US EPA ARCHIVE DOCUMENT

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR No. 0050580

MEMORANDUM

DATE: 03/31/2004

SUBJECT: 0F06092. Lambda-Cyhalothrin Toxicology Data Evaluation Records

PC Code: 128897 DP Barcode: D281492
Submission: S574546

TO: George LaRocca, Product Manager # 13
Insecticide Branch
Registration Division (7505C)

FROM: Pamela M. Hurley, Toxicologist Pamela M Hurley
Reregistration Branch 3
Health Effects Division (7509C)

THRU: Richard Loranger R. Loranger
Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

Background and Summary:

The Health Effects Division was asked to review and update all the major toxicology studies conducted with cyhalothrin and lambda-cyhalothrin for use in human health risk assessments in response to requested new uses on lambda-cyhalothrin.

Lambda-cyhalothrin is an enriched isomer of cyhalothrin. Cyhalothrin is a mixture of 16 stereoisomers. The eight trans forms comprise less than 5%. Four of the cis forms comprise less than 2%. Therefore, the majority of cyhalothrin comprises a mixture of 4 stereoisomers. Lambda-cyhalothrin is a combination of 2 of the 4 stereoisomers. The toxicology database for lambda-cyhalothrin includes studies conducted with cyhalothrin. Through the use of bridging data, the toxicology database for lambda-cyhalothrin has been completed using developmental, reproduction, chronic (rodent) and oncogenicity studies conducted with cyhalothrin. With the exception of the subchronic and developmental neurotoxicity studies, the toxicology database for

04/04

lambda-cyhalothrin, when bridged with cyhalothrin, is complete and there are no data gaps. The scientific quality is relatively high and the toxicity profile of lambda-cyhalothrin can be characterized for all effects, including potential developmental, reproductive and neurotoxic effects. The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to cyhalothrin.

The requirements (CFR 158.340) for food uses for lamba-cyhalothrin are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes[1]
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	-
No guideline	21-Day Inhalation	yes	yes
870.3465	90-Day Inhalation	no	-
870.3700a	Developmental Toxicity (rodent)	yes	yes[2]
870.3700b	Developmental Toxicity (nonrodent)	yes	yes[2]
870.3800	Reproduction	yes	yes[2]
870.4100a	Chronic Toxicity (rodent)	yes	yes[2,3]
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes[2,3]
870.4200b	Oncogenicity (mouse)	yes	yes[2]
870.4300	Chronic/Oncogenicity	yes	yes[2]
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—*In Vivo* Cytogenetics	no	yes
870.5xxx	Mutagenicity—*In Vitro* Cytogenetics	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	yes
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	yes
870.6200b	90 Day Neuro. Screening Battery (rat)	yes	no
870.6300	Develop. Neuro	yes	no
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	yes

Test	Technical	
	Required	Satisfied
Special Studies for Ocular Effects		-
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	

[1] The requirement for a nonrodent oral subchronic study for lambda-cyhalothrin is satisfied by a 26-week oral study conducted with cyhalothrin and a 52-week oral study conducted with lambda-cyhalothrin; both using dogs.

[2] The requirements for developmental, reproduction, chronic/oncogenicity rat and oncogenicity mouse studies for lambda-cyhalothrin are satisified by studies conducted with cyhalothrin.

[3] The requirements for a chronic rodent and an oncogenicity study in the rat are satisfied by a combined chronic/oncogenicity study conducted with cyhalothrin, using the rat.

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Data Evaluation Report

Chemical Lambda-Cyhalothrin

Study type Oral and Dermal Absorption and metabolism human not guideline

TXR No. 0050580

Citation

The metabolism and pharmacokinetics of Lambda-Cyhalothrin in Man. J.R. Marsh, B.H. Woolen & M.F. Wilks. Zenica. Report No. CTL/P/4208 Study No. XH2429. Jan 28, 1994. MRID 443338-01

11/4/97

Reviewed by Robert P. Zendzian Ph.D.
Senior Pharmacologist

Core Classification Acceptable nonguideline

Summary

Lambda-Cyhalothrin was administered to adult male volunteers. Phase I 1.25 mg/50cm^2 dermally to 6 individuals to determine direct dermal effects. No irritant effects were observed. Phase II 5 mg Lambda-Cyhalothrin orally per individual. Phase III 20 mg Lambda-Cyhalothrin/800 cm^2/individual on the back. Application site washed quantitatively at 8 hours. Subjects wore clean cotton T-shirt to 24 hours after dosing, second T-shirt 24 - 48 hours after dosing. T-shirts extracted and analysed for Lambda-Cyhalothrin. In phases II and III: 1. Venous blood samples collected pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 31 and 48 hours post dosing, 2. Complete urine collections 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-24 and then for 12 hour intervals up to 120 hours, 3. Feces samples collected for the periods of 0-1, 1-2, and 2-3 days oral dosing. Samples were analysed for three metabolites TFMCVA, 3-PBA and 4-OH3PBA. Dose of Lambda-Cyhalothrin followed quantitatively either by analyzing quantitatively for TFMCVA or 3-PBA plus 4-OH3PBA. Mean dose distribution following oral dose (as Lambda-Cyhalothrin) was:

TFMCVA	3PBA + 4OH3PBA	
56.71%	50.35%	Mean Urinary Excretion
+2.19%	+2.19%	Mean fecal excretion as LCH
58.90%	52.54%	Total excratory recovery
41.10%	47.56	Missing

Minimal oral abosrption 50.35 - 56.71%

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Mean dose distribution following dermal dose (as Lambda-Cyhalothrin) was:

TFMCVA	3PBA + 4OH3PBA	
0.122%	0.115%	Mean Urinary Excretion
<L Detc	<L Detc	Mean fecal excretion as LCH
0.122%	0.115%	Mean Total excratory recovery
49.90 %	49.90 %	Mean Swabs (wash)
24.34 %	24.34 %	Mean T-shirt 8-24 hrs
3.92 %	3.92 %	Mean T-shirt 24-48 hrs
78.16 %	78.16 %	Mean Total dose site recovery
78.282%	78.275%	Mean total recovery
21.718 %	21.282%	Missing

minimum dermal absorption 0.115 - 0.122%

Metabolites found near limit of detection in plasma from oral dose, none in RBC. Blood not analysed from dermal dose. See DER for detailed dose distribution with time.

Materials

Lambda-Cyhalothrin	CTL Y02537/240/001 purity 99.6%
Corn oil	CTL Y00790/004/181
WF1303 Blank formulation	CTL Y02537/246/001

Subjects

6 adult male volunteers. One volunteer was dropped from Phase II and III of the study due to failure to maintain urine collections during phase II.

"After explanation of the study purpose by the Responsible Physician, the subjects, who were all Zenecz employees, gave their written informed consent. They were free to withdraw from the study at any time. The subjects were healthy and during the week prior to the study they received a full medical examination including electrocardiography, lung function tests and standard hematological, biochemical and urine screening tests. The blood and urine tests were repeated after completion of the study."

Physical parameters for the subjects are summerised in table 1 from the report.

Study design

The study was carried out in 3 phases, Phase I a dermal tolerance test to Lambda-Cyhalothrin. Phase II oral administration to 5 volunteers and dermal administration to one volunteer. Phase III dermal dermal administration to four volunteers and oral administration to the volunteer dosed dermally in phase II. One volunteer was dropped from the study due to failure to maintain urine collections during phase II.

Dosing

Phase I 1.25 mg Lambda-Cyhalothrin per individual.
Phase II 5 mg Lambda-Cyhalothrin per individual.
Phase III 20mg Lambda-Cyhalothrin/800 cm^2/individual.

"Dermal Tolerence Test: The volunteers stripped to the waist and lay face down on a bed. A 50 cm^2 area of the central top half of the back was marked out using a template to define the corners of a rectangle. The dosing solution (0.25 ml containing 1.25 mg Lambda-Cyhalothrin) was applied with a Glison M250 positive displacement pipette as a series of drops which were spread evenly over the rectangle using the side of the pipette tip. After the application had dried volunteers put on a cotton T-shirt and the application site was inspected after 1, 3, 7 and 24 hours and any reported subjective sensations were recorded. Volunteers remained in the CPU for the first 7 hours."

"Oral dosing: Volunteers were asked to swallow the capsule containing the dosing solution, followed by 150 ml water. A light breakfast was provided 1 hour after dosing. Volunteers remained in the CPU for 24 hours and standard meals were provided during this period."

"Dermal dosing: The volunteers stripped to the waist and lay face down on a bed. A grid of 16 rectangles, each of 50 cm^2 was marked on the back of each volunteer using a plastic template. The dosing solution was applied with a Glison M250 positive displacement pipette as a series of drops which were spread evenly over each rectangle using the side of the pipette tip. Air blown from a hair dryer was used to prevent run off at the edges ofthe application site."

"Eight hours after dosing the subjects lay in a prone position while the application site wasa washed. This was done using one cotton wool swab for each of the 16 rectangles on the grid. Each rectangle was washed gently by rubbing with a cotton wool swab moistened with 2 ml of 3% Teepol in water. The sixteen swabs were pooled and retained for extraction and analysis for Lambda-Cyhalothrin."

"Following the washing procedure each volunteer was given a loose fitting cotton T-shirt to wear continiously until 24 hours after dosing. Another T-shirt was worn between 24 and 48 hours after dosing. The T-shirts were extracted and analysed for Lambda-Cyhalothrin."

Blood, urine and feces sampling (phases II and III)

"An indwelling intravenous cannula was fitted in a vein in the forearm and maintained by a heprin lock. A blood sample (10 ml) was taken from this cannula pre-dose, further samples (10 ml each time point) were also taken from this cannula at 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours post-dosing and by venepuncture (10 ml each time point) at approximately 24, 31 and 48 hours post dosing. Plasma and red blood cells were prepared from each sample by centrifugation then stored frozen."

"Complete urine collections were made for the periods 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-24 and then for 12 hour intervals up to 120 hours. At the end of each time period the total urine volume and urine pH were recorded and aliquots taken and stored deep frozen until analysed for Lambda-Cyhalothrin and its metabolites. Urine samples were also analysed for creatinine.... Feces samples were collected for the periods of 0-1. 1-2. and 2-3 days following oral dosing of Lambda-Cyhalothrin."

Lambda-Cyhalothrin and its metabolites were determined in red blood cells, plasma, urine and feces.

Results

Results are presented in figures 1-3 and tables 1-15 from the report.

Toxicity was not observed in any of the volunteers nor were there changes in the blood chemistry following dosing.

Mild paraesthesia of varying degrees was observed following dermal dosing (Table 3 from the report).

Excretion data following oral administration are presented in Tables 4-8 from the report and Figures 2 and 3.

Excretion data following dermal administration are presented in Tables 9-12 from the report.

Results of plasma analysis following oral administration are presented in Table 13 from the report. No 4OH3PBA was detected in the plasma. No Lambda-cyhalothrin or its metabolites was detected in red blood cell fractions.

Blood samples from the dermal dose were not analysed because of the low levels of metabolites excreted in the urine.

Discussion

Previous work has shown that absorbed Lambda-Cyhalothrin is completely metabollized to three major metabolites. (Figure 1) The first step is hydrolysis of the ester link yielding TFMCVA and 3-PBA. A portion of the 3-PBA is ring hydroxylated yielding 4-OH3PBA. Thus, a dose of Lambda-Cyhalothrin can be followed quantitatively either by analyzing quantitatively for TFMCVA or 3-PBA plus 4-OH3PBA.

Following oral dosing, the three metabolites are excreted rapidly in the urine (Figure 2) with mean half lives of 17 hrs TFMCVA, 14 hrs 3PBA and 15 hours 4OH3PBA. Considering the half lives and the 120 urine collection one may reasonabilly assume that at least 98% of the absorbed material was excreted. Feces was also collected and analysed. Therefore, if the assumption that the three matabolites are indicative of Lambda-Cyhalothrin passage through the body is correct one would expect the sum of urinary and fecal excrection to essentialy equal the oral dose. Mean total recovery of the dose is as follows. Data are from Table 7, excretion following oral doses.

TFMCVA	3PBA + 4OH3PBA	
56.71%	50.35%	Mean Urinary Excretion
+2.19%	+2.19%	Mean fecal excretion as LCH
58.90%	52.54%	Total excratory recovery

Whether one follows TFMCVA or the sum of 3PBA and 4OH3PBA 41.1 to 47.46 percent of the oral dose was not recovered. Either the dose was excreted as metabolites that were not determined and/or it was retained in the body perhaps as fat soluble metabolites. This is one of the problems that can occur in a metabolism study if one follows metabolites rather than a radiolabel. In general one would consider such incomplete recovery as unaceptable but the are data available to allow one to make acceptable assumptions about the missing material

There is an oral dosing study in the rat which used radiolabel material (Acc#073217). As part of this study male and female rats were dosed orally with radiolabeled test masterial at 1 mg/kg. Radiolabel distribution, as percent of dose was as follows;

	Males	Females
Urine	20.1%	36.5%
Cage Wash	9.7%	5.0%
Feces	61.4%	46.5%
Carcass	1.9%	3.3%
Total	93.2%	89.3%

The rat study accounts for essentially all of the dose and clearly shows that a major portion of the 'label' was excreted in the feces. Metabolite identification in the excreta was limited and far from complete. On the other hand there was very little residual radiolabel in the carcass. From this one can reasonally assume that the missing human material was excreted in the feces as additional and unidentified metabolites. This additional metabolism could well have been bacterial. On this basis one may reasonabily conclude that human urinary excretion of the three metabolites tested for essentially represents absorbed test material.

Determination of dermal absorption

The mean dose distribution following the dermal dose (as Lambda-Cyhalothrin) was:

TFMCVA	3PBA + 4OH3PBA	
0.122%	0.115%	Mean Urinary Excretion
<L Detc	<L Detc	Mean fecal excretion as LCH
0.122%	0.115%	Mean Total excratory recovery
49.90 %	49.90 %	Mean Swabs (wash)
24.34 %	24.34 %	Mean T-shirt 8-24 hrs
3.92 %	3.92 %	Mean T-shirt 24-48 hrs
78.16 %	78.16 %	Mean Total dose site recovery
78.282%	78.275%	Mean total recovery
21.718 %	21.282%	Missing

Human dermal absorption studies suffer from one major problem the inability to determine the complete distribution of the test material. A measured amount of material is applied to the test site for the exposure duration. The site is then washed quantitatively. This determines the quantity that did not enter the skin. Urine collection is the only determination of absorption, fecal excretion is usually impractical. Invariably some material is missing (in this case 21.282%-21.718%) and the question is was it absorbed or not. The solution to this problem is to administer an intravenous dose (100 percent absorbed) and determine the urinary excretion as percent of dose. This percent value is used to correct the urinary excretion of the dermal dose.

