
Liver								
mean	22.0	23.06	24.0	25.0	12.4	12.1	12.6	12.6
mean adjusted for body weight	22.0	23.4	23.6	25.7*	11.9	11.7	12.1	13.8**
Terminal								
Adrenals								
mean	0.066	0.106	0.075	0.072	0.120	0.111	0.097	0.093*
mean adjusted for body weight	0.066	0.109	0.074	0.069	0.127	0.109	0.095**	0.087**
Spleen								
mean	1.75	1.66	1.60	1.42	0.86	1.04	1.26	0.87
mean adjusted for body weight	1.74	1.59	1.62	1.49	0.69	1.10	1.32*	1.02

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

Several rats in all groups had gaseous distention of the intestines. This lesion was not treatment related.

L. Histopathology: The majority of pathological lesions in dosed animals, both neoplastic and nonneoplastic, were similar to those present in control rats in this study. Except for oro-nasal fistulation and other associated lesions, there were no compound-related pathological lesions in any tissue in either sex.

Noteworthy lesions were associated with the fibrous nature of the feed and consisted of oral food granuloma and oro-nasal fistulation. This was first noted at week 65 and the incidence was greater in the males than females in all groups. Also associated with the oro-nasal fistulation was marked rhinitis which was the leading cause of death or moribund kill in male rats and second in female rats. Also associated with the oro-nasal finding was the gaseous distention of the intestine (observed grossly) and a reactive lymphoid hyperplasia of the cervical lymph nodes with an increase in the number of plasma cells.

The number of animals with bronchopneumonia or chronic pneumonitis was higher than expected in SPF rats of this strain. The animals with marked lung lesions also had severe oro-nasal lesions.

The highest incidence of tumors occurred in the pituitary gland. This was the most common cause of death in the females. However, the incidence of pituitary adenoma, the most frequent type, was consistent with historical incidence of this strain of rat.

Selected histopathologic findings are tabulated in Tables 5 and 6. Table 5 summarizes histologic lesions in animals at the terminal sacrifice; similar incidences were seen in animals that died on study.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The authors concluded that 250 ppm cyhalothrin fed in the diet to rats for two years caused decreased body weight and produced other minor indications of toxicity. Although there was a high incidence of palatine fistulation and marked rhinitis this was not compound related but was produced by long pointed fibers in the food. There were no neurologic or carcinogenic effects associated with ingestion of cyhalothrin. They concluded that 50 ppm is the NOEL.

B. The protocol and an amendment to the protocol were examined by the quality assurance staff. The conduct of the study was examined 16 times during the course of the study. The draft report and the final report were audited for consistency of performance according to the protocol and that the reports accurately represented the data.

TABLE 5. Incidence of Selected Histologic Lesions in Two-Year Feeding Study on Cyhalothrin (Results are in Rats Killed at Termination)

Pathologic Findings	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
Mouth - Number Examined	21	23	25	28	22	20	25	30
Not remarkable	0	1	0	2	1	0	2	0
Malocclusion	1	0	1	3	0	1	1	0
Periodontitis	15	16	15	17	18	14	12	22
Hyperplasia palate	0	0	2	0	1	0	0	0
Food granuloma palate	6	4	3	5	8	5	5	10
Food granuloma lower gum	8	11	13	11	6	6	9	5
Granuloma maxilla	0	0	0	0	0	0	1	0
Food granuloma palate (gross finding)	0	1	1	2	1	2	1	2
Food granuloma lower (gross finding)	2	0	0	1	0	0	1	0
Palatine fistula	9	12	12	11	5	6	10	11
Granuloma gum	0	0	0	1	0	0	0	0
Broken incisor	0	0	0	0	0	0	1	0
Mononuclear cell infiltration palate	0	0	1	0	0	0	0	0
Nasal Passage - Number Examined	21	23	25	28	22	20	25	30
Not remarkable	7	5	4	9	10	5	6	12
Rhinitis	12	15	20	18	12	15	16	15
Maxillary sinusitis	8	8	5	3	2	4	5	4
Squamous metaplasia	9	7	12	12	7	4	8	9
Cervical Lymph Node - Number Examined	20	23	25	28	22	20	25	30
Not remarkable	0	2	4	4	6	2	5	9
Cystic change	12	16	14	20	12	12	15	18
Congested	1	1	0	0	0	0	0	0
Lymphoid hyperplasia	8	9	9	7	8	7	9	8
Increased plasma cells	14	13	14	14	11	14	12	12
Reactive	0	1	1	0	0	0	0	1
Dilated blood filled sinus	0	0	1	1	0	0	1	0
Pigmented	0	0	0	0	1	0	0	0

TABLE 5. Incidence of Selected Histologic Lesions in Two-Year Feeding Study on Cyhalothrin (Results are in Rats Killed at Termination) (continued)

Pathologic Findings	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
Colon - Number Examined	21	23	24	27	27	20	25	28
Not remarkable	17	19	15	26	20	19	24	28
Dilated	4	4	8	1	1	1	1	0
Dilated (gross only)	0	0	0	0	1	0	0	0
Lung - Number Examined	21	23	25	28	22	20	25	30
Not remarkable	16	18	18	23	21	15	22	27
Congested	0	0	0	0	0	0	1	0
Alveolar histocytosis	1	5	4	3	0	1	1	3
Alveolar cell calcification	1	0	1	0	0	0	1	0
Chronic pneumonia	0	0	1	1	0	3	0	0
Granuloma	0	0	0	1	0	0	0	0
Hemorrhage	1	0	1	0	1	1	0	0
Alveolar cell hyperplasia	1	0	2	0	0	0	0	0
Mononuclear cell infiltration	1	0	0	0	0	0	0	0
Adrenal - Number Examined	21	23	25	28	20	20	24	28
Not remarkable	7	10	7	9	1	1	2	0
Vascular ectasia	4	2	3	1	18	18	20	24
Hyperplasia cortex	2	0	0	0	1	0	1	0
Vascular degeneration	10	9	17	18	3	2	3	4
Hyperplasia medulla	0	0	0	0	0	0	0	1
Cortical necrosis	0	1	0	0	0	1	0	0
Cortex reduced	0	1	0	0	0	0	0	0
Mononuclear cell infiltration medulla	0	1	0	0	0	0	0	0

TABLE 5. Incidence of Selected Histologic Lesions in Two-Year Feeding Study on Cyhalothrin (Results are in Rats Killed at Termination) (continued)

	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
Pathologic Findings	0	10	50	250	0	10	50	250
Mammary Gland - Number Examined					22	20	24	30
Not remarkable					9	3	2	2
Increased secretory activity					13	17	21	27
Granuloma					0	1	0	0
Cyst					1	1	0	1
Hyperplasia					0	0	1	1
Abcess					0	0	1	1
Prominent nipple					0	0	1	0
Adenocarcinoma					1	1	1	1
Fibroadenoma					1	1	2	5
Cyst adenoma					1	0	0	0
Adenoma					0	0	1	2
Squamous cell adenoma					0	1	0	0
Cyst fibroadenoma					0	1	0	1
Pituitary Gland - Number Examined	20	19	25	23	20	20	24	29
Adenoma	10	5	13	8	17	18	19	24
Neurofibrosarcoma	0	0	0	0	0	0	0	1
Adenocarcinoma	0	0	0	0	0	0	1	0

TABLE 6. Incidence of Selected Mammary Gland Lesions in Two-Year Feeding Study on Cyhalothrin

Pathologic Findings	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
Mammary Gland - Number Examined					71	72	69	72
Adenocarcinoma					6	4	5	4
Fibroadenoma					5	4	6	9
Cyst adenoma					2	1	0	2
Adenoma					1	2	2	3
Squamous cell adenoma					0	2	0	0
Cyst fibroadenoma					0	1	0	1

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. The cyhalothrin in the diet was stable and homogeneously mixed. The dietary content generally met the intended level. Ingestion of diets containing up to 250 ppm cyhalothrin for two years produced no changes in the following parameters as compared to the control values: signs toxicity or clinical observations, mortality, ophthalmoscopic findings, mean cell volume, mean cell hemoglobin, mean neutrophil counts, prothombin time, Kaolin-cephalin time, gross pathology, and histopathology. The following values had occasional statistically different values as compared to control values but the differences were not considered by our reviewers to be related to the test material because of lack of dose-effect relationship, a consistent time relationship, or due to an unusual control values: hemoglobin, mean hematocrit, red blood cell counts, cell volume, cell hemoglobin concentration, cell hemoglobin, white blood cell count, lymphocyte, monocyte count, eosinophila, platelet count, plasma glucose, plasma urea, alkaline phosphatase, alanine transaminase, and aspartate transaminase activity, albumin, protein, urinary pH, protein, and glucose.

Mean plasma triglyceride values were consistently lower than controls from 13 to 78 weeks. These values were statistically significant primarily in the females. Although this is felt by our reviewers to be compound related, the toxicological significance is not highly meaningful.

Body weights were decreased in both sexes due to ingestion of feed containing 250 ppm cyhalothrin. The effect was more significant in the female rats. There was consistently reduced feed consumption in male rats fed 250 ppm cyhalothrin. A similar but less severe effect was seen in the high level females, but the effect was not often statistically significant. Slightly increased feed efficiency was apparent in the male 250 ppm group in the first 4 weeks of the study. The females fed 250 ppm cyhalothrin showed reduced feed efficiency in the period 9-12 weeks. Neither of these feed efficiency effects are large and are of little biological significance.

Liver weights (corrected for body weight) were elevated for both sexes when fed 250 ppm cyhalothrin for 52 weeks. Since there were no similar effects at termination and no correlative pathology at either times this is not considered biologically significant. Reduced brain weights at 52 weeks in female rats fed 10 or 50 ppm are likewise of no significance as there was no morphologic effect. Adrenal weights (when corrected for body weight) at termination showed a significant decrease in the female 50 or 250 ppm group as compared to the controls. No morphologic effect correlated with this weight change; nevertheless, the effect cannot be dismissed due to its dose-effect relationship and the high degree of significance. However, since the adrenals are difficult to trim properly at necropsy and since the female control values appear high when compared to males; the decrease in adrenal weights are probably not of toxicological significance.

8. There were no problems, discrepancies, or inaccuracies in the design, conduct or reporting of this study, so the study must be considered a valid study.

Item 15 - see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 3-15.

APPENDIX A

Materials and Methods

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 271 through 283 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

005100

EPA: 68-01-6561
DYNAMAC No. 029E(1-3)
November 13, 1985

DATA EVALUATION RECORD

GRENADE (Cyhalothrin)

Chronic Toxicity and Oncogenicity Feeding Study in Mice

STUDY IDENTIFICATION: Colley, J., Dawe, S., Heywood, R., Almond, R., Gibson, W. A., Gregson, R., and Gopinath, C. Cyhalothrin: potential tumorigenic and toxic effects in prolonged dietary administration to mice. (Unpublished study No. CTL/C/1260 CTL [study No. PMO 400] prepared by Huntingdon Research Centre, Cambridgeshire, England, for Imperial Chemical Industries, Cheshire, England; dated May 31, 1984.) Accession No. 073214-073215.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 11-14-86

005100

1. CHEMICAL: Grenade, cyhalothrin (ICI 146,814: PP563).

2. TEST MATERIAL: Cyhalothrin, batch No. YOO 102/010/005, was described as a brown viscous liquid. Its purity was not specified.

3. STUDY/ACTION TYPE: Chronic toxicity and oncogenicity feeding study in mice.

4. STUDY IDENTIFICATION: Colley, J., Dawe, S., Heywood, R., Almond, R., Gibson, W. A., Gregson, R., and Gopinath, C. Cyhalothrin: potential tumorigenic and toxic effects in prolonged dietary administration to mice. (Unpublished study No. CTL/C/1260 [study No. PMO 400] prepared by Huntingdon Research Centre, Cambridgeshire, England, for Imperial Chemical Industries, Cheshire, England; dated May 31, 1984.) Accession No. 073214-073216.

5. REVIEWED BY:

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Date: 5/5/86

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7. CONCLUSIONS:

A. Under the conditions of the study cyhalothrin was not oncogenic when fed to mice for 104 weeks at levels of 20, 100, or 500 ppm in the diet. There was a significant increase in mammary adenocarcinomas in females receiving 100 and 500 ppm compared to controls; however, the concurrent control incidence was unusually low and the increased incidence was therefore judged not to be of biological significance. A LOEL for systemic chronic toxicity, based on decreased weight gain in males during the first 13 weeks of the study, was 500 ppm, and the NOEL was set at 100 ppm. The only other toxic effect noted was an increase in the number of animals observed with piloerection and hunched posture at a dose level of 100 ppm in males and females; this was of minimal toxicologic importance.

B. The study is considered Core Minimum; it has not been adequately demonstrated that the highest dose tested was a maximum tolerated dose.

8. RECOMMENDATIONS:

It is recommended that the sponsor provide the rationale for dose selection so reviewers can be ensured that a maximum tolerated dose was used in the chronic oncogenicity study.

Items 9 and 10—see footnote

11. MATERIALS AND METHODS PROTOCOLS

See Appendix A for details

A. Materials and Methods

1. The test material cyhalothrin, batch No. 700 102/010/005, was described as a brown viscous liquid. The purity was not specified. The mixed feed was tested for homogeneity and dietary stability prior to the start of treatment. At 3-monthly intervals during the study, samples of the diets were analysed for cyhalothrin concentration.

2. Four main groups of 50 CD-1 mice of each sex, including an untreated control group that received the diet only, were administered the test material in the diet at concentrations of 0, 20, 100 and 500 ppm for 104 weeks (termination of study). A further four satellite groups of 12 mice of

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On y sections appropriate to the DER are included.

each sex, fed the same diet concentrations, were maintained for laboratory investigation and terminated at week 52 of study (interim sacrifice).

3. Animals were observed daily for toxic signs; palpations for masses were also performed. After the first four weeks the observations for clinical reactions to treatment and the palpations for masses were only conducted once per week. Body weights and food consumptions were appropriately measured weekly and recorded throughout the study. Water consumption was monitored daily and was actually measured during week 48. All cages were checked daily for dead and moribund animals.

4. Blood for hematology and blood chemistry testing and pooled urine samples from each cage for urinalysis were collected from all mice in the satellite groups prior to the interim (week 52) sacrifice and from 12 male and 12 female animals from each main group at the terminal (week 104) sacrifice. The following hematology measurements were taken: packed cell volume (PCV), hemoglobin (Hb), red cell count (RBC), mean corpuscular hemoglobin concentration (MCHC), mean cell volume (MCV), total white cell count (WBC Total), differential count and platelet count (Plts).

   The following blood biochemistry measurements were taken: plasma urea nitrogen (urea N), plasma glucose, plasma total protein, plasma albumen (Alb), plasma globulin (Glob), plasma alkaline phosphatase (AP), plasma glutamic-pyruvic transaminase (GOT) and plasma cholesterol (Chol).

   The following urinalysis measurements were taken: volume, pH, specific gravity, protein concentration, glucose, and ketones.

5. At the interim sacrifice and at termination of the study, all surviving mice in the satellite and main groups respectively were killed using CO_2; these animals and those that died or were sacrificed moribund were subjected to an extensive gross examination. Major organs and all gross lesions were examined microscopically, when feasible, from all animals on study. Major organs were also weighed; the organ weights from mice that died during the course of te study were taken under the discretion of the pathologist. Samples of the following tissues were preserved for microscopic examination: adrenals, bone, brain (medullary, crebellar and cortical sections), caecum, duodenum, eyes, gall bladder, Harderian gland, head (nasal cavity, paranasal sinuses, tongue, oral cavity, nasopharynx and middle ear), heart, ileum, jejunum, kidneys, liver (from at least two lobes, multiple sections when possible metastasis), lungs (all lobes and mainstem bronchi, multiple sections when possible metastasis), lymph nodes (cervical and mesenteric, multiple sections as above), mammary gland, midcolon, esophagus, ovaries, pancreas, pituitary, prostate,

salivary gland, sciatic nerve, seminal vesicles, skeletal muscle, skin, spinal cord (at least two levels), spleen, sternum (for bone marrow), stomach (glandular and non-glandular), testes, thymus (where present), thyroid (with parathyroid), trachea, urinary bladder, uterus (plus cervix) and all abnormal tissues. In addition, three coronal sections through the head were examined in ten males and ten females from each group and in any other animal in which there was evidence of disease.

6. Statistical Analysis: Analysis of variance was used to assess the significance of intergroup differences, and intergroup comparisons were assessed using the Student's t test. Tumor incidence was analyzed following adjustment for intergroup differences in mortality patterns by log rank methods as described by Peto et al.[2]

12. REPORTED RESULTS:

Dietary Analysis: The concentration of cyhalothrin in the test diets was analyzed at 13-week intervals throughout the study. The mean concentrations (from duplicate analyses) of the test material in the diets at 20, 100, and 500 ppm were within 9 percent of the nominal values, with the exception of one result at week 52 (which was found to be 2i.5 percent for the 20-ppm diet). Homogeneity was determined from duplicate samples randomly taken from the top, middle, and bottom of the blender. The mean concentration ranges were 19.3 to 19.6 ppm for the 20-ppm level and 477 to 492 ppm for the 500-ppm level. Test material was stable in diets stored at ambient temperature in the animal rooms for at least 6 weeks. The mean concentrations at weeks 0, 3, and 6 were, respectivey, 19.3, 19.9, and 19.2 ppm for the 20-ppm level and 487, 492, and 494 ppm for the 500-ppm level at the same sampling periods.

Clinical Observations and Mortality: There was an increased incidence of piloerection in the mice at the highest dose (500 ppm) tested, particularly in males. This observation was also noted in the male mice in the mid-dose (100 ppm) group (Table 1). There was also a higher incidence of hunched posture in the highest dose groups compared to the control groups. This increased incidence continued throughout most of the study (Table 1). In the final week of the study, the incidences of both findings among treated and control mice were considered by the authors to be age-related rather than treatment-related changes.

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[2] WHO International Agency for Research on Cancer (1980). Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal. Supplement 2, pp. 311-426.

TABLE 1. Summary of Clinical Observations at Selected Intervals in Mice Fed Cyhalothrin

Finding/Dose Group (ppm)	Percentage[a] of Animals with Finding at Week					
	4	13	26	52	78	104
			Males			
Piloerection						
Control	0	6	18	32	45	52
20	0	3	19	27	46	84
100	2	19	36	46	47	73
500	78	78	73	81	87	95
			Females			
Control	0	0	3	5	10	19
20	3	0	7	18	21	48
100	6	3	8	8	5	44
500	38	34	22	25	38	50
Hunched Posture						
			Males			
Control	2	0	0	0	0	39
20	0	2	0	0	5	26
100	0	2	3	2	5	47
500	6	19	20	30	18	32
			Females			
Control	0	0	0	0	2	19
20	3	0	0	0	0	5
100	0	3	2	3	3	24
500	8	6	3	7	9	9

[a] $\frac{\text{Number of mice showing finding during week}}{\text{Number of mice surviving at start of week}} \times 100$

Mortality was similar among all groups with the exception of a slightly increased mortality at 104 weeks in males receiving 100 ppm. Survival at study termination ranged from 27-40 percent in male groups and 38-48 percent in female groups (Table 2).

Body Weights: The mean weight gain in males receiving 500 ppm was significantly lower than in the control males during the first 13 weeks of the study, which resulted in an overall decreased weight gain for the 104 weeks of the study (Table 3). The mean body weight of the males receiving 500 ppm was 10 percent lower than controls at week 13 but only 2 percent lower at week 104. Mean body weights of females receiving 20 ppm were higher than controls throughout most of the study; they gained more weight than controls during the first 26 weeks.

Food Consumption: Mean food intake was slightly higher in the male dosed groups throughout the study when compared to controls, with a statistically significant increase in the high-dose group. A significant increase in food consumption was also reported for female mice in the low-dose (20 ppm) group when compared to controls during the first 26 weeks; however, over the 104 weeks of the study the difference from the controls was not significant (Table 4).

Hematology: Hematological values were similar but with some sporadic variability for dosed and control mice; however, these differences were not considered to be of toxicological significance.

Biochemistry: At week 100, there were significant ($p < 0.05$ except for 500-ppm males, which was $p < 0.01$) increases in mean values of serum glutamic oxaloacetic transaminase (SGOT) for both male and female mice receiving 100 and 500 ppm and significant increases in mean values of serum glutamic pyruvic transaminase (SGPT) for female mice in all dosed groups (Table 5). These increases in mean enzyme levels were due to some abnormally high individual levels and were considered to be age-related rather than compound-related changes.

There were minor differences noted in glucose, globulin, and urea nitrogen; however, these differences were not consistent with time or dose and were not considered to be of toxicological significance by the report authors.

Urinalysis: Urinalysis parameters were similar in control and dosed groups.