In this study Lambda-Cyhalothrin was administered orally and the excretion of three metabolites followed in urine and fecal excretion of the parent compound (converted from TFMCVA). As noted above, recovery was incomplete. This leaves one with the question of what to do with the urinary metabolite excretion following the dermal dose. Should this be considered indicative of dermal absorption or can a correction factor be used?

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The answer is simply no, a correction factor cannnot be used and the dermal absorption must be considered as at least 0.122%-0.115% of the applied dose.

Reference

Cyhalothrin: The disposition and metabolism of ^{14}C-ICI 146,814 in rats Parts II and II. M.P. Harrison & D.E. Chase. ICI 146,814 MPH 01, Oct 8, 1981, Sept 17, 1984. Acc# 073217

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US EPA ARCHIVE DOCUMENT

LAMBDA-CYHALOTHRIN **Dermal Penetration Study - Rats (§85-3a)**

Primary Reviewer: Robert P. Zendzian PhD
Senior Pharmacologist
Toxicology Branch, HED (7509C)

03/16/04

TXR No. 0050580

DATA EVALUATION REPORT

STUDY TYPE: Dermal Penetration - Rat
OPPTS Number: 870.7600 OPP Guideline Number: §85-3a

DP BARCODE: SUBMISSION CODE:
P.C. CODE: 128897 TOX. CHEM. NO.:

TEST MATERIAL (RADIOCHEMICAL PURITY): Lambda-Cyhalothrin (>98%)

SYNONYMS: (R+S)a-cyano-3phenoxybenzy)(IS+R)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-l-enyl)-2,2dimethyl cyclopropane carboxylate

CITATION: Lambda-cyhalothrin: in vivo percutaneous absorption study in the rat. S.P. McAsey & R.E. Lythgoe. ICI Central toxicology laboratory. Report No. CTL/P/3453. Study No. UR0356. 4 Nov 1991. MRID 44990402 Unpublished.

SPONSOR:

EXECUTIVE SUMMARY: In a dermal penetration study (MRID 44990402) Lambda-Cyhalothrin was applied to the back of young adult male rats. Dosing material was the formular concentrate, and1/10, 1/100 or 1/1000 aqueous dilutions thereof. These corrisponded to measured doses of 9.79, 0.99, 0.010 and 0.008 mg/ rat (0.979, 0.099,0.001 and 0.0008 mg/cm^2). For each dose groups of four rats were exposed for 0.5, 1, 2, 4, 10 and 24 hours.

Application of the formular concentrate caused paraesthesia in all rats several hours after dosing (approximately 39 mg/kg). No toxic effects were observed at lower doses. Percent absorbed was as follows:

Exposure (hours)	Percent Absorbed			
	0.8 ug/cm^2	10 ug/cm^2	99.9 ug/cm^2	979 ug/cm^2
0.5	1.26	0.24	3.30	5.72
1	1.57	0.35	0.42	9.82
2	1.56	1.23	1.76	6.85
4	1.64	0.56	1.38	10.24
10	3.20	1.48	2.15	16.36
24	3.95	3.46	4.36	15.89

Absorbed is the sum of carcass, urine, feces and cage wash.

The relatively high percent absorption at 979 ug/cm^2 was explained in the report as due to the paraesthesia which activity loosened the protective cover over the dosing site and resulted in spreading of test material over the rat's skin. This resulted in a relatively high percentage of the dose being found in the carcass (16% at 24 hours exposure). The report further noted " "A mean of 5.8% of the applied dose was present in the digested carcasses of four unused substitutes which were killed 24 hours after dosing followed by the removal of unwashed skin from the application sites." However, there were no individual animal observations of dose related toxicity and no individual report of analysis of the four 'unused substitues'. The explanation cannot be supported.

The pattern of absorption observed in this study is most likely due to dermal irritation caused by the formulation.

Study/report deficiencies

1. No post dose individual animal observations.
2. No individual report of analysis of the four 'unused substitues'

This study is classified as **acceptable/guideline** and may be used for risk assessment

MATERIALS AND METHODS

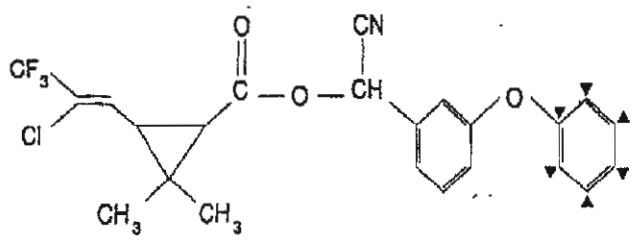
Test Substance Specification

Unlabeled Test Substance:

Lambda-Cyhalothrin, (R+S)a-cyano-3phenoxybenzy)(IS+R)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-l-enyl)-2,2dimethyl cyclopropane carboxylate
molecular weight 449.9
CTL reference Y02537/140 was used.
off-white powder
purity of 96.9%.
Source ICI Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire, UK.

Radiolabeled Test Substance:

[^{14}C]-Phenyl-labeled lambda cyhalothrin
CTL reference Y02537/160
specific activity 2.018GBq/mmol
radiochemical purity >98%.
Source ICI Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire, UK.



▶denotes position of radiolabel

blank formulation concentrate

CTL reference Y02537/161.
supplied by ICI Americas Inc. Western Research Center, Richmond, California, USA.

Water

deionized and sterile
CTL reference number Y04517/015.

Preparation and Analysis of Dosing Suspensions

The following is abstracted from the report
This study comprised four separate experiments, one for each of the four dose levels of test substance investigated. These dose levels corresponded to the formulation concentrate (120g active ingredient/1) and three aqueous dilutions thereof, nominally 1/10, 1/100 and 1/1000. For each preparation, the required amount of a stock solution of [^{14}C]-labeled test substance was transferred to a glass vial and the solvent evaporated under a stream of nitrogen. The amount of unlabeled test substance required to give the appropriate specific activity was added to the vial and mixed with the radiolabeled material. The required amount of blank formulation was then added and allowed to mix with the test substance, Finally, the required amount of deionized water was added and the suspension mixed by stirring. The quantities of each component used in each dose preparation are detailed in Appendix C of the report. For each of the aqueous dilutions this procedure was followed by sonication to assist dispersion.

The radioactivity content of each suspension was assessed prior to dosing. Throughout the dosing phase of each experiment the dosing suspension was stirred continuously. Weighed duplicate samples of each dose preparation were taken prior to, at intervals during and after dosing. The radioactivity concentration of each dose preparation was calculated as the mean of these determinations. The calculated concentration of test substance/g and the specific activity of [^{14}C]-labeled test substance in each dose preparation are also shown in Appendix C.

Samples of each dose preparation were also analyzed by tlc as described in Section 2.10. Lambda-cyhalothrin was shown to be stable in each dose preparation for longer than the period

of use in this study.

Animals and Dosing

Animal Supply: One hundred and forty-two male Wistar strain rats (Hsd/Ola:Wistar), approximately 6-8 weeks old, were obtained from HarlanOlac, Blackthorn, Bicester, Oxon, UK. These rats were acquired in groups of 35 or 36 for each experiment.

Preparation of Animals for Dosing: Approximately 24 hours before dosing the fur from the shoulders and back of each rat was shaved, After several hours the condition of the shaved skin was examined and only animals with undamaged skin were retained in the study -The shaved area of skin was washed with acetone to remove sebum and two 25.5mm internal diameter, 3mm thick nitrile rubber 'O' rings (Ash Instruments, Macclesfield, Cheshire, UK) were glued to the skin surface, one behind each shoulder, using cyano-acrylate glue (Loctite UK, Welwyn Garden City, Herts, UK). Those rats dosed at 1mg/rat, 0.1mg/rat and 0.01mg/rat received a further application of Zap-a-Gap glue (Pacer Technology, California, USA), to form a seal between the skin and each 'O' ring. The internal surface area of skin encompassed by each ring was approximately $5cm^2$, giving a total defined skin application area of approximately $10cm^2$ per rat. A Queen Anne plastic collar was secured around the neck of each animal and the rats were transferred to individual stainless steel metabolism cages (Modular Systems and Development Company Ltd, London, UK) and were allowed to acclimatise overnight.

Animal Dosing: Prior to dosing the rats were re-examined and only those with undamaged rings were used. Each of 30 rats was removed from its metabolism cage, its plastic collar removed and the body weight recorded. Using a 50 ul capacity positive displacement pipette, (Gilson Microman, Enichem, Luton, Bedfordshire, UK) and a disposable polypropylene tip, 40 ul of dose suspension was applied to the skin surface within one 'O' ring and was spread over the 5 cm^2 application area using the side and end of the pipette tip, which was retained for analysis. The applied suspension was allowed to dry. The application site was then protected by applying cyano-acrylate glue around the surface of the 'O' ring and superimposing a second similar rubber 'O' ring covered with a fine permeable nylon gauze (100gm bolting cloth, Lockertex, Warrington, Cheshire, UK), glued to the surface of the ring with Bostik (Bostik Ltd, Leicester, UK). This dosing procedure was then repeated for the second application site. The rat was identified by tail marking and the time of dosing each rat was recorded. The two pipette tips used to dose each animal were retained in one vial and were subsequently washed with ethanol to determine the amount of radioactivity retained after dosing. Weighed duplicate 40 ul samples of the dosing suspension were taken into volumetric flasks in a similar manner before the commencement of dosing, after the dosing period and at intervals of at least every fourth rat during dosing,

The amount of radioactivity applied to each rat was calculated as a moving average of the amount of radiolabel recovered from the volumetric flasks, taken before and after each group of up to four rats, plus the radioactivity retained in each polypropylene pipette tip used in sampling,

minus the amount of radioactivity retained on the pair of pipette tips used to apply the dose to each animal. The body weights of the animals used and the individual doses given are detailed in Appendix D of the report.

Following dosing, the Queen Anne collar was replaced and each rat was returned to its metabolism cage. Cards providing study number, rat identity, details of dosing including Project Licence, Licence Holder and Animal Licensee were attached to each cage. Urine and faeces were frozen upon excretion by collection over solid carbon dioxide for the duration of each experiment.

Skin Washing and Collection of Tissues

At 0.5, 1, 2, 4, 10 and 24 hours after dosing, four acceptable rats were selected and were anaesthetized with FLUOTHANE vapour. Animals with detached or badly damaged protective rings were deemed unacceptable and were excluded from the study.

For each rat, the nylon gauze covering both application sites was detached and retained in a single vial. The skin surface was carefully washed with a 3% aqueous solution of Teepol-L using natural sponge swabs (Boots The Chemist plc, Notts, OK). The skin surface was then rinsed with water using natural sponge swabs. All swabs used to wash and rinse each animal were retained in a single vial and were retained for radioactivity analysis.

Under deeper anaesthesia the animals were exsanguinated by cardiac puncture. The blood sample was retained in a heparinated vial and the weight of blood taken recorded. After weighing, a subsample was transferred to a second heparinized vial. The rubber 'O' rings were detached from the skin surface and were retained in the same vial as the nylon gauze covers for subsequent solvent extraction. The skin encompassing both application sites was then removed and transferred to a separate vial for each animal. The bladder was exposed and any residual urine was removed and added to the corresponding sample collected from the metabolism cage. Each carcass was transferred to a separate Polythene bag. With the exception of blood samples, which were stored at +4° C, all other samples were stored at -20° C prior to analysis.

Additionally, 4 of the unused rats dosed with the formulation concentrate were killed 24 hours after dosing. The unwashed skin at the application sites was removed and radioactivity measured in the residual carcasses.

Collection of Urine, Faeces and Cage Washes

Immediately following the removal of rats from their metabolism cages, the frozen urine and faecal samples were collected and the cages were washed with approximately 100ml of ethanol:water (1:1 v/v).

End of abstraction from the report

Results

Dose distribution, as wash and cover, dosed skin, absorbed and total recovered are summarized in Table A. Percent dose distribution by dose are presented in Tables 2, 4, 6 and 8 from the report. Blood and plasma concentration are presented in Table 9 from the report.

The results section of the report stated that "The application of the formulation concentrate to rat skin caused paraesthesia which was observed as an agitated behavior in all rats several hours after dosing." This was a dose of 9.79 mg/rat (979 ug/cm^2) or approximately 39 mg/kg. It was further stated in the discussion section that "No evidence of paraesthesia occurred in rats dosed with the aqueous dilutions of the formulation." Doses of 0.99, 0.01 and 0.008 mg/rat. However, nowhere in the report was there a section reporting observations of the test animals folowing dosing.

Percent absorbed was similar for doses of 0.8, 10 and 99 ug/cm^2 but was significantly increased at the high dose of 979 ug/cm^2.

Discussion

A number of unexpected results were observed in this study. In general, if a nonvolatile chemical does not effect the skin (damage it) the percent absorbed decreases with increasing dose. This is because dermal absorption is a saturatable process in that increasing the dose increases the absorption to a lessor extent until absorption becomes a constant. For this chemical percent absorption was similar for the three dilution doses and increased significantly for the formulation concentrate, the high dose. This is a pattern commonly found in chemicals which directly damage the skin but technical Lambda-Cyhalithrin is reported to be negative in dermal irritation studies.

However, the electronic Pesticide Directory for 2000 provides the following information that indicates that the formulation damages the skin.

"PROTECTIVE CLOTHING: Coveralls over a long-sleeved shirt and long pants, chemical resistant foot wear, chemical tight goggles and impervious gloves"

"HANDLING AND STORAGE CONDITIONS: Skin and eye protection when handling concentrate."