Organ Weights: At study termination, the mean ovarian weights of female mice receiving cyhalothrin were significantly lower (0.068-0.107 g) when compared to the controls (0.274 g). This decrease was associated with a decreased incidence of distension of the periovarian sacs noted in dosed females. All other mean organ weights were similar among treated and control mice. A slight but significant

TABLE 2. Mortality and Percent Survival of Mice Fed Cyhalothrin for 104 Weeks

Dose Group[a] (ppm)	Mortality (Percent Survival) at Week				
	13	26	52	78	104
Males					
Control	2(96)	3(94)	5(90)	10(81)	31(40)
20	0(100)	1(98)	5(90)	15(71)	34(35)
100	0(100)	1(98)	5(90)	16(69)	38(27)
500	1(98)	4(92)	8(84)	15(71)	35(33)
Females					
Control	0(100)	1(98)	4(92)	11(79)	27(48)
20	2(96)	3(94)	9(83)	14(73)	32(38)
100	0(100)	1(98)	5(90)	13(75)	27(48)
500	0(100)	1(98)	4(92)	9(83)	32(38)

[a]Fifty-two mice per group per sex (main group).

TABLE 3. Mean Body Weight Gain of Mice Fed Cyhalothrin for 104 Weeks

Dose Group (ppm)	Mean Weight Gain in the Intervals Between Weeks				
	0-13	13-26	26-52	52-104	0-104
Males					
Control	11.4 ± 3.54	1.1 ± 2.82	3.7 ± 2.50	2.1 ± 4.13	18.0 ± 3.97
20	12.2 ± 3.79	0.6 ± 3.12	4.8 ± 3.33*	2.0 ± 4.77	20.3 ± 7.14
100	10.7 ± 2.94	2.7 ± 2.52	4.1 ± 3.19	0.6 ± 5.18	18.3 ± 5.21
500	6.2 ± 3.90***	1.5 ± 3.82	3.0 ± 3.41	1.8 ± 2.58	13.9 ± 3.25*
Females					
Control	5.5 ± 2.59	1.9 ± 2.35	3.4 ± 2.87	3.5 ± 3.15	13.8 ± 5.28
20	7.3 ± 3.29***	3.0 ± 2.75*	4.3 ± 3.54	2.0 ± 4.24	15.6 ± 5.10
100	6.8 ± 3.01*	1.5 ± 2.80	3.9 ± 3.19	2.8 ± 4.18	14.7 ± 5.86
500	5.6 ± 2.78	2.1 ± 2.33	4.3 ± 3.00	2.5 ± 4.85	15.8 ± 5.04

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

***Statistically significantly different from control at $p < 0.001$.

TABLE 4. Mean Food Consumption of Mice Fed Cyhalothrin for 104 Weeks

Dose Group (ppm)	Mean Food Consumption (g/mouse/week) in the Intervals Between Weeks				
	0-13	14-26	27-52	53-104	1-104
Males					
Control	27 ± 2.1	26 ± 2.7	28 ± 3.7	27 ± 2.7	27 ± 2.2
20	28 ± 1.4*	28 ± 2.4	30 ± 3.1	30 ± 4.4	29 ± 3.1
100	28 ± 1.5**	29 ± 2.7**	30 ± 3.3	29 ± 1.8	28 ± 1.5
500	27 ± 1.5	29 ± 2.5*	32 ± 3.5**	30 ± 4.1	30 ± 3.1*
Females					
Control	24 ± 1.6	24 ± 1.6	25 ± 2.0	26 ± 2.5	25 ± 2.0
20	26 ± 2.0***	25 ± 1.6*	26 ± 1.9	27 ± 3.4	27 ± 2.4
100	24 ± 1.3	25 ± 2.0	26 ± 2.9	26 ± 2.6	26 ± 1.8
500	24 ± 1.8	24 ± 2.5	25 ± 2.5	25 ± 2.7	25 ± 2.2

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

**Statistically significantly different from control at $p < 0.01$.

***Statistically significantly different from control at $p < 0.001$.

TABLE 5. Serum Enzyme Levels (mU/mL) in Mice Fed Cyhalothrin for 104 Weeks

Dose Group ppm	SGOT		SGPT	
	Week 50[a]	Week 100[b]	Week 50[a]	Week 100[b]
Males				
Control	54 ± 6.4	52 ± 10.8	47 ± 10.3	51 ± 38.6
20	71 ± 36.7	61 ± 18.1	47 ± 18.1	62 ± 25.4
100	57 ± 21.9	80 ± 34.5*	45 ± 13.9	83 ± 56.4
500	71 ± 26.3	88 ± 66.7**	52 ± 27.7	80 ± 75.2
Females				
Control	67 ± 17.2	71 ± 22.6	47 ± 19.1	36 ± 11.7
20	84 ± 42.2	80 ± 29.6	50 ± 35.9	63 ± 51.7*
100	72 ± 24.0	118 ± 63.4*	47 ± 25.7	59 ± 34.6*
500	59 ± 8.7	100 ± 39.4*	40 ± 13.5	54 ± 16.2*

[a]Results from satellite groups.

[b]Results from main groups.

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

**Statistically significantly different from control at $p < 0.01$.

increase in mean brain weight was noted at the 12-month sacrifice in males receiving 500 ppm. However, this was not considered of biological importance because the brain weights were within the normal range and there were no brain weight changes at terminal sacrifice.

Gross Pathology: There were no gross findings in mice that were considered to be related to dosing. A slight increase in incidence of subcutaneous masses in females was noted (3/52 in control versus 7/52 and 6/52 in the 100- and 500-ppm groups, respectively); a marginal decrease in incidence of distension of the peri-ovarian sac (18/52 in controls and 16/52, 14/15, and 10/52 in the 20-, 100-, and 500-ppm groups of females, respectively) and an increase in incidence of thickening of the non-glandular epithelium of the forestomach (1/52 in controls and 10/52, 13/52, and 9/52 in the 20-, 100-, and 500-ppm groups of females, respectively) were noted. There were no corresponding histologic correlates.

Histopathology: Table 6 summarizes the incidence of neoplastic lesions. There was an increased incidence of mammary adenocarcinomas in female mice receiving cyhalothrin at 100 ppm ($p = 0.03$) or 500 ppm ($p = 0.04$). This was supported by a positive trend analysis ($p = 0.016$). However, there was a lack of a consistent dose-related response and the incidence was slightly higher than the laboratory's historical range (2-12%; average of 17 studies was 81/1156 or 7.0%); therefore, the increased incidence was not considered to be related to dosing. Occurrence of other tumors was incidental, small numbers were found but there were no dose-related increases.

Nonneoplastic lesions considered of toxicologic importance were not seen histologically. There was disseminated amyloidosis in several organs but no apparent increase in dosed groups; it was the most common factor contributing to death.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The authors concluded that "the higher incidence of mammary tumors noted in females of some treated groups in comparison to the controls is not unduly at variance with the incidence normally seen in this strain of mouse at our laboratory. This finding is, in our opinion, not an indication of the carcinogenic potential of cyhalothrin." There were signs of minimal toxicity for male and female mice receiving 500 ppm cyhalothrin and male mice receiving 100 ppm. The authors considered the LOEL for chronic systemic toxicity to be 00 ppm and the NOEL to be 20 ppm.

B. A signed quality assurance statement, dated 22/3/84, was present.

TABLE 6. Neoplastic Lesions in Mice Fed Cyhalothrin for 104 Weeks[a]

Organ/Neoplasm	Males/Dose Level (ppm) 0	20	100	500	Female/Dose Level (ppm) 0	20	100	500
Lymphoreticular	(64)[b]	(64)	(64)	(64)	(64)	(64)	(64)	(64)
leukemias and lymphomas	2	6	7	2	9	10	8	14
Lung	(64)[b]	(63)	(64)	(64)	(63)	(64)	(64)	(64)
adenoma	7	5	4	7	6	6	0	7[c]
adenocarcinoma	10[c]	4	10	8	5[c]	8	6[d]	4
Liver	(64)[b]	(63)	(64)	(62)	(62)	(64)	(63)	(64)
benign	9	9	9	6	1	2	1	0
malignant	9	6	11	2	0	1	0	0
Harderian gland	(64)[b]	(62)	(64)	(63)	(62)	(64)	(63)	(64)
adenoma	5	4[b]	3	1	3	3	4	1
Mammary gland					(52)[b]	(52)	(52)	(52)
adenocarcinoma					1	0	7	6
Uterus					(63)[b]	(63)	(63)	(63)
leiomyoma					1	0	3	2
leiomyosarcoma					0	0	0	3
total tumors					1	0	3	5
Ovary								
granulosa cell tumor					(62)	(62)	(64)	(63)
					2	0	2	0

[a]If a tumor occurred only once in any group it was not included in this table.

[b]Number of tissues examined; includes 10-12 animals sacrificed at 12 months (except for mammary gland) since laboratory historical data did not include animals 12 months on study.

[c]One neoplasm occurred at the 12-month sacrifice.

[d]Two neoplasms occurred at the 12-month sacrifice.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

The protocol was complete and adequate to assess the oncogenicity and chronic toxicity of cyhalothrin. The summary data presented in the report were supported by individual animal data and the summary data were accurate. The report was well organized and well written. Under the conditions of the study the test compound was clearly nononcogenic. Historical laboratory data on mammary adenocarcinomas were available to assess that the significant increase in the incidence of this tumor in some dosed groups was not biologically important.

However, the evidence for use of a maximum tolerated dose was weak; there was no decrease in mean body weights in dosed females throughout the study, and the mean weight gains in males were only significantly lower than controls during the first 13 weeks of the study. Mean body weights at 13 weeks were 10 percent lower in the 500-ppm group of males (36.6 ± 4.1) than in controls (40.8 ± 3.2), but at week 104 they were only 2.4 percent lower (44.5 ± 3.9) than in the controls (45.6 ± 9.3). Mean body weights in males receiving 20 and 100 ppm were higher than the controls throughout the study.

There were no toxicologically important effects on mortality, food consumption, clinical laboratory parameters, organ weights, or gross histopathologic findings. The authors based their LOEL for systemic chronic toxicity on clinical observations of increased incidence of piloerection and hunched appearance of animals (males receiving 100 ppm and females receiving 500 ppm). However, if these findings are considered toxicologically important, a LOEL based on data for piloerection should be set at 20 ppm, the lowest dose tested (see data for females at 26, 52, and 78 weeks, Table 1). Therefore, a NOEL was not achieved.

We assess that a tentative LOEL should be based on the decreased weight gain in males at 500 ppm and the NOEL should be set at 100 ppm.

No rationale for dose selection was presented in the report. Because there is only a decreased weight gain in males receiving 500 ppm for the first 13 weeks of the study, it is suggested that the sponsor provide more data that will clarify if the dose chosen for a maximum tolerated dose had adequate rationale.

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Method, CBI pp. 2-11.

APPENDIX A

Materials and Methods

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 299 through 308 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

005100

EPA: 68-02-4225
TASK: 29-82
November 26, 1985

DATA EVALUATION RECORD

CYHALOTHRIN

Teratogenicity Study in Rabbits

STUDY IDENTIFICATION: Killick, M. E. Cyhalothrin: Oral (gavage) teratology study in the New Zealand white rabbit. (Unpublished study No. RB 0169 and report No. 2700-72/211 by Hazleton Laboratories Europe Ltd., Harroyate, England, for Imperial Chemical Industries Limited, Cheshire, England; dated June 1981., Accession No. 073206.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 11-26-86

005100

1. CHEMICAL: Cyhalothrin; [(R,S)α-cyano-3-phenoxybenzyl-(±)-cis-3,3 (Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2-dimethylcyclopropane carboxylate].

2. TEST MATERIAL: Cyhalothrin, from batch No. 005, was a brown viscous liquid (at room temperature) described as a technical grade pyrethroid mixture containing 89.25 percent cyhalothrin.

3. STUDY/ACTION TYPE: Teratogenicity study in rabbits.

4. STUDY IDENTIFICATION: Killick, M. E. Cyhalothrin: Oral (gavage) teratology study in the New Zealand white rabbit. (Unpublished study No. RB 0169 and report No. 2700-72/211 by Hazleton Laboratories Europe Ltd., Harrogate, England, for Imperial Chemical Industries Limited, Cheshire, England; dated June 1981.) Accession No. 073206.

5. REVIEWED BY:

Guillermo Millicovsky, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: G Millicovsky
Date: 11-25-85

Robin B. Phipps, B.S.
Independent Reviewer
Dynamac Corporation

Signature: Robin B. Phipps
Date: 11-25-85

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
Teratogenicity and Reproductive Effects
Technical Quality Control
Dynamac Corporation

Signature: Ira Cecil Felkner
Date: 11-25-85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela Hurley
Date: 1/23/86

Edwin Budd
EPA Section Head

Signature: Edwin Budd
Date: 5/5/86

Maternal NOEL 10 mg/kg, LEL 30 mg/kg
Devel. Tox. NOEL 30 mg/kg
A/D ratio = 1

005100

7. CONCLUSIONS:

A. We could not assess the NOEL and LOEL for maternal and fetal toxicity of cyhalothrin in this study due to the high incidence of illness-related maternal deaths and to deficiencies in the design and conduct of fetal examinations.

B. This study is classified Core Supplementary it did not provide adequate information for assessing the potential teratogenicity of the test material. Reclassified by TB to Core Minimum (See cover memo)

8. RECOMMENDATIONS:

To upgrade the classification of this study, we recommend that:

1. Healthy animals be used, and that their reproductive history be reported.

2. Pregnancies be terminated on day 29 or 30 of gestation, and not on day 28.

3. Fetuses be sacrificed by carbon dioxide inhalation or intraperitoneal injection, and not by intracardiac injection.

4. A more thorough method for craniofacial examination be implemented. If brain tissues were fixed and saved, they should be sectioned and examined by the methods described by Wilson and the data should be submitted. The methods used for visceral examination should be cited or described.

5. The above recommendations, if implemented, would yield more meaningful results in future studies and would permit the determination of maternal and fetal NOELs and LOELs for cyhalothrin in rabbits.

9. BACKGROUND:

A range-finding study in pregnant rabbits was conducted at Hazleton Laboratories Europe, Ltd. (report No. 2603-72/210) to determine dose levels for the teratogenicity study. The author did not include details or results from this range-finding study.

Item 10--see footnote 1.

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[1]Only items appropriate to this DER have been included.

II. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: Cyhalothrin was described as a brown, viscous liquid consisting of 89.25 percent active ingredient. The test material was supplied by Imperial Chemical Industries, Ltd. under the code No. YOO1U2/010/005. Corn oil was used as the vehicle and control substance. Dosage formulations were prepared once (3 days before the initiation of dosing), divided into daily aliquots, and stored at room temperature until used. The dosage levels of 0, 3, 10, and 30 mg/kg/day were achieved by mixtures containing 0.0, 1.7, 5.6, and 16.8 mg of test material (adjusted for purity) per mL of corn oil. The doses were administered by gavage. Treatment volumes were adjusted to 2 mL/kg of body weight and were based on maternal body weights recorded on gestation day 6. These volumes were reduced for animals whose body weights decreased below their respective reference level of gestation day 6, but were not increased to compensate for body weight gains above their reference level.

2. Test Animals and Test System: New Zealand white rabbits were obtained from Morton Commercial Rabbits, Essex, England. Prior to mating, females were examined by a veterinarian to assure their suitability for the study. Following an acclimatization period of 20 days, 72 sexually mature females (3.14-4.09 kg) were mated to 3 different males; the day of mating was designated gestation day 0. An additional 10 females from a later shipment were mated after an acclimatization period of 8 days, and 6 of these were used as replacements. After mating, each female was injected intravenously with chorionic gonadotropin to stimulate ovulation. A total of 18 females were initially assigned to each group. However, 1, 1, and 4 animals were subsequently assigned to the 0, 3, and 10 mg/kg/day dosage groups, respectively, to replace animals that died early in the study. All surviving females were dosed from gestation day 6 through 18 and sacrificed on gestation day 28.

3. Parameters Measured: Chemical analyses were conducted on samples of dose formulations obtained on the day of preparation and 28 days later when dosing was completed.

All animals were observed at least once daily to determine their health status and to record clinical signs of toxicity. Mortality checks were performed twice daily. Maternal body weights were recorded on gestation days 0, 6 through 19, 24, and 28. Maternal food consumption was recorded on gestation days 0, 3, 6, 9, 12, 15, 18, 21, 24, and 28. Necropsies were conducted on mated females on gestation day 28; at this time, gross maternal findings, gravid uterine weight, and number of corpora lutea were recorded. In addition, the number, type, and location of implantations within uteri were recorded.

Fetal weight, crown-to-rump length, and sex were determined after sacrificing the fetuses with intracardiac injections of Euthatal. Subsequently, all fetuses were examined for gross external abnormalities, skinned, dissected, and examined for visceral abnormalities. Eviscerated fetuses were fixed, and their cranial cavities were examined through single slices at the level of the fronto-parietal suture. Skeletal structures were stained with Alizarin Red and examined for abnormalities. Data were processed where appropriate to give mean values, group mean values and standard deviations. All statistical tests were carried out at 1% significance levels.

12. REPORTED RESULTS:

A. Test Material: Results from gas chromatographic analyses performed at the time of preparation of dose formulations, and at the end of the dosing period, indicate that all formulations ranged from 92-110 percent of intended concentrations and that the test material was stable during the entire dosing period.

B. Maternal Effects: Several mated animals died prior to their scheduled sacrifice date. The mortality incidence was 1/19, 2/19, 6/22, and 2/18 animals in the 0, 3, 10, and 30 mg/kg/day groups, respectively (Table 1). The study author indicated that most of these deaths appeared to be related to pulmonary disorders and not to the test material.

No compound-related clinical observations were noted during gestation. Also, macroscopic examinations of maternal organs conducted during necropsies revealed no abnormalities associated with the test material.

Maternal body weights were slightly reduced in the high-dose group from the initiation of dosing until sacrifice. The resulting reduction in group mean body weight gain from gestation days 6 through 9 was statistically significant for this group of animals when compared with controls. No other notable effects on maternal body weight were reported (Tables 2a and 2b). Statistically significant reductions in food intake were recorded for the 30 mg/kg/day dosage group between gestation days 6 and 15 (Table 3).

According to the study author, the percentage of pregnant animals in this study was within the normal range of historical controls in their laboratory, and no compound-related effects on fertility indices were evident (Table 4). No statistically significant effects related to the test article were noted in gravid uterine weights or in corrected body weight gains (Table 5). The mean numbers of corpora lutea per female were comparable for all groups (Table 6).

TABLE 1. Mated Females Found Dead or Sacrificed Prior to Gestation Day 28

Dosage Group (mg/kg/day)	Animal No.	Died/Sacrificed on Gestation Day	Pregnancy Status	Respiratory/ Pulmonary Involvement
0	4082	6	pregnant	yes
3	4106	6	pregnant	yes
3	4111	21	pregnant	yes
10	4117	12	pregnant	yes
10	4126	9	pregnant	yes
10	4127	23	pregnant	no
10	4128	6	not pregnant	yes
10	4130	22	not pregnant	no
10	4154	25	pregnant	no
30	4135	18	pregnant	yes
30	4138	25	pregnant	no

TABLE 2a. Effects of Cyhalothrin on Mean Maternal Body Weight (kg) During Gestation in Rabbits

Gestation Day	Dosage (mg/kg/day) 0	3	10	30
0	3.54	3.54	3.59	3.58
6	3.73	3.66	3.73	3.76
9	3.74	3.71	3.77	3.66
12	3.83	3.79	3.82	3.71
15	3.91	3.90	3.91	3.80
18	3.96	3.93	3.96	3.87
28	4.19	4.13	4.23	4.15

TABLE 2b. Effects of Cyhalothrin on Mean Maternal Body Weight Gain (kg) During Gestation in Rabbits

Gestation Days	Dosage (mg/kg/day) 0	3	10	30
0 - 6 (predosing)	0.21	0.12	0.14	0.18
6-18 (dosing)	0.23 [6.2%]	0.27 [7.4%]	0.23 [6.2%]	0.11 [2.9%]
18-28 (postdosing)	0.23	0.20	0.27	0.28
0-28 (gestation)	0.65 [18.4%]	0.59 [16.7%]	0.64 [17.8%]	0.57 [15.9%]

TABLE 3. Effects of Cyhalothrin on Mean Maternal Food Consumption (g/day)During Gestation in Rabbits

Gestation Days	Dosage (mg/kg/day)			
	0	3	10	30
0- 3	197	190	196	201
3- 6	223	215	216	229
6- 9	154	164	161	111*
9-12	183	184	188	130**
12-15	185	188	158	143*
15-18	158	159	164	146
18-21	223	202	193	227
21-24	200	181	221	229
24-28	179	157	172	185

*Statistically different from control value ($p < 0.05$).

**Statistically different from control value ($p < 0.01$).

TABLE 4. Effects of Cyhalothrin on Fertility Indices in Rabbits

Parameter	Dosage (mg/kg/day) 0	3	10	30
No. mated	19	19	22	18
No. pregnant	17	15	18	14
% pregnant	90	79	82	78
No. examined on gestation day 28	18	17	16	16
No. pregnant on gestation day 28[a]	16	13	14	12
% pregnant on gestation day 28[a]	89	77	88	75

[a] Based on females surviving until gestation day 28.

TABLE 5. Effects of Cyhalothrin on Adjusted Maternal Body Weight[a] and Gravid Uterine Weight in Rabbits

Parameter	Dosage (mg/kg/day) 0	3	10	30
Group mean body weight (kg) on gestation day 28	4.19	4.13	4.23	4.15
Group mean gravid uterine weight (kg)	0.383	0.364	0.400	0.414
Group mean adjusted body weight (kg) on gestation day 28	3.81	3.77	3.83	3.74
% adjusted gestational body weight gain	7.6	6.5	6.7	4.5

[a] Calculated by subtracting gravid uterine weight from maternal body weight on gestation day 28.

TABLE 6. Effects of Cyhalothrin on Reproductive Indices in Rabbits

Parameter	Dosage (mg/kg/day) 0	3	10	30
No. corpora lutea/female	9.4	9.2	9.3	10.3
No. implantations/litter	7.6	7.5	8.1	8.4
% preimplantation loss	19.9	19.2	12.3	18.5
No. resorptions/litter	0.63	0.69	0.79	0.83
% postimplantation loss	8.3	9.3	9.6	9.9
Live fetuses/litter	6.9	6.8	7.4	7.6
Mean fetal weight (g)	38.8	40.0	38.0	37.6
Fetal male/female ratio	1.22	1.10	0.91	1.17

C. Embryonic/Fetal Effects: No compound-related effects were reported in preimplantation losses. Postimplantation losses were slightly increased in the dosage groups; however, this effect was not statistically significant and was not considered compound related. The group mean number of fetuses, crown-to-rump lengths, and fetal sex ratios were considered to be similar for all groups. Very slight decreases in group mean fetal weight were reported for the mid- and high-dose groups, but these decreases were not statistically significant (Table 6).

No compound-related effects were reported for the type or incidences of malformations or variations.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study author concluded that the only maternal effects associated with cyhalothrin were body weight losses and reductions in food consumption in the high-dose animals. These effects indicated that 30 mg/kg/day elicited maternal toxicity in rabbits. However, no conclusive compound-related effects were noted in any aspect of fetal development, even at the highest dose tested.

B. A quality assurance statement was signed and dated on July 1, 1981.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. 1. Maternal Effects: Very high incidences of maternal mortality were seen for all study groups (Table 7). Data from clinical observations conducted during the in-life portion of the study and from macroscopic observations made during necropsies indicate that most of these deaths resulted from respiratory/pulmonary disease (Table 1). No conclusive compound-related association could be established for these deaths; however, the mortality incidences among dosage groups were at least twice as high as that reported for the control group. Slight reductions in the mean maternal body weight gain, mean adjusted body weight gain, and food consumption in the 30 mg/kg/day dosage group suggested that cyhalothrin elicited mild maternal effects at this dosage level. However, we could not assess the biological significance of these mild effects due to the presence of ongoing maternal illness during gestation.

2. Embryonic/Fetal Effects: The percentage of pregnant females was 90, 79, 82, and 78 percent for the 0, 3, 10, and 30 mg/kg/day dosage groups, respectively; these data suggest a slight increase in the incidence of females with no embryonic implantations or with implantations completely resorbed very early in gestation. However, this could not be verified by the reviewers since no method for confirmation of pregnancy

TABLE 7. Group Incidences of Mortality Among Pregnant Animals

Parameter	Dosage (mg/kg/day) 0	3	10	30
No. pregnant	17	15	18	14
No. dead/sacrificed	1	2	4	2
% dead/sacrificed	6	13	22	14

status (such as immersion of uterine tissues in ammonium sulfide) was presented by the study author. In addition, the mean number of resorptions per litter increased in a dose-related pattern (0.63, 0.69, 0.79, and 0.83 in the 0, 3, 10, and 30 mg/kg/day dosage groups, respectively). These increases resulted in slight dose-related elevations in the percentage of postimplantation losses (8.3, 9.3, 9.6, and 9.9 for the 0, 3, 10, and 30 mg/kg/day dosage groups, respectively); however, these changes were not statistically significant. Mild decreases in fetal body weights were reported for the 30 mg/kg/day dosage group; these body weight reductions may be associated with slight increases in the mean number of live fetuses per litter in this group. The male to female fetal ratios were comparable for all groups.

No compound-related increases in the incidences of malformations or variations were noted except for a slight increase in the incidence of a single extra rib (9, 13, 13, and 15 percent for the 0, 3, 10, and 30 mg/kg/day dosage groups, respectively). This variation is often considered an indication of mild fetotoxicity.

8. The following are differences between the reviewers' and study author's conclusions:

   1. The study author reported that animals were examined by a veterinarian and confirmed as being suitable for this study. However, considering the extremely high incidence of female mortalities, which the study author indicated were attributable to pulmonary disorders (and not to the test material), we conclude that the respiratory illness was associated with an unacceptably high incidence of maternal death. Therefore, we assess that the health status of these animals was unacceptable. Furthermore, because the author did not provide the reproductive history for the females, we could not confirm if these animals were acceptable (i.e., nulligravid) for a teratogenicity study.

   2. We conclude that the mean number of resorptions increased with increasing dosages but that these increases were not statistically significant. Differing from the study author's conclusion, we do not rule out a biologically significant association between the test material and the increases in embryolethality.

   3. We conclude that the deficiencies in methods implemented in fetal examinations (see Section 14C, below) precluded a definitive assessment of the teratogenic potential of the test material. Therefore, we do not agree with the study author's conclusion that cyhalothrin was not teratogenic in this study; instead we consider their assessment to be based on inconclusive data.

C. The following deficiencies in study design and conduct have negatively affected the scientific validity of the study:

1. The high incidence of maternal mortality associated with pulmonary illness is considered unacceptable. A definitive assessment of maternal and fetal toxic effects cannot be made on the basis of animals with such high incidences of illness related deaths. In addition, the data obtained from surviving animals are questionable since it is possible that their health may have also been affected.

2. The following deficiencies in fetal examinations precluded a definitive assessment of teratogenic potential of the test material.

   a. Scheduled Laparotomies: It would have been more acceptable if pregnancies were terminated on gestation day 29 or 30. The sacrifice of study females on gestation day 28 is considered too early and may have contributed to the presence of small pups with reductions in skeletal ossification and an apparent increase in skeletal and visceral variants.

   b. Fetal Euthanasia: The procedure of intracardiac injection is considered unacceptable due to the physical perforation of cardiac structures and the possible distortion of cardiac and major vessel anatomy produced by the volume of fluid injected into the cardiac chambers. The anatomic disruptions resulting from these procedures may have negatively affected the accuracy of cardiovascular examinations by masking the visualization of cardiac septal defects, valve malformations, pericardial hemorrhages, and various other malformations or lesions in the mediastinum of the fetuses.

   c. Fetal Visceral Examinations: The methods used for examination of the thoracic and abdominal cavities were not indicated or described in the study report, nor was it stated whether these examinations were conducted with the aid of a dissecting microscope. This is of particular concern since cardiac structures were perforated during fetal sacrifices prior to examination for intracardiac abnormalities. In addition, the method of intracranial examination, as described in the study report, was precarious. The author stated that fixed heads were sliced through the line of the fronto-parietal suture to examine the fetal brains for "visible abnormalities." It would have been more acceptable to examine the intracranial structures through serial coronal planes to provide sectional views of the nasal cavities and septum, olfactory lobes of the brain, eyes, lateral, third and fourth ventricles, vestibulocochlear apparatus, and

cerebellum. The inherent deficiencies of the single coronal section method described by the author would not permit the visualization of a number of malformations and variations. Therefore, we conclude that the methods used in this study precluded an adequate assessment of the potential teratogenic effects of the test material.

Item 15--see footnote 1.

16. CBI APPENDIX:

Appendix A, Materials and Methods, CBI pp. A4-A23.

APPENDIX A

Materials and Methods

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 326 through 345 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

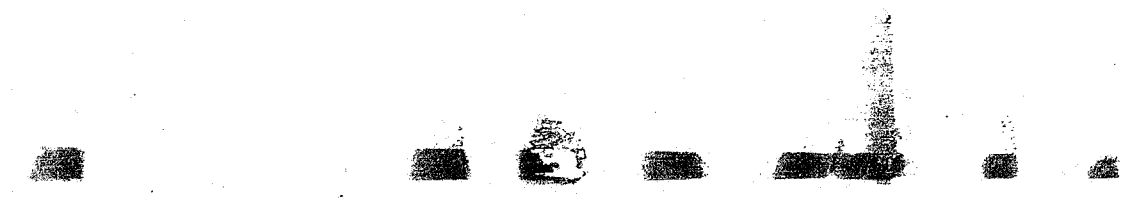
____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.



005100

EPA: 68-02-4225
TASK: 029-81
January 14, 1986

DATA EVALUATION RECORD

CYHALOTHRIN

Teratogenicity Study in Rats

STUDY IDENTIFICATION: Killick, M. E. Cyhalothrin: Oral (gavage) teratology study in the rat. (Unpublished study No. RR 0170 and report No. 2661-72/208 prepared by Hazleton Laboratories Europe Ltd., England, for Imperial Chemical Industries Ltd., England; dated June 1981.) Accession No. 073206.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I Cecil Felkner

Date: 1-14-86

005100

1. CHEMICAL: Cyhalothrin; (R,S)α-cyano-3-phenoxybenzyl (±)-cis-3,3 (Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2-dimethylcyclopropane carboxylate; Grenade.

2. TEST MATERIAL: Cyhalothrin (batch No. 005, ICI code No. Y00102/010/005) was a brown viscous fluid described as a technical grade pyrethroid mixture containing 89.25 percent w/w cyhalothrin.

3. STUDY/ACTION TYPE: Teratogenicity study in rats.

4. STUDY IDENTIFICATION: Killick, M. E. Cyhalothrin: Oral (gavage) teratology study in the rat. (Unpublished study No. RR 0170 and report No. 2661-72/208 prepared by Hazleton Laboratories Europe Ltd., England, for Imperial Chemical Industries Ltd., England; dated June 1981.) Accession No. 073206.

5. REVIEWED BY:

Guillermo Millicovsky, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: G Millicovsky
Date: 1/13/86

Patricia Turck, M.S.
Independent Reviewer
Dynamac Corporation

Signature: G Millicovsky for
Date: 1/13/86

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
Teratogenicity and
Reproductive Effects
Technical Quality Control
Dynamac Corporation

Signature: I Cecil Felkner
Date: 1-14-86

Krystyna Locke, Ph.D.
EPA Reviewer

Signature: Pamela M Stanley for
Date: 1/21/86

Edwin Budd
EPA Section Head

Signature: John Rohrer
Date: 5/5/86

Reclassified to Core Minimum by TB
NOEL fetotox. 15 mg/kg/day (see cover memo) 305100

7. CONCLUSIONS:

A. We assess that the NOEL and LOEL for maternal toxicity are 10 and 15 mg/kg/day, respectively, based on decreases in gestational body weight gains and food consumption reported for the 15 mg/kg/day group. The NOEL for embryolethality is 15 mg/kg/day. The NOEL for fetotoxicity could not be determined due to the presence of minor developmental variations in all dosage groups; therefore, 5 mg/kg/day, the lowest tested dose, is assessed as the LOEL for fetotoxicity.

B. No compound-related teratogenic effects were noted in the presented data; however, the teratogenic potential of cyhalothrin on cardiac and thoracic structures of rat fetuses could not be assessed since the intracardiac injections used in fetal sacrifices may have negatively affected the accuracy of cardiovascular examinations by masking the visualization of cardiac septal defects, valve malformations, pericardial hemorrhages, and various other malformations or lesions in the mediastinum of fetuses.

The registrant should submit data indicating that the method of intracardiac injection used in this study did not affect the findings of the cardiothoracic examinations. In addition, the registrant should submit historical control data (from 1979-1983) on the litter incidence of fetuses with dilated ureters. The classification of this study is pending receipt of the above information.

8. RECOMMENDATIONS: For future studies, we recommend that fetuses be sacrificed by carbon dioxide inhalation or intraperitoneal injection and not by intracardiac injection.

9. BACKGROUND: A range-finding study was conducted at Hazleton Laboratories, Europe (report No. 2586-72/207), to determine dose levels for the teratogenicity study; however, the author did not include details or results from this range-finding study in the teratogenicity study report.

Item 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: Cyhalothrin was described as a brown, viscous fluid consisting of 89.25 percent active ingredient. The test material was supplied by Imperial Chemical Industries Ltd.

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[1] Only items appropriate to this DER have been included.

under the code No. Y00102/010/005. Corn oil was used as the vehicle and control substance. Dosage formulations were prepared once (3 days before the initiation of dosing), divided into daily aliquots, and stored at room temperature until used. The final dosages of 0, 5, 10, and 15 mg/kg/day were achieved by mixtures containing 0.00, 0.56, 1.12, and 16.8 mg of test material (adjusted for purity) per milliliter. Dosing and control volumes were adjusted to 10 mL/kg body weight.

Dosages were based on maternal body weights recorded on gestation day (GD) 6. These dosages were reduced for animals whose body weights decreased below their respective reference level of GD 6, but were not increased to compensate for body weight gains above their reference level.

2. Test Animals and Test System: Specific pathogen-free CD rats were obtained from Charles River Ltd., Kent, England. Animals were examined upon arrival by a veterinarian to assure their suitability for the study. Females were described as being within 227-270 g, and males were reported to be sexually mature. Animals were acclimatized for 17 days and were vaccinated against Sendai virus during this period. Ninety-six females were mated with males on a 2:1 basis; a total of 24 females were assigned to each group. All mated females were dosed from GD 6 through 15 and sacrificed on GD 20.

3. Parameters Measured: Chemical analyses were conducted on samples of dose formulations obtained on the day of preparation and 19 days later.

All animals were observed at least once daily to determine their health status and to record clinical signs of toxicity. Mortality checks were performed twice daily. Maternal body weights were recorded on GD 0, 6 through 15, 18, and 20. Maternal food consumption was recorded on GD 0, 3, 6, 9, 12, 15, 18, and 20. Necropsies were conducted on pregnant animals at GD 20; at this time, gross maternal findings, gravid uterine weight, and number of corpora lutea were recorded. In addition, the number, type, and location of implantations within uteri were recorded.

Fetal body weight, crown-to-rump length, and sex were determined after sacrificing the fetuses with intracardiac injections of Euthatal. Subsequently, all fetuses were examined for gross external abnormalities. Two-thirds of the fetuses from each litter were dissected and examined for visceral abnormalities. Eviscerated fetuses were macerated, stained with Alizarin Red, and examined for skeletal abnormalities. Approximately one-third of the fetuses were fixed in Bouin's fluid and examined by a modification of Wilson's method.

12. REPORTED RESULTS:

A. Test Material: Gas chromatographic analyses were performed at the time dosage formulations were prepared and at the end of the dosing period. Results from these analyses indicate that all formulations were within 104-128 percent of target concentrations and that the test material was stable during the entire dosing period.

B. Maternal Effects: No mortalities were reported for any group. Two animals in the 15 mg/kg/day group exhibited uncoordinated movements of the limbs. No other compound-related clinical findings during pregnancy or gross findings during necropsies were noted.

The author reported that the reduction in mean body weight gain for pregnant animals in the 15 mg/kg/day group was statistically significant, when compared with controls, for the dosing period and for the entire length of gestation. Body weight gains in all other groups were comparable (Table 1). The food consumption of animals in the high-dose group was also significantly reduced (during GD 6-12) compared with controls, while no compound-related effects were noted in the other groups (Table 2).

Data from uterine parameters indicated that the percentage of pregnant animals was comparable for all groups (Table 3), but that the reduction in adjusted body weight gain (calculated by subtracting gravid uterine weight from gestational body weight gain) in the high-dose group was statistically significant (Table 4).

C. Embryonic/Fetal Effects: No compound-related effects were reported for intrauterine deaths. The mean number, body weight, and sex ratio of fetuses from all groups were comparable (Table 5).

Major malformations were noted only in one litter (from the 10 mg/kg/day group); therefore, the study author considered them as incidental (not compound-related) findings. Also considered as incidental was the slight increase in the incidence of minor defects in the high-dose group. Finally, the incidence of skeletal variants was reportedly comparable for all groups (Table 6).

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study author concluded that the only maternal effects associated with cyhalothrin were decreases in body weight gains and reductions in food consumption in the high-dose animals. These effects indicated that 15 mg/kg/day elicited maternal toxicity in pregnant rats. However, no compound-related effects resulted in any aspect of fetal development, even at the highest dose tested.

B. A quality assurance statement was signed and dated on July 3, 1981.

TABLE 1. Effects of Cyhalothrin on Maternal Body Weights and Body Weight Gains During Gestation in Rats

Gestation Day	Maternal Body Weight (g) Dose (mg/kg/day) 0	5	10	15
0	249	248	249	251
6	277	273	274	278
7	275	271	271	267
8	282	275	276	271
9	285	280	279	276
10	290	285	284	279
11	298	292	291	284
12	301	296	295	290
13	305	299	302	295
14	311	305	306	302
15	317	312	311	306
18	349	341	346	337
20	351	346	350	341

Study Period	Maternal Body Weight Gain (g) Dose (mg/kg/day) 0	5	10	15
0 - 6 (predosing)	28	25	25	27
6-15 (dosing)	40 [14.4%][a]	39 [14.3%]	37 [13.5%]	28 [10.1%]**
15-20 (post-(dosing)	34	34	39	35
0-20 (gestation)	102 [41.0%][a]	98 [39.5%]	101 [40.6%]	90 [35.9%]*

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

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

[a][ ], percent change based on body weight at the start of the period.

TABLE 2. Effects of Cyhalothrin on Maternal Food Consumption (g/day) During Gestation in Rats

Gestation Days	Dose (mg/kg/day) 0	5	10	15
0- 3	25.0	23.8	25.0	24.9
3- 6	24.3	23.7	23.9	24.3
6- 9	20.7	18.6	18.7	15.9**
9-12	22.8	21.1	21.6	20.7*[a]
12-15	24.9	22.3	23.5	22.6
15-18	26.1	27.9	26.5	25.9
18-20	16.9	15.3	15.5	15.1

* Statistically different from control value ($p < 0.05$), according to study author's calculations; [a]however, the reviewers did not find this parameter to be different from control by ANOVA and Duncan's test.

** Statistically different from control value ($p < 0.01$).

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TABLE 3. Effects of Cyhalothrin on Fertility Incidences in Rats

Parameter	Dose (mg/kg/day) 0	5	10	15
No. mated	24	24	24	24
No. pregnant at GD 20	23	24	24	24
% pregnant at GD 20	96	100	100	100

TABLE 4. Effects of Cyhalothrin on Adjusted[a] Mean Maternal Body Weight and Gravid Uterine Weight in Rats

Parameter	Dose (mg/kg/day) 0	5	10	15
Body weight (g) at GD 20	351	346	350	341
Gravid uterine weight (g)	70	67	74	71
Adjusted body weight (g)[a] at GD 20	281	279	276	270
% adjusted gestational body weight gain	12	13	11	8**

[a] Calculated by subtracting gravid uterine weight from maternal body weight on GD 20.

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

TABLE 5. Effects of Cyhalothrin on Group Mean Reproductive Indices in Rats

Parameter	Dose (mg/kg/day) 0	5	10	15
No. corpora lutea/female	14.7	15.3	15.3	15.5
No. implantations/litter	13.4	13.0	14.2	13.7
% preimplantation loss	8.8	14.9	7.6	11.8
No. intrauterine deaths/ litter	0.48	0.58	0.25	0.25
% postimplantation loss	3.6	4.5	1.8	1.8
Live fetuses/litter	13.0	12.5	13.9	13.4
Mean fetal weight (g)	3.7	3.7	3.7	3.7
Fetal male/female ratio	0.86	1.03	0.88	0.88

TABLE 6. Effects of Cyhalothrin on the Percentage of Malformations and Variations in Rat Fetuses

Parameter (% Fetuses Affected)	Dose (mg/kg/day) 0	5	10	15
1. External and Visceral Malformations				
Major	0.0	0.0	1.5	0.0
Minor	7.4	14.4	9.0	10.6
2. Skeletal Malformations				
Major	0.0	0.0	1.3	0.0
Minor	15.9	16.6	16.3	20.0
3. Variations	59.9	65.4	54.5	56.4

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. 1. Maternal Effects: The test material was associated with maternal toxicity (decreased body weight gains during gestation, decreased adjusted body weight gains, and reduced food consumption) at the highest dose tested. Review of the data presented for animals in the other dosage groups revealed that there were no compound-related effects.