"FIRST AID Eyes, flush immediately with plenty of water. Skin, wash throughly with soap and water, If allowed to penetrate skin, apply fat based oil or cream. Water is highly polar and after a prolonged period of time will not decrease but may prolong irritation."

The relatively high absorption of the formular concentrate was explained as follows in the DISCUSSION section of the report.

"Interpretation of this study is complicated by the observation of paraesthesia following the application of lambda-cyhalothrin formulation concentrate to rat skin. The paraesthesia was accompanied by hyperactivity which caused the protective covers to become less firmly attached, which in turn lead to some observed leakage beyond the application site during the skin washing procedure. The consequence is that the absorption value of 16% for the formulation concentrate is believed to be an over-estimate, since nearly all of this apparently absorbed radioactivity (>14% of dose) was present in/on the carcass. This contrasted with a mean value of less than 6% in the carcasses of similarly dosed rats which were not given a skin wash. Furthermore, the levels of radioactivity in the blood of rats administered the formulation concentrate were lower than would be expected from the apparent absorption value above. The low recovery of applied radioactivity at the 24 hour time point is also attributed to the paraesthesia effect. This study is still valid since the observed paraesthesia was a direct consequence of the application of formulation concentrate to rat skin. No evidence of paraesthesia occurred in rats dosed with the aqueous dilutions of the formulation."

As noted above, nowhere in the report is there a section on observations of the experimental animals either individually or collectively. Thus we have only the statements in the results and discussion sections that paraesthesia occured at the high dose but not in the other three doses and that leakage was observed in the high dose.

The statement "This contrasted with a mean value of less than 6% in the carcasses of similarly dosed rats which were not given a skin wash." refers to a statement in the results section under the Formulation Concentrate (9.79mg/rat) section. "A mean of 5.8% of the applied dose was present in the digested carcasses of four unused substitutes which were killed 24 hours after dosing followed by the removal of unwashed skin from the application sites." However no individual animal data are given for this group of 'unused substitutes'.

The most likely explanation for the pattern of absorption seen in this study is direct damage to the skin produced by the formulation and manifested as dermal irritation.

The study is **acceptable/guideline** and can be used for risk assessment.

Table A. Lambda-Cyhalothrin.Summary of percent dose distribution following a single dermal dose to male rats. Values are means of four rats. MRID 44990402.

Exposure (hours)	Wash & Cover		Dosed Skin		Absorbed		Total Recovered	
	%	ug/cm^2	%	ug/cm^2	%	ug/cm^2	%	ug/cm^2
0.8 ug/cm^2								
0.5	84.6	0.68	12.81	0.10	1.26	0.01	98.7	0.79
1	89.1	0.71	11.19	0.09	1.57	0.01	102.0	0.82
2	82.9	0.66	16.54	0.15	1.56	0.01	101.0	0.81
4	95.7	0.77	10.22	0.08	1.64	0.01	107.7	0.86
10	85.2	0.68	10.73	0.09	3.20	0.03	99.2	0.79
24	69.7	0.56	23.79	0.19	3.95	0.04	97.5	0.78
10 ug/cm^2								
0.5	90.0	9.00	17.93	1.79	0.24	0.02	108.2	10.8
1	78.3	7.83	19.32	1.93	0.35	0.04	98.1	9.8
2	77.9	7.79	19.93	1.99	1.23	0.12	99.1	9.9
4	74.8	7.48	24.87	2.49	0.56	0.06	100.3	10.0
10	67.7	6.77	22.99	2.30	1.48	0.15	92.2	9.2
24	73.8	7.39	23.36	2.34	3.46	0.35	100.8	10.0
99.9 ug/cm^2								
0.5	85.9	85.8	11.22	11.21	3.30	3.30	100.5	100.4
1	92.7	92.6	8.25	8.24	0.42	4.20	101.5	101.4
2	90.6	90.5	12.46	12.45	1.76	1.76	104.9	104.8
4	83.7	83.6	15.78	15.67	1.38	1.38	100.8	100.7
10	80.4	80.3	19.67	19.65	2.15	2.13	102.2	102.1
24	82.2	82.1	16.95	16.93	4.36	4.36	103.6	103.5
979 ug/cm^2								
0.5	82.1	803.8	5.45	53.36	5.72	56.00	93.3	913.4
1	75.0	734.3	8.84	86.54	9.82	96.14	93.7	917.3
2	72.7	711.7	5.08	49.73	6.85	67.06	94.7	927.1
4	78.1	764.6	5.92	57.96	10.24	100.25	94.2	922.2
10	79.6	779.3	7.83	76.66	16.36	160.16	103.9	1017.2
24	54.2	530.6	10.64	104.17	15.89	155.56	80.8	791.0

Absorbed is the sum of carcass, urine, feces and cage wash.

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Page _____ is not included in this copy.

Pages 37 through 41 are not included in this copy.

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_____ 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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US EPA ARCHIVE DOCUMENT

D

DATA EVALUATION RECORD

LAMBDA-CYHALOTHRIN

Study Type: §81-8a, Neurotoxicity Screening Battery in Rats

Work Assignment No. 2-01-45 (formerly1-01-45) (MRID 44861510)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer
Kelley Van Vreede, M.S.

Signature: Kelley VanVreede
Date: 12/20/99

Secondary Reviewer
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 12/20/99

Program Manager
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 12/20/99

Quality Assurance
Steve Brecher, Ph.D.

Signature: Steven Brecher
Date: 12/20/99

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

LAMBDA-CYHALOTHRIN **Acute neurotoxicity (§81-8[a])**

EPA Reviewer: Pamela M. Hurley, Ph.D. Pamela M Hurley 3/26/2007
Registration Action Branch 2/HED (7509C)

Work Assignment Manager: Sanyvette Williams-Foy, DVM SWF 29 May 2001
Registration Action Branch 2/HED (7509C)
TXR No. 0050580

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Neurotoxicity [Feeding] - rat
OPPTS Number: 870.6200 OPP Guideline Number: §81-8a

DP BARCODE: D257779 SUBMISSION CODE: S565455
P.C. CODE: 128897 TOX. CHEM. NO.: 725C

TEST MATERIAL (PURITY): Lambda-cyhalothrin (87.7%)

SYNONYMS: Karate; α-cyano-3-phenoxybenzyl 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Brammer, A. (1999) Lambda-cyhalothrin: Acute neurotoxicity study in rats. Central Toxicology Laboratory, Cheshire, UK. Laboratory Project Identification Number: CTL/P/6151, Study Number: AR6699. April 13, 1999. MRID 44861510. Unpublished.

SPONSOR: Zeneca Ag Products, Wilmington, Delaware 19897

EXECUTIVE SUMMARY: In this acute oral neurotoxicity study (MRID 44861510), lambda-cyhalothrin in corn oil was administered in a single dose by gavage to 10 Alpk:AP$_f$SD rats/sex/dose at doses of 2.5, 10, or 35 mg/kg. Functional observation battery (FOB) and motor activity measurements were performed during week -1 (acclimation), day 1 (at approximately 7 hours post-dosing), day 8, and day 15. Five animals/sex/group were sacrificed by perfusion fixation and subjected to neuropathological examination.

No animals died during the study. No treatment-related changes in body weight, body weight gain, food consumption, motor activity, or gross pathology were observed. No differences relative to concurrent controls were observed in brain widths or dimensions. No treatment-related findings were observed in the 2.5 mg/kg group.

At 10 mg/kg, the following clinical signs were observed (# incidences): (i) increased breathing rate (males-5, females-5); (ii) slight piloerection (males-1, females-3); (iii) signs of urinary incontinence (1, females only); (iii) upward spine curvature (2, females only); and (iv) urinary incontinence (3, males only). None of the clinical signs were observed in the concurrent

controls. The following observations were noted during the day 1 FOB: slight signs of salivation (1, males only); slight signs of urinary incontinence (1, females only); and slight urinary incontinence (2, males only). None of the clinical observations were observed in the concurrent controls. These findings are not considered to be adverse and very few animals were observed to have effects.

At 35 mg/kg, clinical signs were similar in nature to those observed in the FOB and consisted of the following (# incidences): (i) slightly decreased activity (males-7, females-3); (ii) ataxia (males-5, females-5); (iii) increased breathing rate (males-16, females-13); (iv) piloerection (males-27, females-20); (v) reduced stability (males-2, females-4); (vi) sides pinched in (males-3, females-4); (vii) signs of salivation (males-6, females-11); (viii) signs of urinary incontinence (males-2, females-5); (ix) stains around mouth (males-4, females-3); (x) tip toe gait (males-5, females-3); (xi) ungroomed appearance (males-3, females-2); (xii) upward curvature of the spine (males-25, females-20); and (xiii) urinary incontinence (males-5, females-7). The following findings were noted during the FOB on day 1: (i) slightly decreased activity (2, males only); (ii) slight ataxia (males-3, females 2); (iii) extreme ataxia (2, females only); (iv) lacrimation (males-1, females-2); (v) slight piloerection (males-6, females-7); (vi) moderately reduced stability (1, females only); (vii) extremely reduced stability (1, females only); (viii) moderate salivation (1, males only); (ix) extreme salivation (males-1, females-1); (x) slight signs of salivation (males-6, females-4); (xi) moderate signs of salivation (1, females, only); (xii) sides pinched in (1, females only); (xiii) slight tip toe gait (males-4, females-1); (xiv) upward curvature of the spine (males-8, females-8); (xv) tremors (1, females only); (xvi) slight signs of urinary incontinence (males-1, females-1); and (xvii) slight urinary incontinence (males-3, females-6). Landing foot-splay values were decreased on day 1 (decreased 21%, p less than or equal to 0.05), and decreased (p less than or equal to 0.05 or 0.01) hindlimb grip strength was observed on days 1, 8, and 15 (decreased 19%, 31% and 32%, respectively) in males. Females displayed increased time to tail-flick on day 1 (increased 71%, p less than or equal to 0.05). In addition, one female was found to have minimal pigmentation of the olfactory bulb, but no other associated pathology. Minimal fiber degeneration of the sciatic nerve was observed in another female.

The LOAEL for this study is 35 mg/kg based on clinical observations indicative of neurotoxicity and changes in FOB parameters.

The NOAEL for this study is 10 mg/kg.

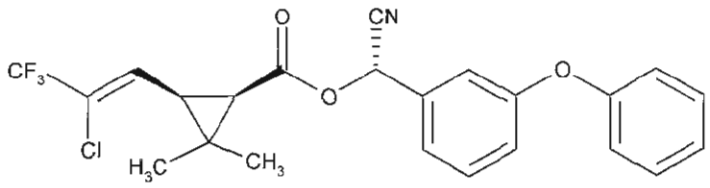
This acute oral neurotoxicity study is classified as **acceptable (§81-8[a])** and satisfies the guideline requirements for an acute neurotoxicity screening battery in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Lambda-cyhalothrin
   Description: Dark brown, solidified melt
   Lot/Batch #: P31 (BX E624) R119321
   Purity: 87.7% (w/w)
   Stability of compound: Stable when stored at room temperature for up to 15 days.
   CAS #: 91465-08-6
   Structure:



2. Vehicle: Corn oil

3. Test animals: Species: Rat
   Strain: Alpk:AP$_f$SD
   Age and weight at the start of dosing: At least 42 days old; 187-220 g (males), 143-181 g (females)
   Source: Rodent Breeding Unit, Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK
   Housing: Five/cage, in racks suitable for animals of this strain and weight range.
   Diet: CT1 diet (Special Diet Services Limited, Stepfield, Witham, Essex, UK), ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 22±3° C
   Humidity: 30-70%
   Air changes: At least 15 changes/hour
   Photoperiod: 12 hours light/12 hours dark
   Acclimation period: At least 2 weeks

B. STUDY DESIGN

1. In life dates - start: 10/05/98 end: 11/05/98

2. Animal assignment - The rats were randomly assigned (stratified by body weight and tail flick response) to the test groups shown in Table 1.

Table 1. Study design

Test Group	Dose (mg/kg)	Animals Assigned	
		Male	Female
Control	0	10	10
Low	2.5	10	10
Mid	10	10	10
High	35	10	10

3. Dose selection rationale - It was stated that dose levels for this study were based on the results of a previous study in the Alpk:AP$_f$SD rat. No further information was provided.

4. Treatment preparation and dosing - The test substance was weighed (adjusted for purity), diluted with corn oil, and stored at room temperature. Test formulations were warmed to 60°C prior to dosing, in order to sufficiently dissolve the solidified melt and ensure homogeneity. Homogeneity was not determined because the dosing formulations were solutions. Prior to the study, dose formulations of 0.25 mg/mL and 3.5 mg/mL were evaluated for stability when stored at room temperature for 13 and 15 days, respectively. Before the start of dosing, concentration analyses were performed on all formulations to determine test substance content.

   Results - Stability (as % of day 0): 13 days, 0.25 mg/mL, 100%; 15 days, 3.5 mg/mL, 100%

   Homogeneity/concentration analysis (range as % of nominal): 92.0-94.3%.

   The analytical data indicated that the variation between nominal and actual dosage to the study animals was acceptable.

5. Statistics - Body weight, food consumption, motor activity, time to tail-flick, landing foot splay, grip strength, and brain weight and dimension data were evaluated using analysis of variance and/or covariance (ProcGLM, SAS)

C. METHODS

1. Observations

   A. Clinical signs - Animals were examined carefully once a day.

   B. Functional observational battery and motor activity - All animals were subjected to a

functional observational battery (FOB) and motor activity measurement in week -1 (acclimation), day 1 (at approximately 7 hours post-dosing), day 8, and day 15. The FOB assessment included, but was not limited to, the following parameters:

Clinical observations

Lacrimation	Tremors	Abnormal behavior
Salivation	Abnormal movements	Stereotypes
Piloerection	Removal from the cage	Emaciation
Exophthalmus	Handling	Dehydration
Urinary incontinence	Arousal	Hypotonia/hypertonia
Diarrhea	Posture	Altered fur appearance
Pupillary response	Gait	Red or crusty deposits
Ptosis	Auditory response	
Convulsions		

Quantitative Assessments

Landing foot splay	Hindlimb grip strength
Forelimb grip strength	Tail-flick test

Motor activity was measured on the same day the FOB was conducted. The number of movements was tabulated for 10 intervals, each lasting 5 minutes.