2. Embryonic/Fetal Effects: No compound-related effects were noted in the mean group number of pre- and postimplantation losses and in the number, size, weight, and sex ratio of fetuses. However, slight increases (which were not statistically significant) in the fetal and litter incidences of several skeletal and visceral variations (including decreases in skeletal ossification, dilations of ureters, etc.--see Table 7) suggest that the test material may have been fetotoxic even at the lowest dose level tested.

No clear pattern of compound-related malformations was noted in the data presented; however, the methods implemented in this study may have precluded a conclusive examination of cardiac and mediastinal structures in fetuses (see section 14C).

B. The following are differences between the reviewers' and study author's conclusions:

1. We assess that the increases in the incidence of developmental variations noted at all dosage levels are indicative of mild fetotoxic effects, whereas the study author considered these findings as incidental and not compound related.

2. Due to the deficiencies in methodology (see section 14C) we assess that the data in this study are inconclusive; hence, we cannot rule out the possibility that compound-related cardiac and thoracic malformations may have been present, but not noted.

C. The following deficiency in study design and conduct has negatively affected the scientific validity of the study:

The procedure of intracardiac injection is considered unacceptable due to the physical perforation of cardiac structures and to the possible distortion of cardiac and major vessel anatomy produced by the volume of fluid injected into the cardiac chambers. The anatomic disruptions resulting from these procedures may have negatively affected the accuracy of cardiovascular examinations by masking the visualization of cardiac septal defects, valve malformations, pericardial hemorrhages, and various other malformations or lesions in the mediastinum of fetuses.

TABLE 7. Effects of Cyhalothrin on the Incidence of Selected Variations in Fetal Rats

Parameter (% Fetuses Affected)	Dose (mg/kg/day) 0	5	10	15
Fetuses with dilated ureter	1/298	16/299	3/334	12/322
% affected	0.3	5.4	0.9	3.7
Litters with dilated ureter	1/23	4/24	3/24	6/24
% affected	4.2	16.7	12.5	25.0
Fetuses with unossified hyoid	4/207	9/205	15/233	10/220
% affected	1.9	4.4	6.4	4.5
Litters with unossified hyoid	4/23	7/24	7/24	5/24
% affected	17.4	29.2	29.2	20.8

Item 15--see footnote 1.

16. CBI APPENDIX:

Appendix A, Materials and Methods, CBI pp. A4-A22.

APPENDIX A

Materials and Methods

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 361 through 379 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

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EPA: 68-02-4225
DYNAMAC No. 1-029-C
January 13, 1986

DATA EVALUATION RECORD

CYHALOTHRIN

Three-Generation Reproduction Study in Rats

STUDY IDENTIFICATION: Milburn, G. M., Banham, P., Godley, M. J., Pigott, G., and Robinson, M. Cyhalothrin: Three generation reproduction study in the rat. (Unpublished study for project CTL/P/906 7/HD/007119 prepared by Imperial Chemical Industries PLC; dated May 13, 1984.) Accession Nos. 073207-073209.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 1-13-86

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1. CHEMICAL: Cyhalothrin; (RS) α-cyano-3-phenoxybenzyl (Z)-(1RS, 3RS)-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate.

2. TEST MATERIAL: Cyhalothrin technical from batch No. ADM/46156/80 (CTL Reference number Y00102/010/007) had a purity of 89.2% (w/w).

3. STUDY/ACTION TYPE: Three-generation reproduction study in rats.

4. STUDY IDENTIFICATION: Milburn, G. M., Banham, P., Godley, M. J., Pigott, G., and Robinson, M. Cyhalothrin: Three generation reproduction study in the rat. (Unpublished study for project CTL/P/906 7/HD/007119 prepared by Imperial Chemical Industries PLC; dated May 13, 1984.) Accession Nos. 073207-073209.

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7. CONCLUSIONS:

A. We assess that the NOEL and LOEL for parental toxicity are 10 ppm and 30 ppm, respectively. The NOEL for offspring toxicity could not be determined because of compound-related effects even at the lowest dose level tested. Therefore, 10 ppm is assessed as the LOEL for offspring toxicity, based on statistically significant reductions in parental and offspring body weights. In addition, a statistically significant reduction in offspring viability was observed at 100 ppm.

B. This study had two major deficiencies:

- Compound-related toxicity occurred at all doses; hence, the NOEL for offspring toxicity could not be established.
- There were discrepancies between the summary tables and individual animal data.

Due to these deficiencies, this study is classified Core Supplementary until the discrepancies between the summary tables and individual animal data are corrected, at which time it may be reclassified as Core Minimum.

Reclassified to Core Guideline by TB. NOEL for offspring 10ppm. LEL 30ppm

8. RECOMMENDATIONS: (See cover memo)

1. The toxicity of the test material in the offspring of rats should be assessed at lower dose levels.

2. The data submitted for the present study should be revised by the study authors to remove possible errors in the summary tables and/or individual animal data.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS): (See Appendix A for details.)

Cyhalothrin technical (89.2% pure) was mixed into one of two cereal-based open formula diets at doses of 0, 10, 30, and 100 ppm throughout the duration of the study.

Male and female weanling SPF Wistar-derived rats were subjected to a quarantine/acclimatization period, individually identified, and randomly assigned to one of the dose groups. Prior to mating, each of the four dose groups consisted of 30 females (housed two per cage) and 15 males (housed one per cage). Male and female rats were housed in adjacent stainless steel cages in a temperature-, humidity-, and light-controlled room with a minimum of 15 air changes per hour. Feed and water were provided ad libitum.

---

[1] Only items appropriate to this DER have been included.

Microbiological sentinels were included in the study design.

During the study, all rats were observed once daily for abnormalities in clinical condition and behavior; a detailed examination of each rat was made once each week.

At 7-8 weeks of age (maturity), each female rat was examined for imperforate vagina.

The premating periods were 12 weeks for the F_0 animals and 11 weeks for the F_1 and F_2 animals. During these periods, body weight and food consumption values were recorded weekly. Following mating, the males were weighed approximately every 4 weeks until termination, and the females were weighed on days 1, 8, 15, and 22 of pregnancy.

Two females were housed with one male during the mating period, and daily vaginal examinations were performed to confirm mating. In cases of suspected male infertility, the first male was replaced with a male of proven fertility. Females with a positive vaginal smear were individually housed during the gestation and lactation periods.

Females from each generation were mated to males from the same dose group and allowed to produce the A litter; 10 days after the last A litter was weaned, females were remated with a different male to produce a second (B) litter. The interval between mating for the A and B litters was approximately 2.5 to 3 months; brother-sister matings were avoided.

The F_1B and F_2B litters were weaned at day 29 but remained housed as litters until day 36. Thirty females and 15 males were selected from each dose group of the F_1B and F_2B litters to produce the subsequent generations.

All parental animals that died or were sacrificed were subjected to a full postmortem examination, and the reproductive organs and other selected tissues were taken for histopathological examination.

All live and stillborn pups were counted, checked for clinical abnormalities, and their sex and individual body weights were recorded within 24 hours of parturition and at days 5, 11, 22, and 29 postpartum. Litters were examined once daily; dead or grossly abnormal pups were removed for soft tissue examination. All grossly abnormal pups and those found dead within the first 18 days were examined teratologically by the methods described by Wilson.

Moribund or dead pups older than 18 days of age were subjected to a full postmortem examination.

At approximately 36 days postpartum, all offspring from the A litters and those from the B litters not selected to produce the subsequent generation were sacrificed. Approximately half of the A litter offspring (including those with externally visible abnormalities) were subjected to a gross autopsy and abnormal tissues were examined histologically. The remaining half were discarded after gross external

examination. Approximately five male and five female pups per group from the F_1B and F_2B litters and 10 male and 10 female pups per group from the F_3B litters were subjected to a full postmortem examination, and selected tissues were examined histologically. The remaining pups from B litters were subjected to a gross postmortem examination with only abnormal tissues submitted for examination. Normally distributed parametric data such as body weight, weight gain, and food consumption were subjected to analysis of variance and/or analysis of covariance and Student's t-test. Parametric data such as litter sizes and proportional data were analyzed by analysis of variance on transformed data or by one-tailed Fisher's exact test.

12. REPORTED RESULTS:

A. Dietary Analyses: Twenty-three batches of feed were analyzed for concentrations of cyhalothrin at each dose level, including the control feed. No test material was detected (at a level of sensitivity of less than 0.1 ppm) in any of the control diets. The maximum deviation of the doses from nominal concentration was 16.7%, and in all but four instances, the mean concentrations were within 10% of nominal value. In five different batches of feed the test material was found to be stable when stored for up to 2 months at levels between 10 and 100 ppm.

The homogeneity of the test material was found to be satisfactory in three batches of diet containing 10, 30, or 100 ppm cyhalothrin.

B. Parents:

1. Mortality: One F_1 male from the 10-ppm dose group was found dead. Unscheduled sacrifices were performed on two females (one F_0 control and one F_2 from the 30-ppm dose group) because of parturition difficulties.

2. Clinical Observations: None of the parental animals exhibited clinical signs related to administration of the test material.

3. Body Weight Gain: During the first week of study, F_0 males in the high-dose group showed small (but statistically significant) reductions in weight gain. For the remainder of the study, the weight gain of F_0 males was comparable to that of controls. There was a statistically significant reduction in the mean body weight gain of F_1 and F_2 males in the high-dose group. According to the text of the study report, the low-dose F_1 males showed a slight, but not statistically significant, reduction in body weight gain. However, the study authors' analyses of the tabulated data (p. 36 of the report) indicated that this reduction was statistically significant. These data are presented in Table 1.

TABLE 1. Effects of Cyhalothrin on Mean Body Weight Gain (g) During the Premating Period in Rats

End of Week	Dose Level (ppm) 0	10	30	100
		F_0 Males		
1	54.7	53.8	53.7	50.5*
6	302.3	297.0	301.7	295.8
12	422.7	414.1	418.8	415.0
		F_1 Males		
1	59.3	56.6	57.6	54.9*
6	276.8	271.8	283.5	266.4
11	382.7	351.7*	363.5	349.0*
		F_2 Males		
1	61.2	60.3	58.5	56.7
6	287.0	291.7	280.7	264.7
11	385.7	391.5	373.1	352.8*
		F_0 Females		
1	40.0	41.0	42.6*	38.3
6	161.2	160.2	165.9	160.3
12	211.5	209.9	219.0*	208.4
		F_1 Females		
1	40.6	39.9	40.4	40.4
6	142.7	137.4	134.2*	131.4**
11	182.3	173.2	168.9**	165.1**
		F_2 Females		
1	37.6	41.7*	37.6	37.7
6	131.4	135.9	129.0	122.3*
11	166.0	169.0	160.6	156.0*

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

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

Female F_0 rats in the mid-dose group showed a statistically significant increase in body weight during the premating period.

Female F_1 rats in the mid- and high-dose groups showed statistically significant reductions in body weight gain during the premating period. The F_2 females in the high-dose group showed statistically significant reductions in body weight gain during the premating period (Table 1).

During pregnancy, there was no consistent evidence of decreased body weight gain for the F_0 animals. The mean body weights of F_1 and F_2 females at the initiation of pregnancy were significantly reduced for all of the 100-ppm and most of the 30-ppm groups. There were significant reductions in body weight gain during pregnancy for the F_2 animals in the high-dose groups (Table 2).

4. Food Consumption: Variations in food consumption measurements during the premating period precluded interpretation of any results on food consumption or calculations of dosage rates. However, the study authors noted that no consistent differences were evident between dosage groups. Food consumption was not measured during pregnancy or lactation.

5. Fertility: Male fertility was comparable among all groups (Table 3).

   No effects on female fertility were noted except for a statistically significant reduction in the fertility of F_2 females from the mid-dose group producing the F_3B generation when compared to controls (Table 3). However, the study authors did not consider this reduction compound related.

6. Precoital Interval: The test article did not affect the length of the precoital interval during this study.

7. Gestation Period: The test article did not affect the length of gestation during this study.

8. Maternal Neglect: The test article did not affect maternal neglect during this study (Table 4).

C. Offspring:

1. Litter Size: There was a statistically significant reduction in litter size for the F_2A and F_3B litters of high-dose females (Table 5).

TABLE 2. Effects of Cyhalothrin on Mean Maternal Body Weight (g) and Weight Gain (g) During Gestation in Rats

	Dose Level (ppm)			
	0	10	30	100
		F_0, Litter A		
Initial weight	289.0	288.5	298.6	286.1
Wt. gain at day				
8	23.7	27.5*	26.6	23.0
15	55.7	60.6	58.4	56.0
22	127.2	129.5	132.7	127.6
		F_0, Litter B		
Initial weight	328.3	326.5	330.2	323.5
Wt. gain at day				
8	21.6	26.0	25.1	25.2
15	55.2	59.3	60.3	54.5
22	125.4	129.4	143.9**	132.8
		F_1, Litter A		
Initial weight	306.3	298.3	282.7**	287.0*
Wt. gain at day				
8	23.4	24.7	23.4	24.0
15	55.3	55.9	53.0	55.4
22	134.5	132.1	130.1	133.2
		F_1, Litter B		
Initial weight	348.3	344.6	321.7**	323.0**
Wt. gain at day				
8	23.9	25.3	20.8	22.0
15	56.1	58.0	51.1	56.7
22	131.3	132.3	120.8	128.2

(Continued)

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

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

TABLE 2. Effects of Cyhalothrin on Mean Maternal Body Weight (g) and Weight Gain (g) During Gestation in Rats (Continued)

	Dose Level (ppm)			
	0	10	30	100
		F_2, Litter A		
Initial weight	297.1	296.9	284.6	278.7*
Wt. gain at day				
8	26.3	26.0	26.1	22.4*
15	54.2	56.8	54.1	50.8
22	123.7	124.4	128.5	119.4
		F_2, Litter B		
Initial weight	331.1	330.9	315.5*	312.4**
Wt. gain at day				
8	23.4	25.5	21.8	20.8
15	53.6	55.5	54.4	50.3
22	142.2	137.0	136.7	127.2*

(Concluded)

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

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

TABLE 3. Effects of Cyhalothrin on Group Mean Percentage Parental Fertility in Rats

	Dose Level (ppm)			
	0	10	30	100
		Males		
F_0, Litter A	100%[a]	93%	92%	87%
F_0, Litter B	100%	93%	100%	100%
F_1, Litter A	93%	93%	86%	100%
F_1, Litter B	93%	85%	93%	100%
F_2, Litter A	93%	93%	100%	100%
F_2, Litter B	100%	93%	80%	93%
		Females		
F_0, Litter A	77%[b]	87%	88%	96%
F_0, Litter B	73%	86%	77%	89%
F_1, Litter A	89%	80%	78%	87%
F_1, Litter B	83%	75%	87%	90%
F_2, Litter A	90%	90%	86%	79%
F_2, Litter B	97%	83%	77%*	83%

[a]Based on approximately 15 males per group.

[b]Based on approximately 30 females per group.

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

TABLE 4. Effects of Cyhalothrin on the Mean Percentage of Viable Litters that Did Not Survive Due to Maternal Neglect in Rats

Litter	Dose Level (ppm)			
	0	10	30	100
F_1A	4%[a]	4%	5%	4%
F_1B	5%	8%	0%	8%
F_2A	8%	0%	0%	12%
F_2B	0%	5%	0%	0%
F_3A	0%	0%	0%	0%
F_3B	0%	0%	0%	4%

[a]Based on 21-29 litters per group.

TABLE 5. Effect of Cyhalothrin on Mean Litter Size in Rats

Postnatal Day	Dose Level (ppm) 0	10	30	100
		F_1A		
1	12.0	11.8	12.1	10.9
5	10.5	11.0	11.0	10.3
11	10.5	10.8	10.9	10.0
22	10.4	10.8	10.9	9.9
29	10.4	10.8	10.8	9.9
		F_1B		
1	9.8	10.1	11.9	11.5
5	9.2	9.7	11.6	10.3
11	8.7	9.5	11.6	10.1
22	8.6	9.5	11.6	9.9
29	8.6	9.5	11.5	9.9
		F_2A		
1	11.6	11.3	11.3	10.0
5	10.9	10.7	11.3	8.7*
11	10.8	10.6	11.2	8.6*
22	10.7	10.4	11.2	8.6*
29	10.7	10.4	11.2	8.6*
		F_2B		
1	10.2	10.3	9.6	9.9
5	9.7	9.9	9.2	9.5
11	9.5	9.7	9.2	9.5
22	9.5	9.7	9.2	9.5
29	9.5	9.7	9.2	9.4
		F_3A		
1	10.8	10.9	11.2	10.2
5	10.4	10.7	11.1	10.0
11	10.4	10.7	11.1	9.9
22	10.4	10.7	11.1	9.9
29	10.4	10.7	11.1	9.9

(Continued)

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

TABLE 5. Effect of Cyhalothrin on Mean Litter Size in Cats (Continued)

Postnatal Day	Dose Level (ppm) 0	10	30	100
		F_3B		
1	11.3	10.9	11.3	10.0
5	11.0	10.8	10.8	9.6
11	10.9	10.7	10.7	9.5*
22	10.9	10.7	10.7	9.5*
29	10.9	10.7	10.7	9.5*

(Concluded)

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

2. Live-Born Index: The only statistically significant decreases in the percentage of live-born pups were noted in the F_1B pups dosed with 10 ppm and in the F_3B groups dosed with 30 and 100 ppm. The study authors considered only the effects in the F_3B generation to be compound related (Table 6).

3. Survival to Day 22: The test article did not affect pup survival to day 22 in this study (Table 7).

4. Clinical Condition: The test article did not affect the clinical condition of pups in this study.

5. Body Weight Gain: Statistically significant reductions in body weight gain were noted in F_1A females from the 10-ppm group, F_1B female pups from the 30- and 100-ppm groups, F_1B males from the 100-ppm group, F_2B males from the 100-ppm group, F_3A females from the 30- and 100-ppm groups, F_3A males from the 10-, 30-, and 100-ppm groups, and F_3B females and males from the 30-ppm groups (Table 8).

6. Soft Tissue Examination: The quality of the soft tissues was adversely affected by autolysis. The hearts of three pups from F_2 dams in the high-dose group were reportedly "apparently" absent. However, the study authors stated that there were no consistent differences in findings between dose groups or between A and B litters.

D. Pathology:

1. Gross Pathology: The test material did not affect the gross pathologic findings reported in the parental animals or pups in this study.

2. Histopathology: No compound-related findings were noted.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study authors concluded that 100 ppm of cyhalothrin in the diet of rats was associated with reductions in body weights in the F_2B, F_3A, and F_3B generations. No other parameter was affected. They assessed 30 ppm as the NOEL.

B. A quality assurance statement was signed and dated May 14, 1984.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. Diets containing cyhalothrin at concentrations of 30 and 100 ppm were associated with reductions in parental and offspring body weight in rats. No distinct compound-related effects on body weights were noted in the 10-ppm groups, except for occasional reductions in pup body weights that, at times, had statistical

TABLE 6. Effects of Cyhalothrin on Mean Percentage of Pups Born Alive in Rats

Litter	Dose Level (ppm)			
	0	10	30	100
F_1A	96.2%[a]	99.5%	99.3%	98.7%
F_1B	98.3%	93.2%*	98.9%	99.2%
F_2A	99.5%	99.5%	100.0%	98.5%
F_2B	99.0%	99.2%	97.4%	98.1%
F_3A	99.7%	100.0%	98.5%	98.8%
F_3B	99.2%	97.9%	97.0%*	93.6%**

[a]Based on 232-329 pups per group.