C. Positive controls -Summaries were provided for two neurotoxicity studies performed on Alpk:AP and Alpk:APfSD rats to generate positive control data, validate the procedures of the performing lab, and prove inter-observer reliability in performing the FOB and assessing motor activity, neurotoxicity and behavioral effects. The chemicals used in these studies were acrylamide (12.5, or 25 mg/kg/day, administered in the diet for 29 days) and trimethyltin chloride (0.2, or 0.4 mg/kg/day, administered in the diet for 29 days).

Clinical signs of neuropathy such as piloerection and changes in motor activity were observed after administration of both chemicals. Tail erection, tiptoe gait, upward and downward curvature of the spine, pinched-in sides, abnormal gait, and reduced reflex responses were noted after dosing with acrylamide. Urinary incontinence, hunched posture, aggression in males, shaking, and clonic convulsions were noted after dosing with trimethyltin chloride. Histopathological evidence of nervous system changes were observed following administration of both compounds.

2. Body weight - Animals were weighed on days when the FOB was performed (week -1; and days 1, 8, and 15).

3. Food consumption - Food consumption was monitored throughout the study and

calculated as a weekly mean (g food/rat/day) for each cage.

4. Sacrifice and pathology - Five animals/sex/group were sacrificed by perfusion fixation and subjected to neuropathological examinations. The brain was removed, weighed, and measured. The following tissues were embedded in paraffin or ARALDITE®, sectioned, stained with toluidine blue or hematoxylin-eosin, and examined qualitatively:

Central Nervous System		
Brain (examined in traverse plane at 7 levels)	Spinal cord, cervical swelling (C3-C6)	Spinal cord, lumbar swelling (L1-L4)
Peripheral Nervous System		
Sciatic nerve	Sural nerve	Tibial nerve
Spinal root (C3-C6)	Dorsal root ganglion (C3-C6)	Gastrocnemius muscle
Spinal root (L1-L4)	Dorsal root ganglion (L1-L4)	Gasserian ganglion

II. RESULTS

A. Observations

1. Mortality - No animals died during the study.

2. Clinical signs - Selected clinical signs noted during the 15 day post-dosing period are presented in Table 2. Observations in the high-dose animals were similar in nature to those observed in the FOB and consisted of the following (# incidences): (i) slightly decreased activity (males-7, females-3); (ii) ataxia (males-5, females-5); (iii) increased breathing rate (males-16, females-13); (iv) piloerection (males-27, females-20); (v) reduced stability (males-2, females-4); (vi) sides pinched in (males-3, females-4); (vii) signs of salivation (males-6, females-11); (viii) signs of urinary incontinence (males-2, females-5); (ix) stains around mouth (males-4, females-3); (x) tip toe gait (males-5, females-3); (xi) ungroomed appearance (males-3, females-2); (xii) upward curvature of the spine (males-25, females-20); and (xiii) urinary incontinence (males-5, females-7).

   The following clinical signs were observed in the 10 mg/kg group (# incidences): (i) increased breathing rate (males-5, females-5); (ii) slight piloerection (males-1, females-3); (iii) signs of urinary incontinence (1, females only); (iii) upward spine curvature (2, females only); and (iv) urinary incontinence (3, males only).

   None of the clinical signs observed in the 35 mg/kg or 10 mg/kg groups were observed in the concurrent controls, however, the findings in a few animals at 10 mg/kg are not

considered to be adverse. There were no treatment-related clinical signs observed in the 2.5 mg/kg dose group.

Table 2. Selected clinical observations following acute dosing with lambda-cyhalothrin [a]

Clinical Observations	Males			Females		
	# incidences / 15 days			# incidences / 15 days		
	0 mg/kg	10 mg/kg	35 mg/kg	0 mg/kg	10 mg/kg	35 mg/kg
decreased activity, slight	0	0	7 (3)	0	0	3 (3)
ataxia	0	0	5 (2)	0	0	5 (1)
increased breathing rate	0	5 (5)	16 (8)	0	5 (0)	13 (5)
piloerection, slight	0	1 (1)	27 (10)	0	3 (2)	20 (8)
reduced stability	0	0	2 (2)	0	0	4 (2)
sides pinched in	0	0	3 (3)	0	0	4 (2)
signs of salivation	0	0	6 (6)	0	0	11 (6)
signs of urinary incontinence	0	0	2 (2)	0	1 (0)	5 (4)
stained around mouth	0	0	4 (3)	0	0	3 (2)
tip toe gait, slight	0	0	5 (1)	0	0	3 (2)
ungroomed	0	0	3 (2)	0	0	2 (2)
upward curvature of the spine	0	0	25 (9)	0	2 (1)	20(5)
urinary incontinence	0	3 (1)	5 (1)	0	0	7 (1)

a Data obtained from the study report Table 3, pages 36, 40-43, and 45-48; and Appendix 1 pages 159 through 178. Number of affected animals listed parenthetically; n=10. Discrepancies were noted by reviewers between individual and summary data (number of affected animals); only summary data were reported.

3. Functional observational battery - Treatment-related FOB clinical observations on day 1 post-dosing are presented in Table 3. The following observations were noted in the 35 mg/kg animals: (i) slightly decreased activity (2, males only); (ii) slight ataxia (males-3, females 2); (iii) extreme ataxia (2, females only); (iv) lacrimation (males-1, females-2); (v) slight piloerection (males-6, females-7); (vi) moderately reduced stability (1, females only); (vii) extremely reduced stability (1, females only); (viii) moderate salivation (1, males only); (ix) extreme salivation (males-1, females-1); (x) slight signs of salivation (males-6, females-4); (xi) moderate signs of salivation (1, females, only); (xii) sides pinched in (1, females only); (xiii) slight tip toe gait (males-4, females-1); (xiv) upward curvature of the spine (males-8, females-8); (xv) tremors (1, females only); (xvi) slight

signs of urinary incontinence (males-1, females-1); and (xvii) slight urinary incontinence (males-3, females-6). The following observations were noted in the 10 mg/kg animals: slight signs of salivation (1, males only); slight signs of urinary incontinence (1, females only); and slight urinary incontinence (2, males only). None of the clinical observations noted in the 35 mg/kg or 10mg/kg animals were observed in the concurrent controls. The findings at 10 mg/kg are not considered to be adverse. These FOB data were not subjected to statistical analysis. There were no treatment-related FOB clinical observations in any dose group on days 8 or 15.

Table 3. Selected FOB clinical observations (#incidences) in rats on day 1 post-dosing with lambda-cyhalothrin [a]

FOB Clinical Observations	Dose (mg/kg)							
	Males				Females			
	0	2.5	10	35	0	2.5	10	35
decreased activity slight	0	0	0	2	0	0	0	0
ataxia slight extreme	0 0	0 0	0 0	3 0	0 0	0 0	0 0	2 2
lacrimation	0	0	0	1	0	0	0	2
piloerection slight	0	0	0	6	0	0	0	7
reduced stability moderate extreme	0 0	0 0	0 0	0 0	0 0	0 0	0 0	1 1
salivation moderate extreme	0 0	0 0	0 0	1 1	0 0	0 0	0 0	0 1
signs of salivation slight moderate	0 0	0 0	1 0	6 0	0 0	0 0	0 0	4 1
sides pinched in	0	0	0	0	0	0	0	1
tip toe gait slight	0	0	0	4	0	0	0	1
upward curvature of the spine, slight	0	0	0	8	0	0	0	8
tremors	0	0	0	0	0	0	0	1
signs of urinary incontinence slight	0	0	0	1	0	0	1	1
urinary incontinence slight	0	0	2	3	0	0	0	6

a Data obtained from the study report Table 6, pages 59 through 64; n=10

Quantitative FOB findings are presented in Table 4. Landing foot-splay values were decreased in high-dose males on day 1 (↓21%, $p \leq 0.05$). Decreased ($p \leq 0.05$ or 0.01) hindlimb grip strength was observed on days 1, 8, and 15 in high-dose (↓19%, ↓31%, ↓32%) and low-dose (↓21%, ↓22%, and ↓26%) males. Forelimb grip strength was increased ($p \leq 0.05$) in low-dose males on days 8 and 15 (↑21% and ↑18%, respectively); however, the lack of dose-response suggests that this finding was not treatment-related. Furthermore, the increase in forelimb grip strength is contradictory to the decrease in hindlimb grip strength at the low dose; therefore, these findings at the low dose are of equivocal toxicological significance. High-dose females displayed increased time to tail-flick on day 1 (↑71%, $p \leq 0.05$). No other treatment-related differences were noted in FOB parameters in any of the treated groups.

Table 4. Selected quantitative findings observed during FOB performed on Alpk:AP$_f$SD rats treated with lambda-cyhalothrin.[a]

Dose (mg/kg)	Day			
	(week) -1	1	8	15
Landing Foot-Splay - Males				
0	46.1	66.7	70.0	62.0
2.5	45.4	64.0	69.6	69.3
10	48.5	61.9	70.8	67.8
35	47.5	53.0* (↓21%)	78.0	72.0
Grip Strength Hindlimbs - Males				
0	488	655	690	750
2.5	433	518* (↓21%)	540* (↓22%)	555* (↓26%)
10	653	590	578	643
35	595	528* (↓19%)	478** (↓31%)	513** (↓32%)
Time to Tail Flick - Females				
0	6.0	5.8	8.0	4.2
2.5	5.7	5.5	6.2	5.1
10	5.3	6.9	5.0	6.6
35	6.7	9.9* (↑71%)	7.6	5.0

a Data obtained from the study report Tables 7, 8, and 9, pages 77 through 80. Percentage change from controls is listed parenthetically.

* Significantly different from controls at $p \leq 0.05$.

** Significantly different from controls at $p \leq 0.01$.

4. Motor activity - No differences in overall motor activity were observed.

   The following interval data were statistically significant ($p \leq 0.05$ or 0.01), but considered non treatment-related because they were sporadic and/or incidental:

   - ↓61% in high-dose males during minutes 41-45, day 1
   - ↓78% in high-dose males during minutes 36-40, day 8
   - ↓47% in high-dose females during minutes 11-15, day 1
   - ↓57% in high-dose females during minutes 21-25, day 1
   - ↓60% in mid-dose males during minutes 46-50, day 1
   - ↓82% in mid-dose males during minutes 36-40, day 8
   - ↓72% in mid-dose females during minutes 26-30, day 15
   - ↓72% in low-dose males during minutes 36-40, day 8
   - ↓26% in low-dose females during minutes 6-10, day 15
   - ↓66% in low-dose females during minutes 21-25, day 15
   - ↑82% in low-dose females during minutes 16-20, day 1

B. Body weight and body weight gain - Decreased body weight (after adjustment for initial weight) was observed in high-dose males on day 8 (↓4%, $p \leq 0.05$). This change is considered minor and not treatment-related. No treatment-related changes in body weight were observed in males in the mid or low-dose groups, or in females in any group. Furthermore, there were no obvious treatment-related differences in body weight gain (as calculated by reviewers).

C. Food consumption - When compared to concurrent controls, high-dose males and females displayed decreased food consumption during week 1 (↓9-18%, $p \leq 0.05$). Due to the lack of correlating changes in body weight, decreased food consumption was not considered treatment-related. Food consumption in the mid or low-dose groups was unaffected by treatment.

D. Sacrifice and pathology

1. Brain weight and measurement - Increased brain width was observed in high-dose females (↑4%, $p \leq 0.05$). This change is minor and not treatment-related.

2. Gross pathology - There were no treatment-related gross pathological findings.

3. Histopathology - One high-dose female was found to have minimal pigmentation of the olfactory bulb. Minimal fiber degeneration of the sciatic nerve was observed in another high-dose female. No other microscopic abnormalities were noted in any of the other treatment groups.

III. DISCUSSION

A. Investigator's conclusions - Lambda-cyhalothrin, administered to rats in a single dose by gavage, was clinically neurotoxic at 35 mg/kg. The test compound at this dose caused minor changes in the FOB on the day of dosing which reversed by day 5. There were no pathological changes. The NOAEL for this study is 35 mg/kg due to the reversibility of the clinical effects.

B. Reviewer's discussion - In this acute oral neurotoxicity study, lambda-cyhalothrin was administered in a single dose by gavage to 10 Alpk:AP$_f$SD rats/sex/dose at doses of 2.5, 10, and 35 mg/kg. The analytical data indicated that the variation between nominal and actual dosage to the study animals was acceptable.

No animals died during the study. No treatment-related changes in body weight, body weight gain, food consumption, motor activity, or gross pathology were observed. No differences relative to concurrent controls were observed in brain widths or dimension. No treatment-related findings were observed in the 2.5 mg/kg group.

Clinical signs observed in the 35 mg/kg animals were similar in nature to those observed in the FOB and consisted of the following (# incidences): (i) slightly decreased activity (males-7, females-3); (ii) ataxia (males-5, females-5); (iii) increased breathing rate (males-16, females-13); (iv) piloerection (males-27, females-20); (v) reduced stability (males-2, females-4); (vi) sides pinched in (males-3, females-4); (vii) signs of salivation (males-6, females-11); (viii) signs of urinary incontinence (males-2, females-5); (ix) stains around mouth (males-4, females-3); (x) tip toe gait (males-5, females-3); (xi) ungroomed appearance (males-3, females-2); (xii) upward curvature of the spine (males-25, females-20); and (xiii) urinary incontinence (males-5, females-7). The following clinical signs were observed in the 10 mg/kg group (# incidences): (i) increased breathing rate (males-5, females-5); (ii) slight piloerection (males-1, females-3); (iii) signs of urinary incontinence (1, females only); (iii) upward spine curvature (2, females only); and (iv) urinary incontinence (3, males only). None of the clinical signs observed in the 35 mg/kg or 10 mg/kg groups were observed in the concurrent controls. The clinical signs observed in a few animals at 10 mg/kg are not considered to be adverse.

The following findings were noted during the FOB in the 35 mg/kg animals: (i) slightly decreased activity (2, males only); (ii) slight ataxia (males-3, females 2); (iii) extreme ataxia (2, females only); (iv) lacrimation (males-1, females-2); (v) slight piloerection (males-6, females-7); (vi) moderately reduced stability (1, females only); (vii) extremely reduced stability (1, females only); (viii) moderate salivation (1, males only); (ix) extreme salivation (males-1, females-1); (x) slight signs of salivation (males-6, females-4); (xi) moderate signs of salivation (1, females, only); (xii) sides pinched in (1, females only); (xiii) slight tip toe gait (males-4, females-1); (xiv) upward curvature of the spine (males-8, females-8); (xv) tremors (1, females only); (xvi) slight signs of urinary incontinence (males-1, females-1); and (xvii) slight urinary incontinence (males-3, females-6). The following observations were noted in the 10 mg/kg animals: slight signs of salivation (1, males only); slight signs of urinary incontinence (1, females only); and slight urinary incontinence (2, males only). None

of the clinical observations noted in the 35 mg/kg or 10mg/kg animals were observed in the concurrent controls. The findings observed in a few animals at 10 mg/kg are not considered to be adverse. These FOB data were not subjected to statistical analysis. There were no treatment-related FOB clinical observations in any dose group on days 8 or 15.

Landing foot-splay values were decreased in high-dose males on day 1 (↓21%, $p \leq 0.05$). Decreased ($p \leq 0.05$ or 0.01) hindlimb grip strength was observed on days 1, 8, and 15 in high-dose (↓19%, ↓31%, ↓32%) males. High-dose females displayed increased time to tail-flick on day 1 (↑71%, $p \leq 0.05$). No other treatment-related differences were noted in FOB parameters in any of the treated groups.

One high-dose female was found to have minimal pigmentation of the olfactory bulb, but no other associated pathology. Minimal fiber degeneration of the sciatic nerve was observed in another high-dose female. No other microscopic abnormalities were noted in any of the other treatment groups.

The LOAEL for this study is 35 mg/kg based on clinical observations indicative of neurotoxicity and changes in FOB parameters.

The NOAEL for this study is 10 mg/kg.

This acute oral neurotoxicity study is classified as **acceptable (§81-8[a])** and satisfies the guideline requirements for an acute neurotoxicity screening battery in rats.

C. Study deficiencies - The following deficiencies and/or deviations were noted, but do not change the conclusions of this review:

No dose rationale was provided.

DATA EVALUATION RECORD

LAMBDA CYHALOTHRIN

Study Type: 82-2; 21-Day Dermal Toxicity Study in the Rat

Work Assignment No. 3-31A (MRID 44333802)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Pesticides Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
Rockville, MD 20850-3268

Primary Reviewer:
Joan Harlin, M.S.

Signature: Joan L Harlin
Date: 2/26/98

Secondary Reviewer
Kathleen Ferguson, Ph.D.

Signature: Kathleen P. Ferguson
Date: 2/26/98

Program Manager
Mary Menetrez, Ph.D.

Signature: Mary L Menetrez
Date:

Quality Assurance:
Reto Engler, Ph.D.

Signature:
Date:

Disclaimer

This Data Evaluation Report may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

LAMBDA CYHALOTHRIN

Repeated Dose Dermal (82-2)

EPA Reviewer: Pamela M. Hurley, Ph.D.
Registration Action Branch 2 (7509C)

Pamela M Hurley 4/09/2001

Work Assignment Manager: Sanyvette Williams-Foy, D.V.M.
Registration Action Branch 2 (7509C)
TXR No. 0050580

S Williams-Foy 4/9/2001

DATA EVALUATION RECORD

STUDY TYPE: Repeated dose dermal toxicity study - 21-day rat
OPPTS Number: 870.3200 OPP Guideline Number: 82-2

DP BARCODE: D2386940 SUBMISSION CODE: S529292
P.C. CODE: 128897 TOX. CHEM. NO.: 725C

TEST MATERIAL (PURITY): Lambda cyhalothrin (96.6% a.i.)

SYNONYMS: Karate; α-cyano-3-phenoxybenzyl 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

CITATION: Leah, A. (1989) Lambda-cyhalothrin: 21-Day dermal toxicity to the rat. ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK. Laboratory Report Number CTL/P/2532. Laboratory Study Number LR0526. June 20, 1989. MRID 44333802. Unpublished.

SPONSOR: ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK.

EXECUTIVE SUMMARY:

In a repeated dose dermal toxicity study (MRID 44333802), lambda cyhalothrin (96.6% a.i.) was applied to the clipped skin of five albino rats/sex/dose at dose levels of 1 or 10 mg/kg/day for 6 hours/day for 21 consecutive days. Five rats/sex were similarly treated with two or three applications at 100 mg/kg/day, reduced to 50 mg/kg/day for 21 consecutive days.

Two males which were found dead after three applications of 100 mg/kg/day had reduced, moderately atrophied seminal vesicles and slightly atrophied spleens. Clinical signs indicative of neurotoxicity were observed in the 100/50 mg/kg/day treatment groups. Males exhibited reduced splay reflex, downward curvature of the spine, splayed gait, bizarre behavior, pinched in sides, dehydration, reduced stability, and thin appearance. Females exhibited an increased incidence of tip toe gait, upward curvature of the spine, an increased incidence in signs of urinary incontinence, urinary incontinence, chromodacryorrhea, and reduced splay reflex. **The clinical signs commenced on day 2 of dosing.** Body weight gains for males were significantly reduced throughout the study; the final gain was 58% lower than the control gain. The final mean body weight was 19% lower than the mean control value. Body weight gains for females were somewhat reduced only during the first half of the study. Food consumption was somewhat reduced for males throughout the study. No dermal irritation was observed at 100/50 mg/kg/day in either sex. No signs of clinical toxicity or dermal irritation in the 10 or 1 mg/kg/day treatment groups were considered to be treatment-related. No treatment-related differences in hematology or clinical blood chemistry parameters, organ weights or histopathology were observed between the

treatment and control groups. No neoplastic tissue was observed. **The LOAEL is 50 mg/kg/day for both sexes, based on clinical signs of toxicity and decreased body weight and body weight gain. The NOAEL is 10 mg/kg/day for males and females.**

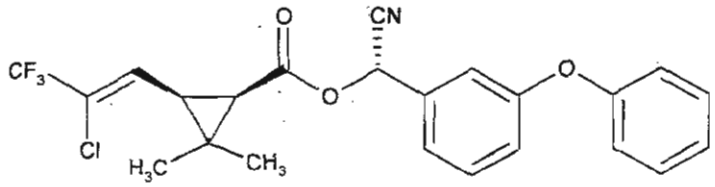
This dermal toxicity study is classified **acceptable (§82-2)** and satisfies the guideline requirement for a repeated dose dermal toxicity study.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, Quality Assurance, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Lambda cyhalothrin
   Description: Light lumpy brown solid
   Lot/Batch #: YO2537/001/012
   Purity: 96.6% a.i.
   Stability of compound: Not reported
   CAS #: 91465-08-6
   Structure:



2. Vehicle and/or positive control: Olive oil

3. Test animals: Species: Rat
   Strain: Alpk:APfSD, Wistar-derived albino
   Age and weight at study initiation: Young adults (age not reported); males, 190-227 g; females, 194-226 g
   Source: Barriered Animal Breeding Unit, ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, UK
   Housing: Housed individually in suspended cages with solid stainless steel sides, a polycarbonate (MAKROLON) front, and stainless steel mesh floor and back. Each cage was partitioned into two equal compartments that each housed one animal.
   Diet: Porton Combined Diet, Special Diet Services Ltd., ad libitum
   Water: Not described, ad libitum
   Environmental conditions:
      Temperature: 15 - 24 C
      Humidity: 50 ± 10%
      Air Changes: 20-30/hour
      Photoperiod: 12-Hour light/dark cycle
   Acclimation period: ≥6 Days

B. STUDY DESIGN

1. In life dates - Not reported

2. Animal assignment

   Rats were assigned to the test groups in Table 1 immediately after receipt using computer-generated random numbers.

Table 1. Study design.

Test Group	Dose to animal (mg/kg/day)	Animals assigned	
		Male	Female
1	0	5	5
2	1	5	5
3	10	5	5
4	100/50[a]	5	5

[a] The dose level was reduced to 50 mg/kg after two or three applications because two males dosed at 100 mg/kg were found dead.

3. Dose selection rationale

Dose levels were selected based on the results of a preliminary study in which groups of two male and two female rats were treated with four or five applications of undiluted lambda cyhalothrin at 10 or 100 mg/kg. Signs of slight toxicity in the high-dose group were the only observed effects. In the second part of the study, rats were treated with the test substance in olive oil at 10 or 100 mg/kg. Both dose groups exhibited slight toxicity; no irritation was observed.

4. Preparation and treatment of animal skin

Fresh dosing preparations of lambda cyhalothrin in olive oil were made approximately every 7 days. The chemical stability of the test substance in olive oil was confirmed in 0.5 and 50 mg/mL preparations following 13 days of room temperature storage (recoveries, 104% of nominal).

Eighteen to 24 hours before the first application of the test substance, the hair of each animal was clipped from the dorso-lumbar area of the trunk over an area approximately 10 cm x 5 cm of the body surface. The test substance in olive oil (2 mL/kg) was spread evenly onto the shorn backs of the animals using a 1 mL sterile disposable plastic syringe. Females were dosed one day later than males. The volume administered to the high-dose animals was reduced to 1 mL/kg after two or three applications because two males were found dead. The treated area was covered with a gauze patch that was covered with a patch of plastic film and held in place with adhesive bandage secured by two pieces of PVC tape wrapped around the animal. The rats were exposed to the test substance for 6 hours/day for 21 consecutive days, with an 18-hour rest period between each application. Plastic collars were put on the animals during the rest periods to prevent oral contamination. After each exposure, the dressings were removed and the application areas were cleaned with lukewarm water and absorbent cotton wool, and dried gently with clean tissue paper.

Rats in the control group were exposed to the vehicle in the same way.

5. Statistics

Mean body weight gain, hematology and clinical blood chemistry parameters, and absolute and relative organ weights for each treatment group were compared to the control group using a Student's t-test conducted at the 5 and 1% two-sided level.

C. METHODS

1. Observations

Animals were observed twice daily, prior to dosing and at decontamination, for gross signs of toxicity and for signs of irritation at the application site.

2. Body weight

Animals were weighed daily prior to dosing throughout the study period.

3. Food consumption and compound intake

Food consumption for each animal was estimated for a 24-hour period between days -1 and 1, 6 and 7, 13 and 14, and 20 and 21.

4. Clinical Pathology

Blood samples were taken from each rat by cardiac puncture immediately after death. It was not stated that the animals were fasted prior to blood collection. The CHECKED (X) parameters were examined in all samples analyzed.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)
X	Platelet count* (thrombocytes)	X	RBC morphology
	Blood clotting measurements*		
	(Partial thromboplastin time)		
	(Capillary clotting time)		
X	(Prothrombin time)		
X	(Kaolin-cephalin)		

* Required for repeated dose dermal toxicity studies based on Subdivision F guidelines.

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium*	X	Albumin*
	Chloride*	X	Blood creatinine*
	Magnesium	X	Blood urea nitrogen*
X	Phosphorus*	X	Cholesterol
X	Potassium*		Globulin
X	Sodium*	X	Glucose*
		X	Total bilirubin
		X	Total serum protein (TP)*
	ENZYMES	X	Triglycerides
X	Alkaline phosphatase		
	Cholinesterase (ChE)		
X	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase		
X	Serum aspartate aminotransferase		
	Gamma glutamyl transferase (GGT)		

* Required for repeated dose dermal toxicity studies based on Subdivision F guidelines.

6. Sacrifice and Pathology

Animals were anesthetized with excessive levels of halothane BP vapor, then euthanized by exsanguination. The bodies were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The skin, liver, kidney, adrenal, brain, heart, sciatic nerve, spinal cord, and spleen from all animals were examined microscopically. The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta*	XX	Brain*
X	Salivary glands*	X	Heart*	X	Sciatic nerve*
X	Esophagus*		Bone marrow*	X	Spinal cord*
X	Stomach*		(sternum)	X	Pituitary*
X	Duodenum*	X	Lymph nodes*	X	Eyes*
X	Jejunum*	X	Spleen*		
X	Ileum*	X	Thymus*		
X	Cecum*				
X	Colon*		UROGENITAL		GLANDULAR
X	Rectum*				
XX	Liver*	XX	Kidneys*	XX	Adrenal gland*
X	Pancreas*	X	Urinary bladder*		Lacrimal gland
		XX	Testes*		Mammary gland
		X	Epididymides	X	Thyroids* with parathyroids*
		X	Prostate		
	RESPIRATORY	X	Seminal vesicle	X	Harderian gland
		XX	Ovaries*		
	Trachea*	X	Uterus*		
X	Lungs*		Vagina		
	Pharynx				OTHER
	Larynx				
					Body (exsanguinated)
				X	Bone* (femur)
					Muscle*
				X	Skin* (treated and untreated)
				X	All gross lesions and masses*

* Required for repeated dose dermal toxicity studies based on Subdivision F guidelines.

II. RESULTS

A. Observations

1. Mortality - Two males treated at 100 mg/kg/day were found dead prior to dosing on Day 4. No other animals died during the study.

2. Toxicity - Males dosed at 50 mg/kg/day exhibited reduced splay reflex (5/5), bizarre behavior (3/5), pinched in sides (3/5), dehydration (3/5), reduced stability (2/5), and thin appearance (2/5); these clinical signs were unique to this dose level (refer to Attachment to this DER). The 50 mg/kg/day group males also exhibited an increased incidence (number of animals affected and/or observations) of tip toe gait (5/5), upward curvature of the spine (5/5), signs of urinary incontinence (4/5) downward curvature of the spine (4/5), and splayed gait (4/5) compared to the other male test groups. Females dosed at 50 mg/kg/day exhibited an increased incidence in signs and occurrence of urinary incontinence (5/5), upward curvature of the spine (5/5), tip toe gait (4/5), chromodacryorrhea (4/5), and reduced splay reflex (3/5) compared to the other female test groups (Attachment). There was no indication of an increase in dermal irritation. No signs of clinical toxicity or dermal irritation in the 10 or 1 mg/kg/day treatment groups were considered to be treatment-related.