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

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

TABLE 7. Effects of Cyhalothrin on Mean Percentage of Pups Alive on Postnatal Day 22 in Rats

Litter	Dose Level (ppm)			
	0	10	30	100
F_1A	85.7%	94.0%	91.5%	91.0%
F_1B	90.3%	96.8%	95.6%	88.2%
F_2A	89.1%	92.8%	99.7%	86.8%
F_2B	94.9%	96.5%	95.5%	95.7%
F_3A	97.0%	98.3%	98.7%	96.6%
F_3B	96.8%	96.7%	95.2%	93.9%

TABLE 8. Effects of Cyhalothrin on Mean Initial Pup Body Weight (g) and Weight Gain (g) in Rats

Weight Gain	Dose Level (ppm) 0	10	30	100
		F_1A Females		
Initial weight	5.4	5.7	5.7	5.7
Postnatal day				
5	2.9	2.3*	2.5	2.5
11	11.3	10.6	10.7	10.5
22	32.4	30.8	30.9	31.1
29	61.6	59.9	61.1	59.8
		F_1A Males		
Initial weight	5.8	6.2	6.1	6.1
Postnatal day				
5	2.9	2.6	2.8	2.7
11	12.1	11.4	11.5	11.0
22	34.2	33.1	32.3	34.0
29	67.0	65.9	65.9	66.6
		F_1B Females		
Initial weight	5.9	6.0	5.9	5.9
Postnatal day				
5	2.5	3.0	2.7	2.5
11	11.8	12.5	11.4	10.8
22	36.6	37.1	32.9*	33.2*
29	67.3	68.8	61.8*	62.2*
		F_1B Males		
Initial weight	6.2	6.4	6.3	6.0
Postnatal day				
5	2.6	3.1	3.0	2.5
11	11.9	13.0	12.0	11.4
22	37.5	38.5	35.2	34.8
29	71.2	72.9	66.8	66.4*

(Continued)

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

TABLE 8. Effects of Cyhalothrin on Mean Initial Pup Body Weight (g) and Weight Gain (g) in Rats (Continued)

Weight Gain	Dose Level (ppm) 0	10	30	100
		F_2A Females		
Initial weight	5.8	5.9	5.8	5.8
Postnatal day				
5	3.3	3.1	3.0	3.0
11	12.6	12.4	12.2	12.7
22	36.7	36.9	33.6	36.5
29	69.0	70.8	67.6	70.0
		F_2A Males		
Initial weight	6.1	6.2	6.2	6.2
Postnatal day				
5	3.2	3.1	2.9	3.3
11	13.1	12.6	12.4	13.6
22	37.1	36.7	35.3	38.9
29	71.8	73.2	72.5	75.8
		F_2B Females		
Initial weight	6.0	5.9	6.0	6.0
Postnatal day				
5	2.6	2.8	3.3	2.7
11	12.4	12.8	13.9	12.1
22	37.9	39.2	38.5	36.6
29	72.5	72.6	73.6	70.4
		F_2B Males		
Initial weight	6.5	6.6	6.4	6.3
Postnatal day				
5	2.9	2.9	3.4	2.7
11	13.5	13.4	14.2	12.2
22	41.0	41.8	41.0	37.4*
29	80.1	79.4	80.0	73.9*

(Continued)

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

TABLE 8. Effects of Cyhalothrin on Mean Initial Pup Body Weight (g) and Weight Gain (g) in Rats (Continued)

Weight Gain	Dose Level (ppm) 0	10	30	100
		F_3A Females		
Initial weight	5.8	5.7	5.7	5.8
Postnatal day				
5	3.2	3.0	2.9	2.9
11	13.3	12.8	12.2	11.7*
22	38.5	36.5	34.7**	34.7*
29	73.7	71.2	67.8**	67.6**
		F_3A Males		
Initial weight	6.2	6.2	6.1	6.1
Postnatal day				
5	3.4	3.1	2.9*	2.9*
11	14.0	12.1**	12.4*	11.7**
22	39.8	37.1*	35.8**	34.8**
29	79.1	75.2	72.1**	69.9**
		F_3B Females		
Initial weight	6.0	6.2	6.1	5.9
Postnatal day				
5	3.4	3.3	3.3	3.5
11	13.7	12.8	13.4	13.3
22	39.3	36.9	37.0	37.7
29	74.7	70.8	70.4*	71.9
		F_3B Males		
Initial weight	6.4	6.5	6.4	6.4
Postnatal day				
5	3.6	3.4	3.3	3.4
11	14.3	13.6	13.0*	13.4
22	40.9	39.0	37.6*	38.4
29	80.0	76.4	74.1*	75.7

(Concluded)

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

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

significance. No compound-related effects on parental fertility or maternal neglect were noted. However, we assess that the statistically significant reductions in the number of viable pups in the 100-ppm groups from the F_2A and F_3B generations were compound related.

B. Our conclusions differed from those of the study authors in that we assess that the NOEL for parental toxicity is 10 ppm, based on the statistically significant reductions in body weights at 30 and 100 ppm; we assess that the LOEL for parental toxicity is 30 ppm. The NOEL for offspring toxicity could not be determined because there were statistically significant reductions in pup body weight, even in some groups dosed with 10 ppm; therefore, this dose (the lowest used) is the LOEL for offspring toxicity in this study.

Although the study authors stated that no other parameters were affected, we conclude that the reductions in viable fetuses noted in two generations dosed with 100 ppm suggest a lethal effect of the test material on the offspring at this dose level.

C. The summary tables had several arithmetic errors when compared to the individual animal data. Specific examples of the errors include:

1. Tables 23-24 (fertility tables): The source of the denominators is not clear. In Table 23 (p. 50), male fertility during production of litter F_1A at 30 ppm was reported as 11/12, but information from Appendix F (pp. 108-109) indicates it should have been 11/14 (male No. 132 was infertile, no litters or positive vaginal smear).

   Litter F_2A (control), the value of 13/14 should have been reported as 13/15 (Appendix N, pp. 297-298).

   Litter F_2A (100 ppm), the value of 14/15 should have been reported as 14/14 (Appendix N, pp. 299-300).

   Litter F_1A (100 ppm), the value reported as 26/27 should have been reported as 26/28 (Appendix F, pp. 110-111).

   Litter F_2A (10 ppm), the value reported as 24/30 should have been reported as 24/29 (Appendix N, pp. 299-300).

2. The following discrepancies were noted in Table 28 (p. 55):

Litter Size, F_1 Generation

Group	Reported as	Should be	Individual Animal Reference
A, control, day 1	12.0 (22)	11.5 (23)	App. F, pp. 104-105
A, 10 ppm, day 1	11.8 (25)	11.3 (26)	App. P, pp. 106-107
A, 30 ppm, day 1	12.1 (21)	12.3 (22)	App. F, pp. 108-109
A, 100 ppm, day 1	10.9 (25)	11.0 (26)	App. F, pp. 110-111
B, control, day 1	9.8 (21)	9.9 (22)	App. F, pp. 112-113
B, control, day 29	8.6 (21)	9.1 (21)	App. F, pp. 112-113
B, 10 ppm, day 1	10.1 (23)	10.1 (25)	App. F, pp. 114-115
B, 10 ppm, day 29	9.5 (23)	9.8 (22)	App. F, pp. 114-115
B, 30 ppm, day 29	11.5 (23)	11.1 (21)	App. F, pp. 116-117
B, 100 ppm, day 1	11.5 (22)	11.5 (24)	App. F, pp. 118-119
B, 100 ppm, day 29	9.9 (22)	9.7 (21)	App. F, pp. 118-119

3. The following discrepancies were noted in Table 29 (p. 26):

Litter Size, F_2 Generation

Litter/Group	Reported as	Should be	Individual Animal Reference
A, control day 1	11.6 (23)	11.0 (25)	App. N, pp. 297-298
A, 30 ppm, day 29	11.2 (21)	11.2 (20)	App. N, pp. 301-302
A, 100 ppm, day 1	10.0 (23)	9.9 (26)	App. N, pp. 303-304
A, 100 ppm, day 29	8.6 (23)	8.5 (21)	App. N, pp. 303-304
B, 10 ppm, day 1	10.3 (20)	10.5 (21)	App. N, pp. 307-308
B, 10 ppm, day 29	9.7 (20)	9.8 (17)	App. N, pp. 311-312
B, 100 ppm, day 29	9.4 (27)	9.6 (25)	

4. The following discrepancies were noted in Table 30 (p. 57):

Litter Size, F_3 Generation

Litter/Group	Reported as	Should be	Individual Animal Reference
B, 100 ppm, day 1	10.0 (24)	9.6 (25)	App. V, pp. 515-516

5. The following discrepancies were noted in Table 31 (p. 58):

Pups Born Live

Litter/Group	Reported as	Should be	Individual Animal Reference
F_1A, control	264/274	264/276	App. F, pp. 104-105
F_2B, 100 ppm	269/275	269/279	App. N, pp. 311-312

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 3-14.

APPENDIX A

Materials and Methods

APPENDIX A

Materials and Methods

CYHALOTHRIN 128567

Page_____ is not included in this copy.

Pages 405 through 416 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

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005100

Reviewed by: Pamela Hurley
Section 2 , Tox. Branch (TS-769C)
Secondary Reviewer: Edwin Budd
Section 2 , Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Metabolism Study 85-1

ACCESSION NUMBER: 073217

TEST MATERIAL: Cyhalothrin

SYNONYMS: (R,S)alpha-cyano-3-phenoxybenzyl (±)-cis-3-(Z-2-chloro-3,3,3-trifluoropropyl-enyl)-2,2-dimethylcyclopropane carboxylate; ICI 146,814; ^{14}CHCN; ^{14}C-cyclopropyl

STUDY NUMBER(S): ICI - 146814 KMR 002/01 and KMR 002/02

REPORT NUMBER: Protocol ICI 146,814 MPH 01

SPONSOR: Imperial Chemical Industries PLC (ICI PLC)

TESTING FACILITY: ICI PLC Pharmaceuticals Division, Safety of Medicines Department

TITLE OF REPORT: Cyhalothrin: The Disposition and Metabolism of ^{14}C-ICI 146,814 In Rats Parts I and II

AUTHOR(S): M. P. Harrison, D. E. Case

REPORT ISSUED: October 8, 1981 and September 17, 1984

IDENTIFYING VOLUME: Volume II, Book 15 of 16 (Tab Reference 19C)

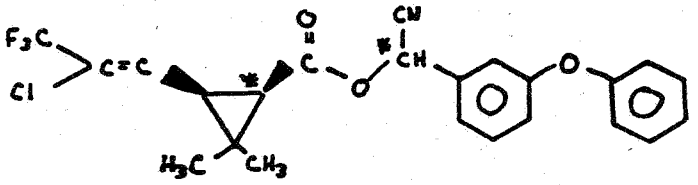
CONCLUSION: This study, in combination with the two following studies, is classified as CORE GUIDELINE. Although there were no indications of any toxic or pharmacologic signs at the highest dose level, the studies were extremely well done and complete.

Classification: CORE GUIDELINE

MATERIALS AND METHODS:

Chemical

Two different radiolabelled forms of cyhalothrin were used for these studies. The positions of radiolabelling are shown in the following figure:



The abbreviations "^{14}CHCN" and "^{14}C-cyclopropyl" were used to refer to the compound labelled at positions marked # or *, respectively, as shown above. Several batches of each were prepared by the Radiochemical Unit of the Drug Metabolism Section at ICI Pharmaceuticals Division and were purified by HPLC. The material used was greater than 99% pure cis isomer, and a racemic mixture of the other possible isomers. Non-labelled cyhalothrin of comparable purity was used for dilutions.

Animals

Male and female 'Alderly Park' Wistar strain 'Specific Pathogen Free' rats weighing between 200-250 grams were used for the studies.

Single Dose Excretion Studies

Three single dose excretion studies were conducted: two oral administration studies (one each with one of the two radiolabelled compounds), and one subcutaneous injection study with only ^{14}CHCN. Six male and six female rats were tested in each study, the dose levels having been set at 1 and 25 mg/kg for the oral studies and 1 mg/kg for the subcutaneous study. For dosing at 1 mg/kg, each ^{14}C compound was dissolved at approximately 0.5 mg/ml in corn oil and for dosing at 25 mg/kg, the ^{14}C compounds were mixed 1:24 w/w with non-labelled cyhalothrin and dissolved in corn oil at 12.5 mg/ml. Specific activities and radiochemical purities were determined for each formulation and the actual radiochemical dose given was determined by measuring the residual ^{14}C-cyhalothrin from each dose. Rats were placed in glass metabolism cages and urine and feces were collected every 24 hours for up to seven days after dosing. At that time, the animals were killed by CO_2 and selected tissues were removed for measurement of residual radioactivity. In the studies where rats were dosed orally at 1mg/kg, the expired air from two males and two females was monitored for CO_2 for the first 48 hours after dosing.

Excretion Studies in Bile Duct Cannulated Rats

Two studies were conducted with bile duct cannulated rats. In the first study, four male and four female cannulated rats were orally dosed with 1 mg/kg ^{14}CHCN. The total bile produced was collected every 12 hours for up to 48 hours and then to 72 and 96 hours after

dosing. Urine and feces were also collected daily for up to 96 hours. In the second study, four pairs of male rats were cannulated such that for each pair, the bile outflow of one rat was introduced into the duodenum of the second rat via the existing bile duct outlet. Each bile recipient rat was given a single oral dose of 1 mg/kg ^{14}CHCN and the bile, urine and feces were collected as in the previous study.

Blood Collection of Radiolabelled Components

Blood Concentrations of Total Radioactivity

Six male and six female rats per dose were given single doses of ^{14}CHCN (1 and 25 mg/kg orally and 1 mg/kg s.c.) and 1 mg/kg ^{14}C-cyclopropyl. Blood samples were taken from the tail vein of each rat into heparinized tubes at the following times: predose and 15 or 30 minutes, 1, 2, 4, 7, 12, 20, 24, 36 and 48-hours after dosing. The whole blood was analyzed for total ^{14}C content.

Blood Concentrations of Total Radioactivity and Unchanged ^{14}C-Cyhalothrin

Twelve male and twelve female rats were dosed orally with either 1 or 25 mg/kg ^{14}CHCN. Three rats of each sex were killed at 2, 7, 24 and 36 hours after dosing, and total blood was collected by cardiac puncture. Each blood sample was analyzed for total ^{14}C concentration, plasma ^{14}C concentration and total cyhalothrin concentration.

Analysis of Sample Radioactivity

The radioactivity in prepared samples of whole urine, bile, plasma, feces and tissues collected from the preceding experiments was measured with an Intertechnique SL 30 or SL 4000 liquid scintillation counter. The concentrations of cyhalothrin in whole blood were determined by solvent extraction followed by gas-liquid chromatography. The radiochemical purity of the ^{14}C-cyhalothrin dose formulations and the patterns of radioactive metabolites in the urine, bile and methanol extracts of feces were determined by thin-layer chromatography. Radioactive areas on the developed chromatograms were located by autoradiography and quantitated, either by means of a chromatogram scanner or by a scintillation counter (using scraped segments from each plate). Selected urine samples were treated with either beta-D-glucuronidase or aryl sulphatase. These were then analyzed along with control samples by thin layer chromatography.

Results

Excretion Studies With ^{14}CHCN

After oral administration of single doses of ^{14}CHCN to male and female rats at 1 and 25 mg/kg, most of the radioactive dose was rapidly eliminated from the body via the urine and feces. Total urinary (including cage washes) and fecal excretion expressed as the percent of the administered dose were as follows: 1 mg/kg - females excreted 41.5±9.4% in the urine and 46.5±7.5% in the feces

and males excreted 30.0±12.4% in the urine and 61.4%±14.4% in the feces; 25 mg/kg - females, 40.9±9.4% in the urine and 40.2±7.6% in the feces, and males, 40.3±10.7% in the urine and 49.7±14.6% in the feces. The majority of the radioactivity excreted by both routes was recovered in the 0-24 hour samples. There was no detectable excretion of $^{14}CO_2$ in exhaled air. The residues of ^{14}CHCN remaining in the carcasses (after removal of some tissues) seven days after dosing were approximately two and three percent of the dose for males and females respectively at both dose levels.

Following subcutaneous administration of one dose of 1 mg/kg ^{14}CHCN to male and female rats, total recovery of ^{14}C from excreta throughout seven days was 22.2±20.5% in males and 24.7±17.1% in females. Urinary excretion was the predominant route of elimination with 16.4±15.8% and 17.6±12.3% in males and females respectively. Most of the radioactivity remained in the carcasses (less tissues) (58.1±28.7% and 58.8±19.1% for males and females respectively). Measurements of the residual radioactivity in twelve tissues removed from animals seven days after dosing with either 1 or 25 mg/kg ^{14}CHCN indicated that the tissue concentrations were very low with the exception of fat. It should be noted here that although it is not entirely clear, it appears that the tissues for 1 mg/kg ^{14}CHCN and for 25 mg/kg ^{14}C-cyclopropyl were stored for approximately three years at -20°C at which time the ^{14}C residues analysis was conducted.

Excretion Studies With Bile Duct Cannulated Rats

Studies with bile duct cannulated rats dosed orally with ^{14}CHCN showed that there was some excretion of radioactivity via the bile. However, with these rats, the total amounts of radioactivity excreted in the urine and bile were significantly less than the amounts excreted by intact rats administered the same dose. When replacement bile was given to bile duct cannulated male rats, the amounts of radioactivity excreted in both the urine and the bile doubled, suggesting that cyhalothrin is absorbed with the fats of the oil formulation used and that the presence of bile greatly enhances its absorption when administered orally.

Excretion Studies With ^{14}C-Cyclopropyl

As with ^{14}CHCN, most of the administered single oral doses of ^{14}C-cyclopropyl to male and female rats were excreted in the urine and the feces; however, at a much slower rate. Less amounts were excreted in the urine than with ^{14}CHCN, but comparable amounts were excreted in the feces. Again, no detected $^{14}CO_2$ was excreted in exhaled air, only 1-3% of the dose was detected in the carcasses of the rats after seven days, and fat was the tissue with the highest amounts of residual radioactivity after seven days. Residues in fat were similar with both forms of ^{14}C-cyhalothrin indicating that the fat residues may be due to unchanged cyhalothrin.

Blood Concentrations of Radiolabelled Components

Following single oral doses of either 1 mg/kg or 25 mg/kg ^{14}CHCN, the blood concentrations of ^{14}C rose and peaked between four

and seven hours after dose administration. There was no difference between males and females. The mean blood ^{14}C profile at 1 mg/kg showed a two exponential decline with a terminal phase $t_{1/2}$ of about 11 hours. The profile at 25 mg/kg showed a single exponential decline with a $t_{1/2}$ of 11 hours.

Rats dosed subcutaneously with 1 mg/kg ^{14}CHCN showed very low blood concentrations with wide inter-animal variation. In males the mean peak concentration was achieved in approximately 20 hours and in females it was approximately four hours.

Blood Concentrations of Total Radioactivity and Unchanged ^{14}C-Cyhalothrin

In this study the concentrations of total radioactivity and unchanged cyhalothrin in the blood were measured in rats at various times following oral administration of either 1 mg/kg or 25 mg/kg ^{14}CHCN. The data show that the majority of the ^{14}C-labelled material in the blood does not correspond to the presence of intact cyhalothrin.

Chromatographic Analysis of Radioactive Material Excreted by Rats

Thin layer chromatography of ^{14}CHCN and its metabolites in both urine and bile indicated extensive metabolism to polar metabolites. No uncharged ^{14}CHCN was found in either urine or bile. The radioactive material which was quantitatively extracted from feces samples consisted of mainly uncharged compound together with small amounts of more polar metabolites. Treatment of the urine samples with beta-glucuronidase or aryl sulphatase produced no change in the chromatography patterns.

Chromatography of ^{14}C-cyclopropyl and its metabolites in the urine also showed that there was no unchanged compound in the urine. The metabolite patterns, however, were completely different from those derived from the ^{14}CHCN sample.

Discussion

The data from this study suggest that cyhalothrin is not completely absorbed when administered orally to rats and that when it is absorbed, it is extensively metabolized. Following oral dosing, there was a high proportion of unchanged compound excreted in the feces and there was an absence of intact compound in the bile. Urinary excretion was the major route of excretion following subcutaneous administration. In this case the ratio of urinary excretion to fecal excretion was approximately 2.5:1. Therefore, since up to 40% of an oral dose was excreted in the urine, an estimate of approximately 55% absorption was calculated for cyhalothrin. A small proportion of cyhalothrin was retained in the animals seven days after oral dosing, mostly in the fat. Over 50% of the dose was retained in the carcass seven days after subcutaneous dosing. This may have been due to retention in the subcutaneous fat. Blood concentrations in the subcutaneous studies were also considerably lower.

The metabolite patterns from cyhalothrin labelled in two separate positions were completely different, suggesting that metabolism includes cleavage of the ester to yield the corresponding cyclopropylcarboxylic acid and phenoxybenzyl derivatives.

005100

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DATA EVALUATION REPORT

STUDY TYPE: Metabolism 85-1

ACCESSION NUMBER: 073217

TEST MATERIAL: Cyhalothrin

SYNONYMS: ^{14}C-ICI 146,814: (R,S)alpha-cyano-3-phenoxybenzyl(±)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane carboxylate; ^{14}C-benzyl-, ^{14}C-cyclopropyl-ICI 146,814; ^{14}CHCN; batches 1R2 (19.52 microCi/mg) and 2R3 (10.49 microCi/mg)

STUDY NUMBER(S): ICI No. 146814 KMR 002/03

REPORT NUMBER: Protocol Number ICI 146814 MPH 01

SPONSOR: Imperial Chemical Industries PLC (ICI)

TESTING FACILITY: ICI Pharmaceuticals Division, Safety of Medicines Dept.

TITLE OF REPORT: Cyhalothrin: The Metabolism and Disposition of ^{14}C-ICI 146,814 in Rats: Part III - Studies to Determine Radioactive Residues in the Rat Following 14 Days Repeated Oral Administration

AUTHOR(S): M. P. Harrison

REPORT ISSUED: September 13, 1984

IDENTIFYING VOLUME: Volume II, Book 15 of 16 (Tab Reference 19C)

CONCLUSION: This study, in combination with the other two metabolism studies on the rat, is considered to be CORE GUIDELINE (see comments on Rat Metabolism Study: Parts I and II.

Classification: CORE GUIDELINE

MATERIALS AND METHODS:

Chemical

As stated in the previous study, two radiolabelled forms of cyhalothrin were used for this study, ^{14}CHCN and ^{14}C-cyclopropyl (see previous review). Both preparations were greater than 99.3% radiochemically pure with less than 0.18% of the trans isomers. Solutions were prepared by dissolving the compound in corn oil to give a solution of nominal concentration 0.5 mg/ml.

Animals

Twelve male and twelve female Alderly Park strain albino rats weighing between 200 and 250 g were used for the study. Six animals of each sex were assigned per treatment group.

Study Design

The first group was treated with one oral dose of 0.5 ml ^{14}CHCN per day by gavage for 14 days and the second group was treated with the same amount of -^{14}C-cyclopropyl. The total dose received by each rat over 14 days was determined by measuring the residual radioactive material in each dose vial and syringe and subtracting this value from the starting amount.

Urine and feces were collected separately every 24 hours at intervals of up to seven days after the final dose until the animals were killed. Two animals of each sex were killed at 48 hours and 120 hours after the last daily dose and tissues were removed for measurement of residual radioactivity. The remaining animals were killed seven days after the final dose and tissues were removed as before. The following tissues were removed and stored at -20°C prior to analysis: heart, brain, lungs, spleen, kidneys, gonads, brown fat, white fat, muscle, bone, blood and residual carcass. Urine, feces and tissues were prepared for liquid scintillation counting. The proportions of radioactive material in rat fat samples corresponding to cyhalothrin were determined by solvent extraction followed by HPLC using cyhalothrin standards.

Results

Excretion of Radioactive Material by Rats After Administration of ^{14}C-Cyhalothrin at 1 mg/kg

Over 90% of the cumulative total dose was eliminated in the urine and feces within seven days of the final dose. The overall recovery of radioactive dose for each group was 96% ± 1. Excretion by each route apparently reached constant rate after the first or second dose. The total elimination was rapid and very similar in each group. The overall excretion rate expressed as a percent of the average daily dose was 94%/day for males and 92%/day for females given ^{14}CHCN, and 91%/day for males and 92%/day for females given the ^{14}C-cyclopropyl label. There were significant differences in the relative proportions of dose excreted in urine and feces by rats given the two labelled forms of cyhalothrin and also between males and females given the same labelled form. With ^{14}CHCN, male rats eliminated equal amounts of radioactivity whereas females excreted a greater proportion in the urine. With ^{14}C-cyclopropyl, males excreted a much smaller amount of the dose in urine (30%) but females excreted a similar amount as with ^{14}CHCN.

Tissue Residues of Radioactive Material

Residual radioactivity was present in all tissues examined. Fatty tissue showed accumulation of material (white fat up to 88 times the blood level) although lungs, liver, kidney and gonads all had

concentrations 2 to 7 times the blood level (0.048 micrograms/ml). The radioactivity level in the latter tissues depleted considerably seven days post dosing period, although still higher than blood levels. White fat levels did not significantly decrease after seven days. White fat samples were analyzed by extraction and HPLC. With the exception of one animal, most of the radioactivity detected in the tissue was due to unchanged cyhalothrin. The exception was excluded because of poor recovery in the solvent extract.

Discussion

The distribution patterns and excretion rates of radioactively labelled cyhalothrin in rats following administration of multiple oral doses over a period of 14 days were very similar to those found in single dose studies. A large proportion of an oral dose was rapidly eliminated from the body. In the multiple dose study, excretion in urine was slightly higher than in the single dose studies, which may have been due to differences in absorption in normally fed animals as opposed to fasted animals. The data indicate that accumulation of unchanged cyhalothrin in the fat will occur on chronic administration. Otherwise, the compound is rapidly metabolized and excreted.

005100

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Secondary Reviewer: Edwin Budd
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DATA EVALUATION REPORT

STUDY TYPE: Metabolism 85-1

ACCESSION NUMBER: 073217

TEST MATERIAL: Cyhalothrin

SYNONYMS: (R,S)alpha-cyano-3-phenoxybenzyl (±)-cis-3-(Z-2-chloro-3,3,3-trifluoropropyl-enyl)-2,2-dimethylcyclopropane carboxylate; ^{14}CHCN; ^{14}C-cyclopropyl; ^{14}C ICI 146,814; ^{14}C-benzyl-ICI 146,814; ^{14}C-Cyclopropyl-ICI 146,814

STUDY NUMBER(S): Not given

REPORT NUMBER: Protocol Number MPH 01

SPONSOR: Imperial Chemical Industries PLC (ICI)

TESTING FACILITY: ICI Pharmaceuticals Division, Safety of Medicines Dept.

TITLE OF REPORT: Cyhalothrin: The Metabolism and Distribution of ICI 146,814 in the Rat: Part IV - Isolation and Identification of the Major Urinary Metabolites Derived From ^{14}C-Benzyl- or ^{14}C-Cyclopropyl-ICI 146,814 Following Oral Administration

AUTHOR(S): M. P. Harrison

REPORT ISSUED: March 23, 1983

IDENTIFYING VOLUME: Volume II, Book 15 of 16 (Tab Reference 19C)

CONCLUSION: This study, in combination with the other two metabolism studies on the rat, is considered to be CORE GUIDELINE (see comments on rat metabolism study: Parts I and II).

Classification: CORE GUIDELINE

MATERIALS AND METHODS:

Chemical

As in the previous two studies, two radiolabelled forms of cyhalothrin were synthesized and used for this study (^{14}CHCN and ^{14}C-cyclopropyl, see previous reviews). Both preparations were greater than 99.7% pure.

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Animals

Male and female Alderly Park rats (Alpk/Ap) were selected for the study.

Study Design

Animals were housed in metabolism cages throughout the study. For the study with ^{14}CHCN, six male and six female rats were administered approximately 12.5 mg/kg/day ^{14}CHCN orally for a period of eight days such that each animal received a total of 25 mg of the chemical. Urine and feces were collected every 24 hours up to three days after the last dose. Total urine samples were pooled for each sex, millipore filtered and acidified to pH 1.5 prior to analysis.

For the studies with ^{14}C-cyclopropyl, pooled urine samples from the previous study (where animals received 14 consecutive daily doses of 1 mg/kg ^{14}C-cyclopropyl) were combined with the residual material from the ^{14}CHCN label metabolism study mentioned in the previous paragraph. It was assumed that the residual material after removal of the ^{14}CHCN-labelled components would contain non-radioactive metabolites of which the cyclopropyl moiety would also be present.

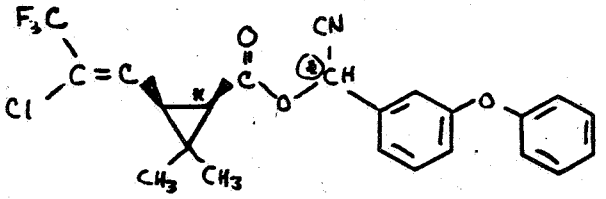
Thin layer chromatography (tlc) was conducted on the prepared urine samples using two solvent systems: chloroform : acetic acid 95:5 (v/v) and ethyl acetate : formic acid : water 70:4:4 (v/v). Radioactive areas on developed tlc plates were detected and quantified using a Berthold LB2722 Radiochromatogram Scanner.

^{14}C-components in urine were also analyzed and purified by reverse phase HPLC using either a Pye Unicam system incorporating an LC3 X P pump, LC X P controller, Altex U.V. detector (254 nm), Berthold LB503 Radioactivity Monitor and Commodore PET computer, or a Dupont 8800 system with a Berthold LB504 Radioactivity Monitor. The solvent systems were various compositions based on acetonitrile:water (+0.1% acetic acid). Purified samples were analyzed via mass spectrometry (electron impact mass spectra and fast atom bombardment mass spectra) and nuclear magnetic resonance spectroscopy.

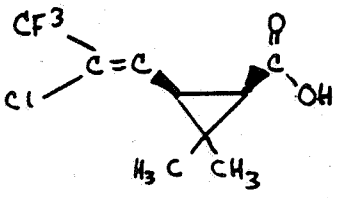
RESULTS:

The analyses conducted above showed that cyhalothrin is extensively metabolized in the rat prior to excretion. The following metabolites were identified in the urine:

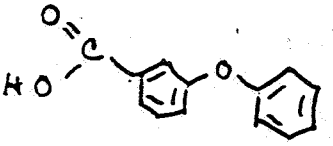
* ⑭ Alternative labels



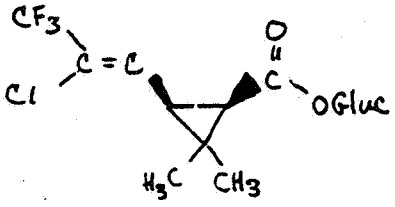
Cyhalothrin (Parent compound - not present in urine)



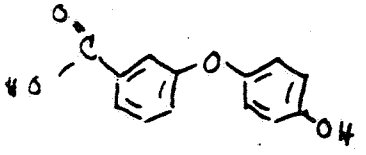
Cyclopropyl carboxylic acid



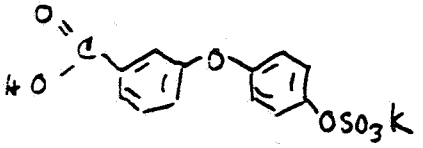
3-Phenoxybenzoic Acid



Glucuronide conjugate



3-(4'-hydroxyphenoxy)benzoic Acid



Sulphate Conjugation

DISCUSSION: (see previous metabolism studies on the rat).

005100

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DATA EVALUATION REPORT

STUDY TYPE: Metabolism Study 85-1

ACCESSION NUMBER: 073217

TEST MATERIAL: Cyhalothrin

SYNONYMS: (R,S)alpha-cyano-3-phenoxybenzyl (±)-cis-3-(Z-2-chloro-3,3,3-trifluoropropyl-enyl)-2,2-dimethylcyclopropane carboxylate; ICI 146,814; ^{14}CHCN; ^{14}C-cyclopropyl- and ^{14}C-benzyl-ICI; benzyl: batch 1R4; cyclopropyl: batches 2R3, 2R2 and 2R4

STUDY NUMBER(S): ICI Study Number 146814 KMD 005

REPORT NUMBER: Quality Assurance Unit (ICI) RA84174Q

SPONSOR: Imperial Chemical Industries PLC

TESTING FACILITY: ICI Pharmaceuticals Division, Safety of Medicines Dept.

TITLE OF REPORT: Cyhalothrin (ICI): The Disposition and Metabolism of (^{14})-ICI 146,814 in The Dog

AUTHOR(S): A. G. Fowkes, M. P. Harrison, T. R. Marten

REPORT ISSUED: September 17, 1984

IDENTIFYING VOLUME: Volume 11, Book 15 of 16 (Tab Reference 20C)

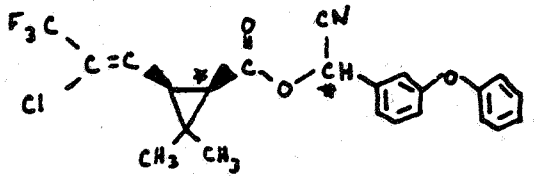
CONCLUSION: This study is classified as CORE MINIMUM because distribution studies were not conducted and a repeated dose absorption, metabolism, distribution and excretion study was not done.

Classification: CORE MINIMUM

MATERIALS AND METHODS:

Chemical Formulations

Two radiolabelled forms of cyhalothrin were used for these studies. The positions of radiolabelling are shown in the following figure:



The abbreviations ^{14}C-benzyl and ^{14}C-cyclopropyl are used to refer to the compound labelled at positions marked # or * respectively, as shown above. The labelled forms were synthesized by the Radiochemical Unit of the Drug Metabolism Section at ICI Pharmaceuticals Division. For the oral formulations, the radiolabelled compounds were diluted with hexane and corn oil and then the hexane was removed under N_2 at 37°C. For the intravenous studies, the hexane was removed first and the material was re-dissolved in absolute ethanol and diluted with saline. For the individual doses, the radiolabelled ICI 146,814 was diluted with non-labelled cyhalothrin from batch ADM 46156/80 (greater than 99% pure cis Z). The radiochemical dose to each animal was approximately 100 microCi for the oral studies and 50 microCi for the intravenous studies.

Animals

The same three male and three female Alderly Park Beagle dogs were used for all the single dose excretion studies. The dogs weighed approximately 15 kg each.

Single Dose Excretion Studies

The oral studies were conducted at dose levels of 1 and 10 mg/kg and the intravenous studies were conducted at a dose level of 0.1 mg/kg. Since the same animals were used for all of the studies, three weeks were allowed to elapse between each dosing. The studies were conducted in the following order: 1 mg/kg oral benzyl label, 1 mg/kg oral cyclopropyl label, 10 mg/kg oral benzyl label, 10 mg/kg oral cyclopropyl label, 0.1 mg/kg i.v. cyclopropyl label and 0.1 mg/kg i.v. benzyl label. The specific activities of each formulation were as follows: 1 mg/kg benzyl (7.78 microCi/mg), 10 mg/kg benzyl (0.64 microCi/mg), 0.1 mg/kg benzyl (30.5 microCi/mg), 1 mg/kg cyclopropyl (7.07 microCi/mg for males and 6.28 microCi/mg for females), 10 mg/kg cyclopropyl (0.69 microCi/mg) and 0.1 mg/kg cyclopropyl (30.8 microCi/mg). The animals were housed in individual metabolism cages. Urine, feces and cage washes were collected at 24-hour intervals from the time of dosing up to seven days. For the oral 10 mg/kg cyclopropyl label study, urine was collected at 0-8 and 8-24 hours in addition to the 24-hour intervals. Blood samples were collected at pre-dose, 1, 2, 4, 6, 12, 24 and

every 24 hours thereafter for up to 168 hours post dosing. For the intravenous studies, additional samples were taken at 0.5 and 8 hours. Samples were stored at -20°C until analyzed.

Determination of Total Radioactivity in Urine, Feces, Cage Washes, Plasma and Whole Blood

Samples were prepared for liquid scintillation counting. Feces and whole blood were prepared by sample oxidation. The CO_2 produced during oxidation was absorbed in 2-methoxyethylamine and mixed with a toluene based scintillant.

Analysis of Sample Radioactivity

Urine samples were either treated with various enzyme preparations; acidified to pH 1 or basified to greater than pH 10 and heated at 80°C for 30 minutes; or left untreated in pH 5 acetate buffer and analyzed further. The enzyme preparations consisted of combined beta-glucuronidase and sulfatase type H-1 (with and without 1,4-saccharolactone which inhibits beta-glucuronidase activity), sulphatase type V with 1,4-saccharolactone, and beta-glucuronidase type IX. Test incubations were conducted using phenolphthalein glucuronide and p-nitrocatechol as substrates. Feces homogenates were extracted with methanol.

The patterns of radioactivity in the urine and feces samples were analyzed by thin layer chromatography (tlc) using one of the following solvent systems: chloroform:acetic acid (95:5 v/v); ethyl acetate:formic acid (98%):water (70:4:4 v/v); toluene:n-hexane:acetonitrile:chloroform (200:100:2:5 v/v) or toluene:ethanol (2:1 v/v). Radioactive areas were located by autoradiography and scanned.

The ^{14}C-benzyl metabolites were extracted from urine samples from one male and one female dog from the 10 mg/kg oral study using n-hexane (male dog only) and ethyl acetate (both dogs) as extraction solvents. The metabolites were then analyzed by tlc using the second solvent system in the list above. Radioactive areas were excised and further purified by preparative tlc using the first solvent system followed by a third tlc in either ethyl acetate:methanol:water (13:2:1 v/v) or chloroform (saturated with 90% formic acid):diethyl ether (10:3 v/v). Samples were then further analyzed by mass spectrometry.

The ^{14}C-cyclopropyl metabolites were extracted from male urine from the 10 mg/kg oral study using ethyl acetate as the extraction solvent. The samples were analyzed by chromatographing and re-chromatographing with tlc using the second solvent system. Samples selected for further clean up were first chromatographed in chloroform:methanol:acetic acid (10:5:2 v/v) followed by preparative tlc in ethyl acetate:methanol:water (13:2:1 v/v) and rechromatographed again in the second solvent system. For the mass spectrometry, metabolites were compared with known reference materials where possible.

RESULTS:

Disposition of ^{14}C-Benzyl-ICI in the Dog

1 Mg/Kg Oral Dose

The diluted ^{14}C-labelled compound used was greater than 97% pure ^{14}C-ICI. Most of the radioactivity was excreted during the first 48 hours after dosing, mainly via the feces (in both males and females). The mean values at 48 hours were: 75.6% of total dose excreted (excluding cage washes), 24.8% in urine and 50.8% in feces. After 7 days the total excretion of radioactivity including cage washes amounted to 86.0 ± 4.5% (54.2 ± 3.9% in feces and 29.7 ± 7.3% in urine).

The radioactivity in whole blood was found to be attributable to the radioactivity in plasma. Plasma concentrations of radioactivity rose rapidly and peaked between 2 and 12 hours post dose. Three dogs gave secondary peaks at 12 hours while others showed a delayed fall in levels. The half-life of the decline in plasma levels was calculated to be 28 hours.

10 Mg/Kg Oral Dose

Excretion rates were similar to the 1 mg/kg group. 68.8% of the radioactivity was excreted in the first 48 hours. Mean plasma levels peaked at 2 hours post dosing and again at 12 hours post dosing. The half-life of the decline in plasma levels was calculated to be 32 hours.

0.1 Mg/Kg Intravenous Dose

The diluted ^{14}C-labelled compound used was greater than 96% pure ^{14}C-ICI. Excretion patterns were different from those in the oral studies in that significant amounts of radioactivity were excreted over the first three days (as opposed to the first 48 hours) and that radioactivity was more evenly distributed between urine and feces in both males and females. The mean values at 72 hours for males and females combined were: 32.7% of the total dose in urine and 37.1% of the total dose in the feces. Approximately 83% of the dose was recovered in urine, feces and cage washes after 7 days.

Plasma concentrations fell rapidly until 4 hours after dosing and then rose to a peak at 12 hours. Thereafter levels fell again with a half-life of 33.6 hours.

Analysis of Radioactivity in the Urine

TLC analysis of 0-24 hour urine samples indicate that ^{14}C-benzyl-ICI is extensively metabolized in the dog. No parent compound was found in the urine. The following metabolites were identified by TLC and mass spectrometry: 3-phenoxybenzoic acid (3-PBA) and glucuronic acid conjugate, 3-(4-hydroxyphenoxy)benzoic acid and sulphate, N-(3-phenoxybenzoyl)-glycine and two unknowns.

Analysis of Radioactivity in Feces

TLC of methanol extracts of feces samples indicated that for both dose levels 1 mg/kg and 10 mg/kg (oral), the main component excreted within the first 24 hours was unchanged cyhalothrin (74.4% of applied radioactivity for a male dog at 1.0 mg/kg and 93% for a female dog at 10 mg/kg). The sample from the male dog also contained three other components, two bands with similar R_F's to 3-PBA, one which was more polar, and one which was less polar than 3-PBA and may have been a metabolite of the intact ester. The female dog also had a component with a similar R_F to 3-PBA. Fecal samples taken from a female dog between 24 and 48 hours post dosing with 1.0 mg/kg contained only 8.5% unchanged compound and 5 or 6 other components. Samples taken from another female dog between 0 and 24 hours post dosing with 0.1 mg/kg ^{14}C-benzyl-ICI intravenously showed a pattern very similar to the 24-48 hour samples from the 1.0 mg/kg dosed dog. Only 1.5% of the radioactivity present was from unchanged cyhalothrin. Five or six other components were present in similar amounts as the 1.0 mg/kg dog, one of which had a similar R_F to 3-PBA (39.9% of the dose).

Disposition of ^{14}C-Cyclopropyl-ICI in the Dog

1 Mg/kg Oral Dose

The diluted ^{14}C-labelled compound used was greater than 98% pure ^{14}C-ICI. Excretion patterns were similar to those with ^{14}C-benzyl-ICI in that most of the dose was excreted during the first 48 hours, mainly via the feces. There were no significant differences between males and females.

Again, the radioactivity in whole blood was found to be attributable to the radioactivity in plasma. Concentrations in plasma peaked at four hours post dose and then fell, rapidly at first and then more slowly.

10 Mg/kg Oral Dose

Oral administration at this dose had an emetic effect on several dogs, which were subsequently excluded from the data. Two of the dogs lost greater than 10% of the dosed radioactivity. There was some difficulty in obtaining fecal samples; however, excretion of radioactivity still appeared to occur predominantly within the first 24 hours after dosing. In females, 2/3 dogs failed to produce feces, which delayed excretion somewhat. Concentrations in plasma peaked at 12 hours and subsequently declined.