B. Body weight and weight gain

Males dosed at 50 mg/kg/day had significantly ($p < 0.05$ or $p < 0.01$) lower mean body

weight gains than the control gains during most study days, and a final mean body weight gain 58% lower than the controls. Females dosed at 50 mg/kg/day had reduced mean body weight gains that differed statistically from the control gains only during the first 3 days of the study. Mean body weight gain for the 10 mg/kg/day group males was ≥20% lower ($p < 0.05$) than the control gain on most days through day 14, and thereafter remained between 9-19% lower than the control group. Although the final body weight gain was still 19% less than the control group, the final mean body weight for this dose group was within 4% of the mean control value. Statistical significance for body weight gain disappeared by day 14. No treatment-related differences in body weight gains were observed between the 10 mg/kg/day female treatment group or the 1 mg/kg/day treatment groups compared to the controls.

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Lambda-Cyhalothrin: 21-Day Dermal Toxicity Study in Rats: Body Weight and Body Weight Gains (g)								
Day	Males				Females			
Dose (mg/kg)	0	1	10	100/50	0	1	10	100/50
Initial Body Weight	206.2 ± 13.8	207.4 ± 11.4	209.6 ± 10.8	200.2 ± 9.7	201.6 ± 9.6	209.8 ± 9.2	215.8 ± 2.3*	216.2 ± 7.8*
2	2.0 ± 5.0	3.4 ± 7.9	-1.2 ± 4.8	-26.2 ± 10.5**	5.4 ± 5.3	-0.2 ± 6.7	-3.4 ± 5.4*	-14.4 ± 6.3**
5	11.0 ± 4.5	10.8 ± 6.1	5.4 ± 3.2	-12.0 ± 13.2*	7.4 ± 9.2	6.4 ± 2.6	7.0 ± 6.9	5.0 ± 11.6
10	38.4 ± 7.0	35.4 ± 11.7	29.4 ± 2.6*	12.3 ± 12.1**	26.0 ± 12.8	22.2 ± 5.8	19.8 ± 2.5	16.4 ± 12.8
15	56.2 ± 29.5	58.0 ± 15.9	46.0± 4.4	20.0 ± 25.5	30.6 ± 11.1	24.4 ± 13.6	27.0± 5.4	25.2 ± 14.8
22	80.8 ± 12.8	76.4 ± 20.4	65.6 ± 8.8	34.3 ± 33.9*	42.4 ± 14.0	35.8 ± 13.4	41.4 ± 2.3	42.6 ± 18.3
Final Body Weight	287.0 ± 14.7	283.8 ± 29.6	275.2 ± 10.4	233.3 ± 42.8*	244.0 ± 14.2	245.6 ± 17.8	257.2 ± 3.8	258.8 ± 13.8

C. Food consumption

Males in the 50 mg/kg/day treatment group consumed 14-28% less food than the controls throughout the study; the decreases were not statistically significant. No other differences in food consumption were observed between the treatment and control groups.

D. Clinical Pathology

1. Hematology - No treatment-related effects in hematology parameters were observed between the treated and control groups. Minor differences in hematology parameters observed between rats in the treated and control groups (female control values were high) remained within normal limits for this strain and age of rat.

2. Clinical Chemistry - No treatment-related differences in clinical chemistry were observed between the treated and control groups. Differences that showed statistical significance were small and/or not dose-related or were due to high individual control values.

E. Sacrifice and Pathology

1. Organ weight - No treatment-related biologically significant differences in absolute or relative organ weights were observed between the treatment and control groups. A decreased mean absolute liver weight for the 50 mg/kg group males ($p<0.05$) was due to one very low individual body weight. A decreased mean relative kidney weight for the 50 mg/kg group females ($p<0.01$) differed by $<10\%$ of the control weight and lacked associated pathological findings.

2. Gross pathology - In the two males treated at 50/100 mg/kg/day that died prematurely, seminal vesicles were reduced. No other gross post-mortem differences were observed between the treated and control groups.

3. Microscopic pathology

a) Non-neoplastic - In the two males treated at 50/100 mg/kg/day that died prematurely, seminal vesicles were moderately atrophied and spleens were slightly atrophied. No other microscopic differences were observed between the treated and control groups.

b) Neoplastic - No neoplastic tissue was observed in the treated or control rats.

III. DISCUSSION

A. Investigator's Conclusions

The study author concluded that the NOAEL for systemic toxicity of lambda cyhalothrin is 10 mg/kg, based on clinical signs of slight general toxicity observed in males and females dosed at 100 mg/kg (reduced to 50 mg/kg after two or three applications) for 21 consecutive days. Abnormalities observed after application of 50 mg/kg were bizarre behavior, reduced stability, pinched in sides, reduced splay reflex, thin appearance, and dehydration. No significant signs of skin irritation were observed in any treatment group. Premature deaths of two males initially treated with two or three applications of

100 mg/kg were likely the result of pyrethroid toxicity.

B. Reviewer's Discussion

We agree with the study author's conclusion that clinical signs of general toxicity were observed in rats dermally treated with 50 mg/kg of the lambda cyhalothrin. Most of the clinical signs were unique to this treatment group or exhibited an increased incidence compared to the other test groups. Males exhibited reduced splay reflex, downward curvature of the spine, splayed gait, bizarre behavior, pinched in sides, dehydration, reduced stability, and thin appearance. Females exhibited an increased incidence of tip toe gait, upward curvature of the spine, an increased incidence in signs of urinary incontinence, urinary incontinence, chromodacryorrhea, and reduced splay reflex. Body weight gain and food consumption were more severely affected in males than females. For males, body weight gains were significantly ($p < 0.05$ or $p < 0.01$) reduced and food consumption was depressed throughout the study. For females, decreases in body weight gains during the first half of the study were eventually recovered, and food consumption was similar to the controls. No dermal irritation was observed at 100/50 mg/kg/day. No signs of clinical toxicity or dermal irritation in the 10 or 1 mg/kg/day treatment groups were considered to be treatment-related.

In conclusion, we agree that the LOAEL for this study is 50 mg/kg/day, based on clinical signs in both sexes, and that the NOAEL is 10 mg/kg/day.

IV. STUDY DEFICIENCIES

No significant deficiencies were noted in this study.

THE FOLLOWING ATTACHMENTS ARE NOT AVAILABLE ELECTRONICALLY.
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US EPA ARCHIVE DOCUMENT

F

EPA Reviewer: Pamela M. Hurley
Registration Action Branch 2 (7509C)
TXR No. 0050580

Pamela M Hurley, Date 3/26/2004

DATA EVALUATION RECORD
Supplement to DER for MRID No.: 43241901 Cyhalothrin: 4-Week Range Finding Study in Mice. TXR No. 011241

STUDY TYPE: 4-Week Oral Study in Mice
OPPTS Number: N/A
OPP Guideline Number: § N/A

DP BARCODE: N/A
SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897
TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (Not specified)

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

CITATION: Colley, J.; Dawe, S.; Heywood, R. et al. (1981) Cyhalothrin: 4-Week Dose Range Finding Study in Mice: Lab Project Number: CTL/C/1039: ICI/379: PMO 399. Unpublished study prepared by Huntingdon Research Center. 222 p. MRID 43241901

SPONSOR: Imperial Chemical Industries, PLC, Macclesfield, Cheshire, U.K.

EXECUTIVE SUMMARY: In a 28-day feeding study in the mouse, cyhalothrin (technical, no purity available) was tested in CD-1 mice as a range-finding study for the carcinogenicity study (MRID 43241901). Twelve mice/sex/dose level were tested at 0, 5, 25, 100, 500 or 2000 ppm in the diet (0, 0.65, 3.30, 13.5, 64.2 or 309 mg/kg/day for males and 0, 0.80, 4.17, 15.2, 77.9 or 294 mg/kg/day for females).

At 2000 ppm, piloerection, abnormal gait (walking on toes), hunched posture, increase in respiration rate and emaciated appearance were observed. Six males and 3 females died during the study. Both males and females had a significant decrease in body weight gain over the treatment period when compared to controls (-1g versus 5 g in controls for males ($p < 0.001$) and 0g versus 3 g in controls for females ($p < 0.001$)). A decrease in food consumption was observed in both sexes during the first week (60.8% of controls for males and 62.5% of controls for females) and in females for the remainder of the study (82% of controls, $p < 0.05$). Males had a slightly lower mean total white blood cell count (68%). The differential white cell count revealed lower lymphocyte counts (58.7%) and higher neutrophil counts (62.5% above controls), $p < 0.01$ for all hematological values in males at this dose level. Significantly higher APDM activity was observed in both sexes (61.9% above controls for males and 77.8% above controls for females). Slight increases in kidney weights (28.8% over controls for males, $p < 0.001$) and liver weights (17% over controls for males ($p < 0.05$) and 3.1 % over controls for females) were

observed. In females, the differences were not statistically significant. Slightly lower heart weights were also observed in females (87.7% of controls, $p < 0.05$)). Minimal centrilobular hepatocyte enlargement was observed in 2/12 females.

At 500 ppm, piloerection was observed in several mice, several males had low white blood cell counts (not statistically significant) as well as marginally lower lymphocyte numbers (80%). Significantly higher APDM activity was observed in females (26.2% over controls). Slightly higher kidney weights were observed in males (13.5% over controls, $p < 0.01$)) and slightly lower heart weights were observed in females (93.0%, $p < 0.05$).

At 100 ppm, piloerection was also observed in several mice. One female had an emaciated appearance. Marginally lower lymphocyte numbers were noted for males (79% of controls). Significantly higher APDM activity was observed in females (24.8% over controls). Slightly higher kidney weights were observed in males (13.0% over controls, $p < 0.01$) and marginally lower heart weights were observed in females (87.7%, $p < 0.01$).

The NOAEL is 500 ppm (64.2/77.9 mg/kg/day (male/female)) and the LOAEL is 2000 ppm (309/294 mg/kg/day (male/female)based on mortality, clinical signs of toxicity, decreases in body weight gain and food consumption, changes in hematology and organ weights and minimal centrilobular hepatocyte enlargement. The minimal effects observed at 500 and 100 ppm are not considered to be toxicologically significant.

This study is classified as **acceptable nonguideline** and does not satisfy any particular guideline requirement.

Reviewed By: Pamela Hurley, Toxicologist
Section I, Tox. Branch (7509C)
Secondary Reviewer: Roger L. Gardner, Section Head
Section I, Tox. Branch (7509C)

DATA EVALUATION RECORD

STUDY TYPE: 4-Week Dose Range Finding Study in Mice

SHAUGHNESSY NO./TOX. CHEM. NO.: 725C, 271F / 128897

TEST MATERIAL: Cyhalothrin

SYNONYMS: PP563

REPORT NUMBER: CTL/C/1039

SPONSOR: Imperial Chemical Industries, Cheshire, England

TESTING FACILITY: Huntingdon Research Center, Huntingdon, Cambridgeshire, England

TITLE OF REPORT: Cyhalothrin: 4-Week Dose Range Finding Study in Mice

AUTHOR(S): J. C. Colley, S. Dawe, R. Heywood, W. Dawn, R. Woodhouse, C. Gopinath, A. Zubaidy, D. Prentice

REPORT ISSUED: 2/27/81

CONCLUSION: Cyhalothrin (technical, no purity available) was tested in a 4-week oral feeding study in CD-1 mice as a range-finding study for the carcinogenicity study. Twelve mice/sex/dose level were tested at 0, 5, 25, 100, 500 or 2000 ppm in the diet (0, 0.65, 3.30, 13.5, 64.2 or 309 mg/kg/day for males and 0, 0.80, 4.17, 15.2, 77.9 or 294 mg/kg/day for females).

At 2000 ppm, piloerection, abnormal gait (walking on toes), hunched posture, increase in respiration rate and emaciated appearance were observed. Six males and 3 females died during the study. Both males and females had a significant decrease in body weight gain over the treatment period when compared to controls (-1g versus 5 g in controls for males ($p < 0.001$) and 0g versus 3 g in controls for females ($p < 0.001$)). A decrease in food consumption was observed in both sexes during the first week (60.8% of controls for males and 62.5% of controls for females) and in females for the remainder of the study (82% of controls, $p < 0.05$). Males had a slightly lower mean total white blood cell count (68%). The differential white cell count revealed lower lymphocyte counts (58.7%) and higher neutrophil counts (62.5% above controls), $p < 0.01$ for all hematological values in males at this dose level. Significantly higher APDM activity was observed in both sexes (61.9% above controls for males and 77.8% above controls for females). Slight increases in kidney weights

(28.8% over controls for males, $p < 0.001$) and liver weights (17% over controls for males ($p < 0.05$) and 3.1 % over controls for females) were observed. In females, the differences were not statistically significant. Slightly lower heart weights were also observed in females (87.7% of controls, $p < 0.05$)). Minimal centrilobular hepatocyte enlargement was observed in 2/12 females.

At 500 ppm, piloerection was observed in several mice, several males had low white blood cell counts (not statistically significant) as well as marginally lower lymphocyte numbers (80%). Significantly higher APDM activity was observed in females (26.2% over controls). Slightly higher kidney weights were observed in males (13.5% over controls, $p < 0.01$)) and slightly lower heart weights were observed in females (93.0%, $p < 0.05$).

At 100 ppm, piloerection was also observed in several mice. One female had an emaciated appearance. Marginally lower lymphocyte numbers were noted for males (79% of controls). Significantly higher APDM activity was observed in females (24.8% over controls). Slightly higher kidney weights were observed in males (13.0% over controls, $p < 0.01$) and marginally lower heart weights were observed in females (87.7%, $p < 0.01$).

The NOEL is 500 ppm and the LEL is 2000 ppm based on mortality, clinical signs of toxicity, decreases in body weight gain and food consumption, changes in hematology and organ weights and minimal centrilobular hepatocyte enlargement. The minimal effects observed at 500 and 100 ppm are not considered to be toxicologically significant.

This study is not a guideline requirement and thus does not satisfy any guideline requirements.

A. MATERIALS AND METHODS:

1. Test Compound(s)

Chemical Name: (RS)-α-cyano-3-phenoxybenzyl (1RS)-cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethyl-cyclopropanecarboxylate

Description: Brown viscous liquid
Batch #: Y00102/010/001
Purity: Not specified
Source: Central Toxicology Laboratories, ICI Ltd., England

2. Test Animals:

Species and Strain (sexes): Male and female CD-1 mice
Age: 24 ± 1 day
Weight(s): 22-23 g (mean) - ♂; 20-21 g (mean) - ♀
Source(s): Charles River, Manston, Kent, England

3. Procedure:

a. Dietary Preparation: A premix was prepared by mixing the test material in corn oil and then diluting it with test diet to the specified amounts.

Frequency of preparation: The premix was diluted to the appropriate concentration weekly.

Storage conditions: Not stated.

Stability Analyses: An analysis at the 5 and 2000 ppm dietary levels was conducted using the diet prepared at week 1. The samples were stored in darkness at ambient temperatures in the animal rooms for up to 18 days. Duplicate sub-samples were prepared after 9 and 18 days storage and analyzed.

Homogeneity Analyses: An analysis at the 5 and 2000 ppm dietary levels was conducted using the diet prepared at week 1. Duplicate samples were taken from the first kilogram discharged, from the approximate center of the discharge and from the final kilogram discharged.

Concentration Analyses: Concentration analyses were conducted in weeks 1 and 4.

b. Basis For Selection of Dose Levels: The dose

levels were selected on the basis of previous studies.

c. Animal Assignment and Dose Levels:

Test Group	Dose Administered ppm	Main Study 4 Weeks male	female
Contr.	0	12	12
1	5	12	12
2	25	12	12
3	100	12	12
4	500	12	12
5	2000	12	12

d. Clinical Observations and Mortality: All animals were checked twice daily for clinical signs of toxicity and mortality.

e. Body Weight Determinations: Weekly.

f. Food and/or Water Consumption: Weekly.

g. Clinical Pathology:

1) Hematology:

Collection times for blood (including # of animals): During week 4, blood samples were taken from all animals under light anesthesia from the orbital sinus.

The following CHECKED (X) parameters were examined:

X		X	
	Hematocrit (HCT)	x	Mean corpuscular HGB (MCH)
x	Hemoglobin (Hb)	x	Mean corpuscular HGB conc. (MCHC)
x	Leukocyte count (WBC)	x	Mean corpuscular volume (MCV)
x	Erythrocyte count (RBC)	x	Reticulocytes
x	Platelet count	x	Packed cell volume (PCV)
	Total plasma protein (TP)		
x	Leukocyte differential count		

2) Urinalysis:

Collection times for urine (including # of animals): During week 4, overnight pooled urine samples were collected from 4 mice of each sex/group. Food was removed. The urine samples were stored for proof of absorption studies.

3) Aminopyrine Demethylase Activity

Aminopyrene demethylation (APDM) assays were conducted on 6 animals/sex/dose using liver homogenate as the enzyme source. The results were expressed as nmoles formaldehyde produced/hour/gram liver.

h. Gross Necropsy:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to end of exposure period and were subjected to complete gross pathological examinations: All animals.

Animals (groups) sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations: All animals.

i. Histopathology:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to the end of the exposure period and were subjected to microscopic examination: All animals.

Animals (groups) which were sacrificed at the end of the treatment/observation period and were subjected to microscopic examination: All controls and high dose animals. Livers from all groups were examined.

Samples of liver approximately 1 mm^3 were obtained from 6 male and 6 female mice/group and fixed in paraformaldehyde-glutaraldehyde fixative and post-fixed in 1% osmium tetroxide. The tissues were dehydrated and embedded in epoxy resin. One µm survey sections were cut and stained with toluidine blue for examination with the light microscope. Silver/gold ultra thin sections of selected areas were cut, mounted on copper grids and stained with uranyl acetate and lead citrate. The ultra thin sections were examined with a Philips EM 300 at an accelerating voltage of 80kv. A qualitative assessment of the smooth endoplasmic reticulum activity was made.

Where practicable, a section of kidney was stained with Periodic Acid Schiff (for basement membranes) and frozen

sections of liver and kidney, fixed in buffered formalin, were cut on a cryostat at 12 µm and stained for fat with Oil Red O. In addition, sections of sciatic nerve and posterior nerve from 5/sex/group from the control and high dose groups were stained with Glees-Marsland silver stain and Luxol Fast Blue.

CHECKED (X) tissues were preserved for histopathological examination in buffered 10% formalin and (XX) tissues were weighed upon removal from the animal. These were embedded in paraffin wax and sections were cut at 5µ, stained with H & E and examined.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
x	Tongue	x	Aorta	xx	Brain
x	Salivary glands	xx	Heart	x	Sciatic nerve
x	Esophagus	x	Bone marrow		Spinal cord
				x	Posterior tibial nerve
x	Stomach	x	Lymph nodes	x	Pituitary
x	Duodenum	x	Spleen	x	Eyes (optic n.)
x	Jejunum	x	Thymus		Glandular
x	Ileum		Urogenital	xx	Adrenals
x	Cecum	xx	Kidneys		Lacrimal gland
x	Colon	x	Urinary bladder	x	Mammary gland
	Rectum	xx	Testes	x	Parathyroids
xx	Liver		Epididymides	x	Thyroids
x	Gall bladder	x	Prostate		Other
x	Pancreas	x	Seminal vesicle	x	Bone
	Respiratory	xx	Ovaries	x	Skeletal muscle
x	Trachea	x	Uterus + Cervix	x	Skin
xx	Lung				All gross lesions and masses

j. Statistical Analyses: An analysis of variance followed by Student's 't' test was performed to assess the significance of intergroup differences in bodyweight, food intake and APDM. Analysis of hematological investigations were performed using analysis of variance followed by Williams' test. Analysis of organ weights was performed using analysis of covariance.

B. RESULTS:

1. Dietary Preparation: An analysis of the dosing concentrations from week 1 revealed a range of -15.0% to +3.6% of the nominal concentrations. At week 4, the range was -1.9% to +5.6%. The -15.0% was for the 500 ppm dose level. All the other dose levels were within the 5.6% range. The homogeneity results indicated a range of 4.98 to 5.24 ppm for a dose level of 5 ppm and 1920 to 1990 ppm for a dose level of 2000 ppm. The stability study indicated that the test material was

stable for a period of 18 days. After 18 days, the concentration at the 5 ppm dose level was 5.18 ppm and the concentration at the 2000 ppm dose level was 1970 ppm.

2. Clinical Observations and Mortality: At 2000 ppm, the following clinical signs were observed: piloerection, abnormal gait (walking on toes), hunched posture, increase in respiration rate and emaciated appearance. Piloerection was also observed in several mice at 25, 100 or 500 ppm, for 1 male at 5 ppm and for 1 control male. One female at 100 ppm had an emaciated appearance. There was no summary table in the report for these observations.

   Six males and 3 females in the 2000 ppm group died during the study. Autopsy examinations revealed congested lungs and autolytic changes in the abdominal viscera for 1 mouse, small thymus and spleen for a second mouse and small spleen in a third mouse. Microscopic examination of the small spleens revealed atrophy of the red pulp, which according to the authors was of unknown toxicological significance.

3. Body Weight Determinations: At 2000 ppm, both males and females had a significant decrease in body weight gain over the treatment period. Males lost weight. No effect was observed at any of the lower dose levels. The following table summarizes the results.

Group Mean Bodyweights (g)

Week	Dose Levels (ppm) 0	5	25	100	500	2000
			Males			
-1	23	22	22	23	23	23
0	27	27	26	26	26	26
1	29	31	30	31	28	23
2	31	33	31	32	30	25
3	32	34	32	33	32	24
4	32	35	34	35	33	25
Weight Gain 0-4	5	8**	8**	9**	7	-1***

Group Mean Bodyweights (g)

Week	Dose Levels (ppm) 0	5	25	100	500	2000
			Females			
-1	21	21	21	20	21	20
0	23	23	23	22	23	22
1	24	25	24	24	24	21
2	25	26	25	25	25	21
3	24	25	25	26	25	21
4	26	27	26	27	26	22
Weight Gain 0-4	3	4	3	5	3	0***

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

4. Food Consumption: At 2000 ppm, a decrease in food consumption was observed in both sexes during the first week and in females for the remainder of the study. The group mean achieved compound intakes were as follows: 0, 0.65, 3.30, 13.5, 64.2 or 309 mg/kg/day for males and 0, 0.80, 4.17, 15.2, 77.9 or 294 mg/kg/day for females. The following table summarizes the results.

Group Mean Food Consumption (g/mouse/week)

Week	Dose Levels (ppm) 0	5	25	100	500	2000
			Males			
1[a]	23	27	25	29	21	14
2	27	27	27	28	28	26
3	27	31	30	31	29	31
4	27	32	31	31	29	32
Total	104	117	113	119	107	103
% of Control	-	113	109	114	103	99

Group Mean Food Consumption (g/mouse/week)

Week	Dose Levels (ppm) 0	5	25	100	500	2000
			Females			
1[a]	24	24	27	22	24	15
2	26	27	28	26	26	20
3	25	28	27	28	25	24
4	29	32	30	29	30	26
Total	104	111	112	105	105	85
% of Control	-	107	108	101	101	82*

[a]Food consumption for a 6-day period.
*p < 0.05 when compared to control value.

5. Hematology: At 2000 ppm, males had a slightly lower mean total white blood cell count. This was particularly true for 3 males. The differential white cell count revealed lower lymphocyte counts and higher neutrophil counts in males at this dose level. At 500 ppm, 2 males had low white blood cell counts that were similar to the high dose males. Marginally lower lymphocyte numbers were noted for males at this dose level and at 100 ppm. The report also stated that marginally lower PCV and Hb values were observed in high dose males, however, these were largely due to low values recorded for 1 mouse. No significant changes were observed in females. The following table summarizes these data.

Group Mean Values for Total White Blood Cell, Lymphocyte and Neutrophil Counts in Males

Dose Levels (ppm)	Total WBC	Lymphocyte	Neutrophil
0	8.5 ± 2.30	7.5 ± 2.16	0.8 ± 0.36
5	7.7 ± 1.41	6.7 ± 1.21	0.9 ± 0.26
25	7.1 ± 1.87	6.2 ± 1.87	0.9 ± 0.37
100	6.7 ± 2.34	5.9 ± 1.92*	0.8 ± 0.42
500	7.0 ± 1.68	6.0 ± 1.46*	0.9 ± 0.30
2000	5.8 ± 2.28**	4.4 ± 1.92**	1.3 ± 0.62**

* p < 0.05
** p < 0.01

6. Aminopyrine Demethylase (APDM) Activity: Significantly higher APDM activity was observed in high dose males and in 100, 500 or 2000 ppm females. The following table summarizes the data.

Mean Aminopyrine Demethylase Activity (μ mole/hr/g liver)

Dose Group (ppm)	Males	Females
0	48.0	50.4
5	40.6	54.3
25	47.4	58.3
100	44.3	62.9*
500	53.3	63.6*
2000	77.7***	89.6***

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

7. Gross Pathology: No treatment-related differences were observed between the treated groups and the control groups.

8. Organ Weights: At 2000 ppm, slight increases in kidney and liver weights were observed in both sexes. In females, the differences were not statistically significant. Slightly lower heart weights were also observed in females. At 500 ppm, slightly higher kidney weights were observed in males and slightly lower heart weights were observed in females. At 100 ppm, slightly higher kidney weights were observed in males and marginally lower heart weights were observed in females. At 25 ppm, slightly higher liver weights were observed in males. This was not considered to be biologically signficant because it was not dose-related. The following table summarizes the results.

Group Mean Organ Weights (g)

Dose Level (ppm)	Bodyweight	Heart	Liver	Kidneys
		Males		
0	32	0.153 (0.150)	1.783 (1.733)	0.525 (0.515)
5	35	0.153 (0.163)	1.656 (1.858)	0.520 (0.559)
25	33	0.167 (0.169)	2.028[b] (2.067)	0.572 (0.579)
100	33	0.172[c] (0.172)	1.881 (1.873)	0.593[b,c] (0.591)
500	33	0.159 (0.162)	1.949 (2.003)	0.596[b,c] (0.607)
2000	26	0.172 (0.149)	2.088[d] (1.613)	0.676[b,c] (0.584)

Group Mean Organ Weights (g)

Dose Level (ppm)	Bodyweight	Heart	Liver	Kidneys
		Females		
0	26	0.138 (0.139)	1.576 (1.607)	0.418 (0.424)
5	26	0.129 (0.132)	1.499 (1.549)	0.403 (0.413)
25	27	0.127 (0.131)	1.492 (1.572)	0.393 (0.409)
100	26	0.121[b,d] (0.122)	1.439[a] (1.470)	0.385 (0.391)
500	26	0.128[d] (0.130)	1.558 (1.589)	0.405 (0.411)
2000	22	0.121[a,d] 0.108	1.625 (1.328)	0.433 (0.372)

Where values adjusted are for final bodyweight as covariate absolute values are given in parenthesis.
[a]p < 0.05 't' test
[b]p < 0.01 't' test
[c]p < 0.001 't' test
[d]p < 0.05 Williams' test
[e]p < 0.01 Williams' test

9. Histopathology: No summary tables were provided. However, the findings were written in script. Minimal centrilobular hepatocyte enlargement was observed in 2/12 females in the 2000 ppm dose group. No other significant differences between the treated and control groups were observed that may account for the organ weight changes. None of the findings were considered to be of toxicological significance.

In the liver, the following observations were noted by the authors of the report:

"a base-line change characterized by minimal fine cytoplasmic vacuolation of hepatocytes (mainly periportal in females and centrilobular in males) with or without foci of parenchymal and/or periportal mononuclear aggregates, also occasional vacuolated and distended hepatocytes or sinusoidal engorgement in a large proportion of mice from control and top dose groups;

foci of hepatocellular degeneration/necrosis with associated inflammatory cells in one or more lobes, haphazard distribution: 1 male, 1 female control; 1 male (100 ppm); 2 males (2000 ppm).

with Oil Red O trace fat droplets noted in occasional mice from control and treated groups;

minimal fat deposits in centrilobular areas: 2 males control; 4 males (5 ppm); 1 female (25 ppm); and in periportal areas: 4 female control; 1 female (100 ppm).

a distended portal area with minimal biliary hyperplasia and fibrosis: 1 male and female (100 ppm)."