0.1 Mg/kg Intravenous Dose

Radioactivity was excreted rapidly via both urine and feces in approximately equal amounts. The mean total recovery over 7 days was 81.9% with 40.0% in the urine and 38.7% in the feces. The balance was in the cage wash. Concentrations in plasma fell rapidly after dosing.

Analysis of Radioactivity in the Urine

Analysis by TLC and mass spectrometry indicate that this part of the molecule is extensively metabolized. At least twelve metabolites were identified in the urine, some present in both the free form and the conjugated form. There was a variation in the pattern of the metabolites which was dependent upon dose level, route or sex.

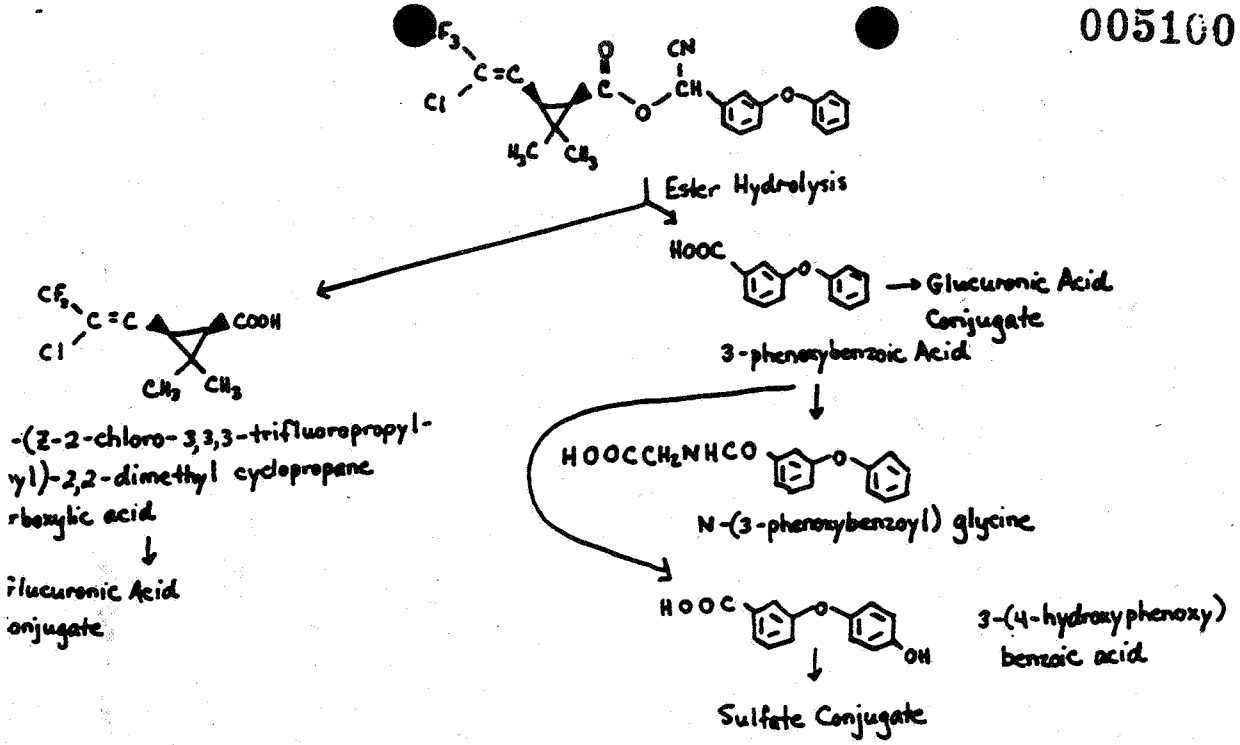
Analysis of Radioactivity in the Feces

At both dose levels 1 mg/kg (oral) and 10 mg/kg (oral), the major component was unchanged cyhalothrin which was mostly excreted during the first 24 hours. Between 24 and 48 hours, 3-5 other components were observed as well, two chromatographing at R_F 0.56 and two more polar components chromatographing at R_F 0.25 and at the origin. Samples were not taken for the 10 mg/kg dose level beyond 24 hours. When ^{14}C-cyclopropyl-ICI was administered intravenously at a dose level of 0.1 mg/kg, the pattern was similar to the pattern observed with 1.0 mg/kg (orally) between 24 and 48 hours. Even less unchanged cyhalothrin was observed in the feces when the compound was administered intravenously (1.4% of the administered dose within the first 24 hours).

DISCUSSION:

Using the urinary excretion data from the intravenous studies and from the lower dose oral studies, the authors concluded that for the ^{14}C-benzyl label the absorption was 80% and for the ^{14}C-cyclopropyl label the absorption was 48%. The high dose oral studies could not be used for this purpose because of fecal contamination of the urine. The authors stated that the discrepancy in absorption rates was probably due to inter-animal variation. This plausible, but is not definitively proven in the study.

The metabolite patterns from each of the two radiolabelled cyhalothrin compounds were quite different from each other indicating extensive cleavage of the ester bond. Urinary metabolites from the ^{14}C-benzyl studies are listed in the results section of this review. There were up to seven metabolites isolated. Twelve metabolites were isolated from the ^{14}C-isopropyl studies. In the feces, a large proportion of the radioactivity was due to unchanged cyhalothrin. One metabolite was found to be common to both labelled studies. Because of its properties, it is thought to be a metabolite of the intact ester. The following figure depicts the identified metabolites of cyhalothrin in the dog:



Excretion in all studies was rapid in both urine and feces, nearly all of it within 48 hours. The difference between the amount of unchanged compound found in the feces in the oral studies versus the intravenous studies was so pronounced that it appears that absorption of the compound is incomplete.

The rat studies indicate that some of the compound is retained in the fat and released slowly. If this is the case with the dog study, then it would partly explain the lack of complete recovery of radioactivity from the initial dose.

005100

wed by: Pamela Hurley
on 2 , Tox. Branch (TS-769C)
dary Reviewer: Irving Mauer
dary Reviewer: Edwin Budd
on 2 , Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity Test 84-2

ACCESSION NUMBER: 073205

TEST MATERIAL: Cyhalothrin

SYNONYMS: (R,S)-alpha-cyano-3-phenoxybenzyl(+)-cis-3,3(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2-dimethylcyclopropane carboxylate; CTL reference number Y00102/010/005, CTL Code No. PP563; sample code ADM46156/80

STUDY NUMBER(S): Imperial Chemical Industries Study (ICI) Number YV0289

REPORT NUMBER: ICI Report Number CTL/P/665

SPONSOR: Imperial Chemical Industries Limited (ICI)

TESTING FACILITY: ICI Central Toxicology Testing Laboratory (CTL)

TITLE OF REPORT: Cyhalothrin: Results from the Salmonella Reverse Mutation Assay

AUTHOR(S): R. W. Trueman

REPORT ISSUED: August 3, 1981

IDENTIFYING VOLUME: Volume II, Book 3 of 16 (Tab Reference 10C)

CONCLUSION: This study is UNACCEPTABLE. The chemical should have been either tested at a higher dose level or justification for not doing so should have been given and the activity of the S-9 mix should have been verified.

Classification: UNACCEPTABLE

MATERIALS AND METHODS:

Cyhalothrin (90.2% pure by HPLC, cis/trans ratio 97.1/2.9) was tested in the Salmonella reverse mutation assay by the method of Ames et al. (1975) using TA 1535, TA 1537, TA 1538, TA 98, and TA 100 as the test strains. The rat liver S-9 mix was derived from AROCLOR 1254 - induced Sprague-Dawley rats. Negative and positive controls were tested concurrently with the test material. Negative controls consisted of a vehicle control (DMSO) and an "absolute" negative control (no solvent). 2-Aminoanthracene was used as a positive control for all strains when

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005100

tested with metabolic activation (i.e. with S-9 fraction derived from AROCLOR 1254 - induced rats). N-Methyl-N'-nitro-N-nitrosoguanidine, 4-nitroquinoline N-oxide, and 9-aminoacridine were used as positive controls for strains TA 1535 and TA 100, TA 1538 and TA 98, and TA 1537 respectively when tested without metabolic activation. The entire assay (with and without metabolic activation) was conducted on two separate occasions. The incubation period was either 3 or 4 days at 37°C (from the tables it appears that the first test was incubated for four days and the second test was incubated for three days). No explanation was given for this. Revertant colonies were counted using an electronic colony counter calibrated to count standard plates (accepted accuracy 90%). The authors set a positive response to be a two-fold or greater increase in the mean number of revertant colonies appearing in the test plates over and above the spontaneous reversion rate of the vehicle controls. In addition, evidence of a dose-response was considered necessary. Plating was done in triplicate for the test chemical and in duplicate for the positive controls. Five dose levels of cyhalothrin were tested: 4.0, 20.0, 100.0, 500.0, and 2500.0 micrograms/plate. Individual plate counts were reported per dose level as well as the mean and standard deviation and the ratio of the test/control.

RESULTS:

Cyhalothrin did not significantly alter the rate of reversion to histidine independence under the conditions of this study. The highest dose level, 2500 micrograms/plate did not appear to be cytotoxic to the strains used in the study. There was no discussion on the solubility of the test chemical in the vehicle used in the study. There may have been difficulty with the activity of the S-9 mix. In the first study, 2-aminoanthracene did not induce a significant positive response in TA 1535 (the ratio of mean test revertants over controls was 1.6), and the response of the same chemical in TA 1537 was only 2.4 fold over controls. The lack of response in TA 1535 may have been partly due to a higher than usual response in the negative controls without the S-9 mix. With S-9 mix, however, the negative control values were closer to normal. The positive control response was greater in the other test strains. In the second study, 2-aminoanthracene did not induce a significant positive response in TA 100 (the ratio was 0.8), and the response in TA 98 was only 2.1 fold over controls. Again, the response was greater in the other test strains. In both studies, the positive controls all induced a significant positive response in each of the test strains in the absence of metabolic activation, thus validating the activity of the test strains. In the second study, cyhalothrin induced an apparent positive response in TA 1535 at 2500 micrograms/plate. This was not validated by replica plating nor was it validated by the results from the first study. However, the negative control values for TA 1535 in the first study were higher than usual. This may have been due to the longer incubation period.

DISCUSSION:

This study is UNACCEPTABLE. There was no evidence of cytotoxicity at the highest dose level (2.5 mg/plate) and no discussion was given on the solubility of the test chemical in the vehicle used in the study. A test for cytotoxicity of the test chemical on the tester

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strains should have been done prior to commencement of the mutagenicity study. If the test chemical is not cytotoxic to the tester strains at levels above 5 mg/plate, then the highest dose level should generally be at least as high as 5 mg/plate. If the chemical is insoluble in the vehicle at the higher dose levels, then it should be tested up to the limits of solubility, and should be described as insoluble at the higher dose levels in the submitted study. In addition to the above points, there was some question concerning the activity of the S-9 mix. It did not allow for a positive response to be induced by all of the positive controls in all of the tester strains in either of the two studies reported. The S-9 mix should probably have been tested for specific activity as well as tested at different concentrations to ensure its activity.

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Secondary Reviewer: Irving Mauer
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Budd 7/2/85

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity Test 84-2

ACCESSION NUMBER: 073205

TEST MATERIAL: Cyhalothrin

SYNONYMS: (R,S)-alpha-cyano-3-phenoxybenzyl(±)cis-3,-3(Z-2-chloro-3,3,3-trifluoro-prop-1-enyl)-2,2 dimethyl-cyclopropane-1-carboxylate; CTL No. Y00102/010/005: Issue No. 24

STUDY NUMBER(S): SR0041

REPORT NUMBER: Central Toxicology Laboratory (CTL) CTL/P/664

SPONSOR: Imperial Chemical Industries PLC (ICI)

TESTING FACILITY: ICI Central Toxicology Laboratory

TITLE OF REPORT: Cyhalothrin: A Cytogenetic Study in the Rat

AUTHOR(S): Diana Anderson, C. R. Richardson, Ayleen Hulme, J. Morris, P. B. Banham, M. J. Godley

REPORT ISSUED: August 25, 1981

IDENTIFYING VOLUME: Volume II, Book 3 of 16 (Tab Reference 12C)

CONCLUSION: This study is INCONCLUSIVE. There are insufficient data to determine whether or not the dose levels were adequately high enough to provide a credible negative response or if the chemical reached the target tissue. In addition, the data should have been presented as numerical counts of chromosomal aberrations per cell as opposed to percentage of aberrant cells.

Classification: INCONCLUSIVE

MATERIALS AND METHODS:

The purity of the test material was 89.2% w/w cyhalothrin (there was no notation of the cis/trans ratio). The dosing solutions were formulated in terms of actual cyhalothrin content. Male Wistar rats, weighing between 200-315 g were used as test animals. Dose levels were selected from a preliminary range finding study. In the preliminary study (Appendix 5), rats received either a single dose by gavage of 100 mg/kg, 50 mg/kg,

or 10 mg/kg, or 4 consecutive daily doses of 30 mg/kg/day, 15 mg/kg/day, or 3 mg/kg/day. All animals were dosed at 1 ml/100g bw. A repeated dose "LD_{50}" value, used for determination of dose levels for the main study, was calculated to be 29.2 mg/kg/day, over four consecutive daily doses using Logit Analysis. Note: this was not a normal acute study.

In the main study, five groups of rats were tested per dosing and/or sacrifice schedule (two controls and three treated). There were eight animals per group and positive (ethyl methane sulphonate (EMS)) and vehicle (corn oil) controls were tested concurrently with the treated animals (controls had twelve animals/group). The experimental dose levels were set at 1.5 mg/kg, 7.5 mg/kg and 15 mg/kg (50% of repeated dose "LD_{50}" from preliminary study) body weight and the chemical was administered in Kraft Wesson 100% corn oil by gavage. All dosing solutions were dosed at 1 ml/100g body weight as was the vehicle control. For the positive control the dose levels were 300 mg/kg bw for the single dose study and 200 mg/kg bw for the consecutive daily dose study. Groups at each dose level were sacrificed at six and 24 hours after a single dose of the chemical and six hours after the last of five consecutive daily doses. The bone marrow samples were prepared according to the method of Sugiyama (1971) with slight modifications. Two hours prior to sacrifice, each rat received 3 mg/kg bw colchicine. Where possible, 50 cells from each animal were examined. Only cells with 40 or more centromeres were considered for analysis. Slides were stained with Giemsa. The data were transformed using a double arcsine transformation (Freeman and Tukey, 1950) and were statistically analyzed using either a one-sided Student's t-test or the Fisher Exact test, one-sided.

RESULTS:

Cyhalothrin was not found to induce chromosomal damage in rat bone marrow under the conditions of the study.

In the preliminary range finding study, the survival rates were as follows:

Dose (mg Cyhalothrin/kg/day)	Survival Rate
3 (4 doses in 4 days)	8/8
10 (1 dose)	8/8
15 (4 doses in 4 days)	8/8
30 (4 doses in 4 days)	3/8
50 (1 dose)	0/16
100 (1 dose)	0/16

These rates included animals which were moribund and suffering from extreme clinical effects from the compound. No further information was submitted on how long the observation period was for consideration of survival. Clinical abnormalities were only seen at the three highest doses: ataxia, unsteady gait, excessive salivation, ungroomed appearance, urinary incontinence and piloerection (100 and 50 mg/kg (1x) and 30 mg/kg/day (4x).

For the main study, the concentrations of cyhalothrin were within ± 15% of desired levels, with the exception of one batch, which was given to only one animal on day 5 (15 mg/kg bw). This animal received

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less than the desired dose on that day. Cyhalothrin was shown to be chemically stable in corn oil for at least ten days when tested at the two lower dose levels. The chemical was not found to induce chromosome damage in rat bone marrow under the conditions of the study. EMS produced a statistically significant increase in the proportion of cells with abnormalities with the single dose 24-hour kill (including gaps) and with the multiple dose six-hour kill (both including and excluding gaps) (one-sided Student's t-test on transformed data). It also produced a statistically significant increase in the proportion of animals with abnormalities other than gaps with the multiple dose six-hour kill (one-sided Fisher exact test).

DISCUSSION:

This study is INCONCLUSIVE. Several points concerning the study which should be addressed. First of all, a 48-hour kill was not conducted. Data at this time period would have picked up any cells that were delayed in their progression through the mitotic cycle. Since a multiple dose study was conducted at the same dose levels as the single dose study, data from the multiple dose study would probably have shown any abnormalities that would have been observed at 48 hours (unless the toxicity of the chemical interfered with the results). No mitotic indices were scored for any treatment level. Therefore, it was difficult to assess whether or not there was any depression of the bone marrow at any of the dose levels (although there was no indication of toxicity based on the observation that sufficient cells were available for cytogenetic analysis). The selected dose levels were based on a preliminary range finding study. The "LD_{50}" was calculated from a repeated dose study which is not a normal acute study. The highest dose level of the main study was one-half the repeated dose "LD_{50}", which appears to be a high enough dose, although no clinical abnormalities were observed at that dose level in either the preliminary study or the main study. It could be that the standard single dose LD_{50} may be a higher value, thus making the doses for the main study too low. The main question that arises concerning this data is, does the chemical reach the bone marrow, the target tissue? Tissue distribution data obtained from another report indicate that a very small amount of residual radioactively labeled cyhalothrin (or a metabolite) is present in whole bone seven days following either a single oral dose or multiple oral doses of the chemical in rats at levels of 1 mg/kg and 25 mg/kg (distribution and metabolism data submitted by same company). It is conceivable that some of the residual radioactivity may be in the bone marrow. However, this has not been definitively proven by the distribution study. Finally, there were no data on numerical (counts) of chromosome aberrations. Data were only given for the number of cells with a given abnormality. "Aberrations should be expressed as the frequency per cell and not as percentage of aberrant cells because different aberrations have different genetic consequences and dose relations" (Gene-Tox Program Preston et al. 1981. Mut. Research 87:149).

005100

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DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity Test 84-2

ACCESSION NUMBER: 073205

TEST MATERIAL: Cyhalothrin

SYNONYMS: (R,S) alpha-cyano-3-phenoxybenzyl (±)-cis-3,3-(Z-2-chloro-3,3,3-trifluoroprop-1-en)-2,2-dimethylcyclopropane carboxylate Batch No. 005, ICI Code No. Y00102/010/005

STUDY NUMBER(S): CTL Study Number RM 0171 (CTL=Central Tox. Lab., ICI)

REPORT NUMBER(S): CTL Report No. CTL/C/1081, Hazleton Report No. 2647-72/213

SPONSOR: Imperial Chemical Industries Ltd. (ICI)

TESTING FACILITY: Hazleton Laboratories Europe Ltd.

TITLE OF REPORT: Cyhalothrin: Oral (Gavage) Dominant Lethal Study in the Male Mouse

AUTHOR(S): Lorraine F. H. Irvine

REPORT ISSUED: July, 1981

IDENTIFYING VOLUME: Volume 11, Book 3 of 16 (Tab Reference 13C)

CONCLUSION: This study is INCONCLUSIVE. There were insufficient data presented to determine whether or not the MTD was appropriately selected or if the chemical reached the germinal tissue in mice. In addition, the route of administration for the positive control was inappropriate.

Classification: INCONCLUSIVE

MATERIALS AND METHODS:

The purity of the test material was 89.2% w/w cyhalothrin (there was no notation of the cis/trans ratio). The dosing solutions were formulated in terms of actual cyhalothrin content. The dose levels of cyhalothrin were selected from a preliminary range finding study performed at Hazleton Laboratories. The actual data from the preliminary study were not submitted. A summary of the preliminary study states that groups of sexually mature male mice were treated orally by gavage with 0, 5, 10, 20, 40 and 80 mg/kg/day cyhalothrin in corn oil daily for five days and then were observed for an

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additional 21 days. The maximum tolerated dose (MTD) was considered to be between 10 and 20 mg/kg/day. No other information or data were submitted. Ten mg/kg/day was used as the highest dose in the main study (no reason was given as to why this dose was selected as opposed to 15 or 20 mg/kg/day).

The male mice that were to be used in the main study were selected from a group of 170 males that were test mated prior to the dosing period. Each male was housed with two females for seven nights. Ten days after the mating period, the females were killed and examined. One hundred male mice were then selected on the basis of their fertilizing ability.

For the main study, the 100 male CD-1 mice were divided in to five groups of 20 animals. Four groups of animals were treated by gavage, once per day for five consecutive days at the following dose levels of cyhalothrin: 0, 1, 5, and 10 mg/kg/day in 10 ml/kg maize oil. The fifth group was treated with cyclophosphamide intraperitoneally, one time on the fifth day (200 mg/kg in 10 ml). This was the positive control. Three days following the last dose, 15 of the healthiest and most fertile males from each group were selected for mating. Two females were placed with each male for seven nights. At the end of this mating period, the females were removed and re-housed together and second sets of females were placed with each male for seven nights. This procedure was repeated each week until eight sets of females had been paired with each male. Ten days after removal from the male cages, the females were killed and examined for gross abnormalities. The ovaries and uteri were removed and examined for the following: normal (live) embryos, early intra-uterine deaths and late intra-uterine deaths. At the end of the eight week mating period, the males were killed and examined macroscopically. Statistical analyses were performed using either a Fisher's exact test, a binomial approximation to Fisher's exact test, or a chi-squared test for equality of proportions.

RESULTS:

Cyhalothrin was not found to increase the frequency of dominant lethal mutations under the conditions of this study. There was no effect of treatment with cyhalothrin on pregnancy index in any mating week.

In the preliminary range finding study, there were mortalities at the top dose and evidence of pyrethroid toxicity with a dose-related increase in severity at doses of 10 mg/kg and above. The MTD was considered to be between 10 and 20 mg/kg/day. In the predose mating study, only 94 males satisfied the criteria of selection for the main study (that both females with which the selected male had mated were pregnant and that each had not more than two intra-uterine deaths in the litter). The six males needed to complete the 100 chosen for the main study were selected from those males that fertilized only one female but the resulting litter had no intra-uterine deaths. The results of these predose mating studies were presented in Appendices 4 and 5. In the main study, one male in the 5 mg/kg/day group appeared hunched and showed abnormal gait, ruffled fur, and ocular discharge on day 4 of the dosing period. It was removed from the study. No other mortalities occurred in either the cyhalothrin-treated males or in any of the females selected for mating. Towards the end of the mating period (weeks 7-9),

six males in the positive control group either died or were killed in moribund condition. Death or morbidity was considered to be related to treatment with cyclophosphamide. During the dosing period, there was a high incidence of male animals showing ruffled fur in the 10 mg/kg/day group and to a lesser extent in the 5 mg/kg/day group than in the control group. There was no indication of an effect of treatment with cyhalothrin for the remainder of the study (including macroscopic lesions). There was a higher incidence of clinical changes, particularly ruffled fur and morbidity in the positive control males. There was also a higher incidence of macroscopic lesions in these animals.

There was no effect of treatment with cyhalothrin on the proportion of females impregnated during any mating week. There were no significant differences in implantation rates, on the mean number of implantations per dam during any mating week, in the incidence of early intra-uterine deaths, in the proportion of pregnant females with any early deaths, in the number of early deaths per dam, or in the proportion of early deaths/implantations between the control groups and the cyhalothrin treated groups during any mating week. In addition, cyhalothrin had no effect on the incidence of late intra-uterine deaths, the proportion of pregnant females with any late deaths, the number of late deaths per dam, or on the proportion of late deaths/viable implantations when compared to control animals. The positive control induced significant effects in all these areas as would be expected from a positive control. The mutagenic index was not significantly increased over controls in any of the cyhalothrin treated animals. In the positive control group, the mutagenic index was significantly increased during the first three weeks of the mating period.

DISCUSSION:

This study is INCONCLUSIVE. There were insufficient data submitted to determine whether or not the MTD was correctly calculated. It appears that the highest dose may not have been high enough. Metabolism and distribution studies that were submitted in a separate report by the same company indicate that a small amount of the chemical reaches germinal tissues with single oral doses of 1 mg/kg and 25 mg/kg cynalothrin in rats. However, the metabolism and distribution of the chemical was not investigated in mice. Therefore, it is not clear that this chemical reaches the germinal tissues in this species. The positive control employed was for intraperitoneal injection studies. There should have been a positive control for an oral study. In general, the study was well conducted, however, and appropriate good laboratory practice methods were employed, animal husbandry and randomization procedures were well performed, animal identification and tracking were carefully monitored, and the dosing solutions were analyzed for stability and concentrations of the test chemical.

005100

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DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity Test 84-2

ACCESSION NUMBER: 073205

TEST MATERIAL: Cyhalothrin

SYNONYMS: (R,S) alpha-cyano-3-phenoxy benzyl (+)-cis-3,3(Z-2-chloro-3,3,3-trifluoroprop-1-en)2,2-dimethylcyclopropane carboxylate, CTL (ICI Central Toxicology Laboratory) Code No. PP563, CTL Reference No. Y00102/010/005

STUDY NUMBER(S): Not given

REPORT NUMBER: CTL/C/1030

SPONSOR: Imperial Chemical Industries Ltd. (ICI)

TESTING FACILITY: Huntingdon Research Centre

TITLE OF REPORT: Cell Transformation Test for Potential Carcinogenicity of Cyhalothrin

AUTHOR(S): Margaret Richold, Jeffrey A. Allen, Alison Williams, Sandra J. Ransome

REPORT ISSUED: February 10, 1981

IDENTIFYING VOLUME: Volume 11, Book 3 of 16 (Tab Reference 11C)

CONCLUSION: This study is INCONCLUSIVE. The results were erratic, a more detailed description of the protocol should have been submitted and the test should have been repeated, especially in light of the erratic results.

Classification: INCONCLUSIVE

MATERIALS AND METHODS:

Cyhalothrin was tested in a cell culture transformation assay based on that of Styles 1977. The study was divided into two parts. In the preliminary toxicity test, the chemical was tested at levels of 0.1, 1, 10, 100, and 1000 micrograms/ml in BHK21 C13 cells (baby hamster kidney cells clone 13). The number of colonies were counted five days after exposure to the chemical. Based upon the results of the preliminary

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toxicity test, the following dose levels were selected for the main study: 1) without rat liver S-9 mix: 1000, 750, 500, 250 and 50 micrograms/ml; 2) with rat liver S-9 mix: 5000, 4000, 3000, 2000 and 1000 micrograms/ml. DMSO was used as the solvent and the positive controls were 4-nitroquinoline-N-oxide (4-NQO) (0.1, 0.05, 0.025, 0.0125 and 0.00625 micrograms/ml) and p-dimethylaminoazobenzene (butter yellow) (400, 200, 100, 50 and 25 micrograms/ml). Untreated cells were seeded onto agar plates at concentrations of $5x10^5$, $2.5x10^5$, $1.25x10^5$ and $0.625x10^5$ cells/plate to produce negative control cultures which simulated 100%, 50%, 25% and 12.5% survival, so that treated cultures may be compared to negative control cultures with similar viable cell densities. Ability to grow in soft agar was the criteria used for determination of cell transformation. The incubation period was 20 days. Colonies greater than 450 micrometers were counted.

RESULTS:

When tested in a cell transformation assay in BHK21 C13 cells in the absence of metabolic activation, cyhalothrin induced an inconclusive response. The chemical did not induce a significant response when tested in the presence of metabolic activation.

Two LD_{50} values were obtained after treatment with cyhalothrin, both with and without metabolic activation. Without the S-9 mix, the LD_{50} values were 613 and 938 micrograms/ml. With the S-9 mix, they were 3063 and 4844 micrograms/ml. At 613 micrograms/ml (without S-9), the transformation frequency was 34 and at 938 micrograms/ml it was 26. These values were extrapolated from a graph. The actual numbers of transformed colonies/dish were counted at 750 micrograms/ml. In this case, the transformation frequency was inconsistent and peaked at approximately 750 micrograms/ml (transformation frequency of 66 or average of 14 transformed colonies per dish) and then decreased as the concentration of the chemical increased beyond the second LD_{50}. For negative controls the transformation frequency was zero at the equivalent cell viability of 50%, increased to 80 (10 transformed colonies/dish) at the equivalent viability of 25% and to 560 (35 transformed colonies/dish) at the equivalent viability of 12.5%. In the presence of S-9 mix, the transformation frequencies were five and eight at 3063 and 4844 micrograms/ml respectively. Actual values at 3000 and 4000 micrograms/ml were one transformed colony/dish (tranformation frequency of four) and two transformed colonies/dish (transformation frequency of 26) respectively. The negative control value at the equivalent cell viability of 100% was two and at the equivalent viability of 50% was 52. For the positive controls, 4-NQO gave a significant positive response without metabolic activation. Butter yellow, however, although it produced a transformation frequency that was 20 times the transformation frequency of the 100% survival negative control cultures, did not maintain the increase in transformed colonies at high concentrations. There was no consistent dose-response.

DISCUSSION:

This study is INCONCLUSIVE. Although the contracting laboratory stated that the results of the cell transformation test on cyhalothrin without metabolic activation was positive, the results were actually inconclusive because of an erratic increase in the numbers of transformed colonies (0,0,2,14,3) with increasing dose and because of an inconsistent dose-response in transformation frequency. This also occurred in the studies using the S-9 mix although the results were not statistically significant. A more complete description of methods should have been provided. The test should have been repeated, especially in light of the erratic results.

Tox Chem No. 271F- Cyhalothrin File Last Updated 01/02/86 Current Date 01/02/86

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute oral-rat/ICI Ltd. Cntrl. Tox. Lab/# AR0329 6/22/81	Cyhalothrin CTL Ref. # Y00102/006/001 94% pyrethroid 97% cis-isomer	073203	LD_{50}:243 (183-312) mg/kg for males & 144 (100-320) mg/kg for females	II	Minimum
Acute oral-mice/ICI Ltd. Cntrl. Tox. Lab./# AM1859; 6/22/81	Cyhalothrin 90.8% pyre-throid, 98% cis-isomer	073203	LD_{50}:36.7 (17.4-58.1) mg/kg for males & 62.3 (40.1-80.4) mg/kg for females	I	Minimum
Acute oral-g.pigs/ICI Ltd. Cntrl. Tox. Lab/# AG1860; 2/22/81	Cyhalothrin 90.8% pyre-throid, 98% cis-isomer	073203	LD_{50}:greater than 5000 mg/kg for males (females not tested)	IV	Supple-mentary
Acute oral, acute de-layed neurotox. - hens/ Huntingdon Res. Cntr./# JX0081; 2/1/82	Cyhalothrin 91.3% pyre-throid, 97.7% cyhalothrin batch ADM46110 /80	073203	LD_{50} greater than 10g/kg. No signs of clinical or histopath. signs of neurotoxicity	IV	Minimum
Acute dermal-rat/ICI Ltd., Cntrl. Tox. Lab./ #CR0353; 6/22/81	Cyhalothrin 90.8% pyre-throid, 98% cis-isomer	073203	LD_{50} greater than 1000mg/kg for both sexes.	II	Minimum
Acute dermal-rabbit/ICI Ltd., Cntrl. Tox. Lab./ #CR0354; 6/22/81	Cyhalothrin 90.8% pyre-throid, 98% cis-isomer	073203	LD_{50} greater than 2 ml/kg for both sexes.	III	Minimum
Acute i.p.-rat/ICI Ltd. Cntrl. Tox. Lab./#JR0097 6/22/81	Cyhalothrin 90.8% pyre-throid, 98% cis-isomer	073203	LD_{50}: 694 (460-999) mg/kg for male rats. Females not tested.	N/A	Acceptable

Study/Lab/Study # /Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Dermal Irritation-rat/ ICI Ltd. Cntrl. Tox. Lab # ER1604; 5/13/81	Cyhalothrin 90.8% pyrethroid, 98% cis-isomer	073203	No dermal irritation or sensitization at dose level of 0.1 ml/rat. PIS=0. Only females tested.	IV	Minimum
Dermal Irrit.-rabbit/ICI Ltd.,Cntrl. Tox. Lab./# EB1602; 5/13/81	Cyhalothrin 90.8% pyrethroid, 98% cis-isomer	073203	Mild dermal irritant in females. Males not tested. 0.5 ml undiluted cyhalothrin. PIS=0.85.	IV	Minimum
Eye Irrita.-rabbit/ICI Ltd.,Cntrl. Tox. Lab. #FB 1835; 2/19/81	Cyhalothrin 90.8% pyrethroid, 98% cyhalothrin	073203	Moderate eye irritant when 0.1 ml instilled into test eye. Max. mean scores 26+29 (unwashed, washed) Corneal opacity noted.	II	Minimum
Skin Sensit-g.pig/ICI Cntrl. Tox. Lab./#GG1881 6/5/81	Cyhalothrin 90.8% pyrethroid, 98% cis-isomer	073203	Cyhalothrin is a sensitizer under the conditions of the study. Male G. Pigs used.		Minimum
Ames Test/ICI Cntrl.Tox. Lab./#YV0289;8/3/81	Cyhalothrin 90.2%,cis/trans ratio:97.1/2.9	073205	Results were negative, however, the highest dose was not high enough. Tested at 4,20,100,500,2500 ug/plate		Unacceptable
Cell Transform./Huntingdon Res. Cntr./Report # CTL/C/1030; 2/10/81	Cyhalothrin Code # PP563	073205	Results were erratic. Inconclusive.		Inconclusive
Cytogenetic Study-rat/ ICI Cntrl. Tox. Lab./# SR0041; 8/25/81	Cyhalothrin 89.2% w/w	073205	Insufficient data to determine if doses were sufficiently high or if chemical reached target tissue. Data should have been presented as numerical counts of chromosomal aberrations/cell.		Inconclusive
Dominant Lethal - male mice/Hazleton Lab. Eur./ #RM 0171; 7/81	Cyhalothrin 89.2% w/w	073205	Insufficient data to determine if MTD was appropriately selected or if chemical reached target tissue. Route of admin. for positive con - trols inappropriate.		Inconclusive

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Subacute Dermal-rabbit/ ICI Cntrl. Tox. Lab.# RB 0021; 3/16/82	Cyhalothrin 90.2% w/v cyhal 97.1% cis & 2.9 % trans.	073203	10, 100, 1000 mg/kg/day, 6hr/day, 5d/wk, 15 applications. Possible systemic effects still under consideration. Irritation due to occlusive dressing. Animals may have had coccidiosis.		Reserved
28-day feeding -rat/ICI Cntrl. Tox. Lab./#PR 0397; 5/15/84	Cyhalothrin 89.2% w/w	073204	NOEL in females 10 ppm and LOEL 20 ppm. NOEL in males 20 ppm and LOEL 250 ppm under scope of study (reduction in body wt gain).		Acceptable for purpose tested
28-day feeding-rat/ICI Cntrl. Tox. Lab/#PR0418 2/3/82	Cyhalothrin Batch ADM/46156 80; 89.2% pure	073980	250 ppm cyhalothrin in diet for 28 days induced SER proliferation & incr. in APDM activ.; reversible after 7 days. Red. in bodyweight		Acceptable for purpose tested
28-day feeding-rat/ICI Cntrl. Tox. Lab/#PR0337 7/12/84	Cyhalothrin (89.0% pure) PP564 (84.0% pure)	073980	Cyhalothrin: males LOEL 20 ppm females NOEL 20 ppm (lowest dose) PP564 less toxic (no NOEL, lowest dose tested 500 ppm) -incr. in hepatic aminopyrine demeth. activ.		Acceptable for purpose tested
90-day feeding -rat/ICI Cntrl. Tox. Lab./#PR0405 7/24/81	Cyhalothrin 92.2% w/w pyrethroid, 96.8% w/w cyhalothrin ADM/46156/80	073204	LOEL 250ppm, NOEL 50ppm based on body weight gain.		Guideline
26-week oral study-dog/ Huntingdon Res. Cntr./ #PDD 395; 8/6/81	Cyhalothrin batches Y 00102 010/001 &002	073205	NOEL 1 mg/kg/day, LOEL 2.5 mg/kg/d. based on liquid feces. Performed prior to Subpart F Guidelines.		Guideline
Teratogenicity - rabbit Hazleton Lab. Eur. Ltd./ #RB 0169; 6/81	Cyhalothrin batch 005 89.2% cyhal.	073206	NOEL for maternal tox. 10 mg/kg/day based on decrease in body weight gain. LOEL 30 mg/kg/day. NOEL for teratogenicity + fetotox. 30 mg/kg/day. Levels tested: 0, 10, 30 mg/kg/day		Minimum

Study/Lab/Study #/Date	Material	Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratogenicity – rat/ Hazleton Europe/#RR 0170 6/91	Cyhalothrin batch #005, 89.25% pure w/w	073206	NOEL for maternal tox. 10 mg/kg/day, LOEL 15 mg/kg/day based on reduced body weight, food consump. NOEL for embryoleth., teratogen., fetotox.= 15 mg/kg/d. Levels tested: 5,10,15 mg/kg/day.		Minimum
Reproduction-3 gen. rat/ ICI PLC/#CTL/P/906 7/HD/ 007119; 5/13/84	Cyhalothrin batch ADM/46156 80. Purity 89.2% w/w.	073207-073209	NOEL for parental tox. 10 ppm. LOEL 30 ppm due to reduced body weight gain preceding pregnancy. Offspring: NOEL 10 ppm, LOEL 30 ppm due to decreased body weight gain during weaning period. 10,30,100 ppm tested		Guideline
Chronic Feeding -rat/ICI Cntrl. Tox. Lab.;#PRO414 6/27/84	Cyhalothrin batch ADM/46156 /80;92.2% (w/w) pyrethroid, 96.8% cyhalo-thrin.	073210-073213	LOEL 250 ppm, NOEL 50 ppm based on reduced bw. gain. No onco. activity Levels tested: 10, 50, 250 ppm.		Guideline
Chronic/Oncogenico/Hunt-ingdon Res. Cntr./#PMO 400; 5/31/84	Cyhalothrin batch YOO 102/ 010/005	073214-073216	Not oncogenic at levels of 20, 100 or 500 ppm. LOEL 500 ppm and NOEL 100 ppm based on decreased body weight gain.		Minimum
Metabolism-rat/ICI PLC Pharmaceut. Div./#146814 KMR 002/01 & 002/02; 9/17/84 & 10/8/81	Cyhalothrin radiolabelled in 2 positions. 99+% pure.	073217	55% oral absorption. Extensively metabolized when absorbed. After s.c admin., urinary/fecal excretion 2.5:1. Over 50% dose remained in carcass 7 days after s.c. dose. Metab. incl. cleavage of ester to cyclopropylcarboxylic acid & phenoxybenzyl deriv.		Guideline when taken with next 2 studies.
Metabolism-rat-ICI Pharm Div./# 146814 KMR 002/03 9/13/84	Cyhalothrin radiolabelled in 2 positions 99.8% pure.Nom. conc. 0.5 mg/ml	073217	Distribution patterns & excretion rates in multiple oral dose studies similar to single oral dose studies. Accumulation of unchanged compound in fat upon chronic admin. Otherwise, rapidly metabolized and excreted.		Guideline when taken with other 2 rat studies.

Tox Chem No. 271F-Cyhalothrin File Last Updated 01/03/86 Current Date 01/03/86

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Metabolism-rat/ICI Pharm. Div./# MPH 01 3/23/83	Cyhalothrin in 2 radiolabelled forms. 99.7+% pure.	073217	Cyclopropyl carboxylic acid, 3-phenoxybenzoic acid, glucuronide conjugate, 3-(4'-hydroxyphenoxy)benzoic acid and suphate conjugation identified in urine.		Guideline when taken with 2 previous studies.
Metabolism-dog/ICI Pharm Div./#146814 KMD 005 9/17/84	Cyhalothrin in 2 radiolabelled forms in corn oil or diluted with unlabelled batch ADM 46156 /80	073217	Absorption of C^{14} benzyl label 80% & of C^{14} cyclopropyl label 48%. Metabolite patterns different indicating extensive cleavage of ester bond. Seven metabolites identified for benzyl (urine) and 12 metabolites identified for isopropyl label In feces, large proportion radioactivity due to unchanged compound. Excretion in urine & feces rapid (nearly all in 48 hrs).		Minimum
Metabolism - rat/ICI PLC Cntrl. Tox. Lab/#UR0169 7/31/84	Cyhalothrin-^{14}C 92.2% pure, 98.6% radiochem pure	073981	Cyhalothrin taken up slowly by fat & released slowly. Rapidly released by blood, kidneys, liver. Rate of metab of both enantiomer pairs likely identical (i.e. PP321 & PP563)		Guideline with prev. studies.
Metabolism - rat; ICI PLC Cntrl. Tox. Lab/ #UR0178; 3/19/85	^{14}C-cyhalothrin 97.4% pure, ^{14}C-PP321 99%, ^{14}C-R157836 93.5% pure	073981	Absorption, distribution, metabolism and excretion patterns of PP321 and cyhalothrin following single dose of 1 mg/kg in male rat appear to be identical.		Guideline with previous studies

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CYHALOTHRIN 128867

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Pages 453 through 454 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

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____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

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Tox Chem No. 271F-Cyhalothrin | File Last Updated 01/24/86 | Current Date 01/24/86

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acceptable Daily Intake-EPA/OPP/HED/TOX	Cyhalothrin		ADI = 0.0050 mg/kg/day Safety Factor = 100 Dated: 1/24/86 Study: 3-Generation Reproduction (rat) NOEL: 0.5 mg/kg/day (10 ppm) Lab: ICI PLC Study No. CTL/P/906 7/HD/007119 Study Date: 5/13/84 Doc. No.: Not yet assigned		