In the kidneys, the following observations were noted:

"Minimal peripelvic mononuclear aggregates in a few mice from control and high dose groups.

a few basophilic cortical tubules in one male and one female at 2000 ppm.

a few foci of mineralization in the papilla of one high dose male mouse.

congested intertubular blood vessels and glomerular capillaries, possibly hypervolemic in 1 high dose male mouse."

10. Quality Assurance Measures: The study was conducted prior to the GLP requirements.

C. DISCUSSION: This study was conducted in order to determine a suitable high dose level for the carcinogenicity study in the mouse. It is not a guideline requirement and thus does not satisfy any requirements.

G

EPA Reviewer: Pamela M. Hurley
Registration Action Branch 2 (7509C)
TXR No. 0050580

Pamela M Hurley, Date 3/26/2004

DATA EVALUATION RECORD
Supplement to DER for MRID Nos.: 40027902, 43227901, 43241903, 43245301, 43232101 Lambda-cyhalothrin: 1-Year Capsule Study in the dog. TXR Nos. 006004, 0011241

STUDY TYPE: 1-Year Capsule Study in the Dog
OPPTS Number: 870.4100 OPP Guideline Number: §83-1

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Lambda-cyhalothrin technical (96.5% a.i.)

SYNONYMS: α-cyano-3-phenoxybenzyl 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate; PP321; Karate, Commodore, Saber

CITATIONS: Hext, P.; Brammer, A.; Chalmers, D.; et al. (1986) PP321: 1 Year Oral Dosing Study in Dogs: Report No. CTL/P/1316: Includes Individual Animal Data Supplement of Report No. CTL/P.1316Sσ. Unpublished study prepared by Imperial Chemical Industries PLC, Central Toxicology Laboratory. 336 p. MRID 40027902

Athis, J. (1994) Comments on February 1993 EPA RfD/Peer Review of Lambda Cyhalothrin 1-Year Dog Study. Unpublished study prepared by ICI Central Toxicology Laboratory. 14 p. MRID 43227901

Athis, J.; Pigott, G. (1994) Additional Comments on February 1993 EPA RfD/Peer Review of Lambda Cyhalothrin 1-Year Dog Study (MRID 40027902). Unpublished study prepared by Zeneca Agrochemicals. 7 p. MRID 43241903

Athis, J. (1994) Additional Comments on February 1993 EPA Rfd/Peer Review of Lambda Cyhalothrin 1-Year Dog Study (MRID 40027902). Unpublished study prepared by Zeneca Agrochemicals, Central Toxicology Lab Cheshire, UK. 4 p. MRID 43245301

Stonard, M. (1991) First Amendment to PP321: 1-Year Oral Dosing Study in Dogs: Lab Project Number: CTL/P/1316. Unpublished study prepared by ICI Central Toxicology Laboratory. 96 p. MRID 43232101

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: In a chronic toxicity study, beagle dogs (6 sex\dose) were given oral administration of gelatin capsules containing lambda-cyhalothrin (96.5%) at 0, 0.1, 0.5 or 3.5 mg/kg/day, 7 days/week for 12 months. The test chemical had been dissolved in corn oil prior to placement in the capsules. The following parameters were measured and/or recorded: daily clinical observations, body weights, food consumption, ophthalmological examinations, clinical biochemistry, urinalysis, gross necropsy and microscopic examinations.

No treatment-related toxicity was observed at 0.1 mg/kg/day. At 0.5 mg/kg/day, 1 male and 1 female dog exhibited gait abnormalities with the effects seen in the male 7-hours post dosing during week 2 and again 2 days later immediately after dosing and in the female 4 times during week 9. Convulsions were seen in two other dogs (both males); the convulsions appeared to be precipitated by the stress of handling or noise. At 3.5 mg/kg/day, the principal neurological clinical signs following dosing were ataxia (all dogs, apparent from day 2 in 2 dogs, observed 3-7 hours post-dosing), muscle tremors and convulsions, occasional subdued behavior; worn or bleeding claws, regurgitation of food during first 2 weeks and fluid feces in all dogs. Treatment had no effect on body weights, hematology, clinical chemistry, urinalysis, gross or histopathology. **The NOAEL is 0.1 mg/kg/day and the LOAEL is 0.5 mg/kg/day based on clinical signs of neurotoxicity.**

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a study (**§83-1**) in the dog.

Notes: This study has been through multiple reassessments at the request of the Registrant. This executive summary and the attached tables reflect the reassessments.

At 0.1 mg/kg/day 1 male had unsteady gait seen during the period between weeks 5-8 on one occasion and 1 female had blood stains on the pen floor with no obvious cause in week 27. The Registrant stated that "'slight ataxia' was the term used in the reporting laboratory (CTL) at the time to describe the observation of 'unsteady gait' which is not a frank and unequivocal sign of ataxic muscular incoordination." Fluid feces were observed, but the incidences were either similar to or less than the incidences in the control group.

At 0.5 mg/kg/day, there were 2 dogs with gait abnormalities, one male and one female. In the male, the first observation occurred in week 2, 7 hours post dosing. The effect was listed in the report as stiffened hind limb movement and flicking of the tarsus was apparent when trotting. It was not listed as ataxia. The second time occurred 2 days later when similar limb movements were observed again immediately after dosing but were reported as ataxia. The second dog was a female. Slight ataxia (unsteady gait) was observed 4 times during week 9. It was recorded, but there was no description of the ataxia in individual animal data. In referring to these two cases, the Registrant states that "isolated incidences of "slight ataxia" were recorded in 2 of the 12 dogs (1 male and 1 female), or on 5 of 13,104 observations made in the 0.5 mg/kg/day dose group (i.e.

in less than 0.04% of the observations)." Convulsions were observed in 2 other dogs, a male in weeks 52 (30 seconds while being carried) and 53 (30 seconds while being carried) and a second male in week 51 (2-3 minutes after being placed in metabolism cage; for 30 seconds 5 minutes later; 3 minutes next morning when taken out of metabolism cage). **These were originally listed as severe ataxia in the study report summary table, which is an error.** Blood stains on the pen floor with no obvious cause were seen in 2 dogs. The frequency of fluid feces was increased in 1 female dog. The incidences of fluid feces observations for this dose group were somewhat increased over controls. The Registrant also submitted comments on the convulsions in the 2 male dogs at the 0.5 mg/kg/day dose level. In their response, they stated that convulsions have been observed in 2 control dogs from 2 other studies, a male and a female, 1 each from each of the studies. In these studies, 1 male dog convulsed during bone marrow sampling and 1 female dog convulsed on being taken into the clinical examination room, on week 53 of the study, just prior to termination. The situation with this dog was similar to the one with the lambda-cyhalothrin dog study. The Registrant also stated that convulsions were observed with other dogs being tested with chemicals that were known not to be neurotoxic (see Appendix III for details).

At 3.5 mg/kg/day, 1 male was killed in extremis in week 46 because of severe ataxia and convulsions which persisted over a period of 2 days, even though the dosage was withheld during this period. Ataxia was observed in all dogs, and was apparent from the first week in some dogs (gait abnormalities were recorded as early as day 2). The ataxia was observed 3-7 hours post-dosing. Other clinical signs included muscle tremors, convulsions (3 males: weeks 46, 25 and 37 and 1 female: # 43 in text but could not find reference to convulsions in individual animal data), occasional subdued behavior, worn or bleeding claws, regurgitation of food during the first 2 weeks, fluid feces in all dogs and occasional decrease in food consumption.

The toxicological significance of the fluid feces in unknown. It was not stated in the report the number of hours (days) after dosing the liquid feces were observed. The Registrant's report states the following: "True diarrhea was not a feature of the condition and the dogs often passed normal feces on the days when fluid feces were also observed. The passing of fluid feces did not reflect the general health of the animals and was not associated with histopathological lesions in the alimentary tract. Increased incidences of fluid feces have been reported in studies where, for example, cypermethrin has been administered to dogs. In this case the compound was administered in capsules but where it has been included in the diet there was no evidence of fluid feces, even at concentrations which were highly toxic. It is reasonable to conclude from the above examples that fluid feces are produced as a result of the method of administration. When given in capsule a bolus of the test compound is presented to the gastrointestinal tract and this may produce a direct local (irritant) effect which stimulates the production of liquid feces." For additional comments on fluid feces provided by the Registrant, refer to Appendix II.

The following tables are to be added to the tables in the original Data Evaluation Record (DER) in order to provide a more complete assessment. The first table is the last page of the ataxia summary table (corrected version).

PP321: 1 YEAR ORAL DOSING STUDY IN DOGS

Table 3 - continued

INCIDENCE AND SEVERITY OF ATAXIA (INDIVIDUAL ANIMALS)[1]

Treatment (mg PP321/kg/day)	Sex	Animal No.	Duration Weeks		
			49-52(53)		
			SLIGHT	MODERATE	SEVERE
0.1	Male	14	0	0	0
0.5	Male	26	0	0	0
		27	0	0	0
		28	0	0	0
	Female	34	0	0	0
3.5	Male	37	3	1	0
		38	0	0	0
		39*	-	-	-
		40	9	1	6
		41	0	0	0
		42	7	0	3
	Female	43	2	0	2
		44	0	0	0
		45	0	0	0
		46	0	0	0
		47	0	0	0
		48	0	0	0

[1]Expressed as number of observations/4 weeks.
Slight = unsteady gait
Moderate = Incoordinated gait
Severe = Straddled gait/recumbency
There was no incidence of ataxia in control animals
* Killed in week 46.

Intergroup Comparison of the Incidences of Liquid Feces Over Entire Study

Incidences	Dose Levels (mg/kg/day)			
	0	0.1	0.5	3.5
		Males		
# Observations/	45[a]	31[b]	98[c]	1373
# Dogs Affected	5	6	6	6
		Females		
# Observations/	32	34[d]	216[e]	1234
# Dogs Affected	6	6	6	6

[a]27 incidences in one animal.
[b]18 incidences in one animal.
[c]39 incidences in one animal.
[d]25 incidences in one animal.
[e]161 incidences in one animal.

Intergroup Comparison of Bodyweight Gain (Kg) From Start of Study - Males

Weeks	Treatment (mg/kg/day)			
	0	0.1	0.5	3.5
Initial Wt.	11.98	11.97	12.05	12.00
4	0.47	0.55	0.70	0.57
8	1.05	1.00	1.28	0.97
12	1.37	1.38	1.63	1.42
16	1.67	1.70	2.05	1.67
20	1.93	1.90	2.28	2.03
24	1.92	2.02	2.38	2.17
28	1.90	1.92	2.43	2.33
32	1.97	2.02	2.65	2.57
36	1.97	1.93	2.67	2.67
40	2.10	2.00	2.62	2.85
44	2.08	1.87	2.70	2.93
48	2.05	1.82	2.55	2.63

Intergroup Comparison of Bodyweight Gain (Kg) From Start of Study - Males

Weeks	Treatment (mg/kg/day)			
	0	0.1	0.5	3.5
52	1.88	1.68	2.42	2.48
Final Weight	13.87	13.65	14.47	14.51

Intergroup Comparison of Bodyweight Gain (Kg) From Start of Study - Females

Weeks	Treatment (mg/kg/day)			
	0	0.1	0.5	3.5
Initial Wt.	10.72	10.80	10.58	10.72
4	0.68	0.80	0.88	0.77
8	0.92	1.33*	1.27	1.27
12	1.20	1.65*	1.53	1.52
16	1.50	2.23*	1.98	1.70
20	1.68	2.48*	2.20	1.87
24	1.83	2.53	2.32	1.67
28	1.90	2.72	2.42	1.72
32	2.03	2.72	2.52	1.92
36	2.03	2.92	2.65	2.00
40	2.17	3.02	2.85	2.25
44	2.08	2.98	2.78	2.12
48	2.08	2.95	2.70	2.03
52	2.17	2.88	2.82	1.77
Final Weight	12.88	13.68	13.40	12.48

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

Intergroup Comparison of Plasma Triglycerides (mg/100ml)

	Treatment (mg/kg/day)			
Weeks	0	0.1	0.5	3.5
		Males		
Pre-experimental	32.3	31.3	31.8	31.0
4	38.9	37.9	37.9	47.7
13	28.8	34.4	29.4	35.1
26	30.9	34.2	33.5	37.0
39	31.5	29.0	29.0	39.7
52	27.6	32.5	27.5	37.3
		Females		
Pre-experimental	36.7	35.3	35.2	31.7
4	35.0	34.6	33.5	43.2
13	34.3	26.4	24.6*	31.1
26	38.6	29.5	33.4	39.6
39	35.8	34.6	30.1	40.0
52	36.1	39.5	30.9	43.8

*Statistically significantly different from controls ($p < 0.05$)

Intergroup Comparison of Plasma Cholesterol (mg/100 ml)

	Treatment (mg/kg/day)			
Weeks	0	0.1	0.5	3.5
		Males		
Pre-experimental	155	166	155	179
4	150	151	139	149
13	147	147	133	133
26	152	157	140	130
39	134	143	132	122
52	129	132	129	104

Intergroup Comparison of Plasma Cholesterol (mg/100 ml)

	Treatment (mg/kg/day)			
Weeks	0	0.1	0.5	3.5
	Females			
Pre-experimental	165	162	156	151
4	139	127	139	137
13	135	136	138	134
26	149	151	158	138
39	124	138	124	141
52	139	142	129	132

*Statistically significantly different from controls ($p < 0.05$)

Intergroup Comparison of Plasma Sodium (mEq/l)

	Treatment (mg/kg/day)			
Weeks	0	0.1	0.5	3.5
	Males			
Pre-experimental	153	153	152	153
4	147	147	147	145
13	148	149	148	147
26	157	157	156	154*
39	153	153	152	152
52	158	158	156*	155**
	Females			
Pre-experimental	153	154	153	154
4	149	148	148	146*
13	150	149	150	148*
26	160	159	158*	157**
39	153	153	154	152
52	157	158	159*	157

*Statistically significantly different from controls ($p < 0.05$)
**Statistically significantly different from controls ($p < 0.01$)

Intergroup Comparison of Plasma Potassium (mEq/l)

	Treatment (mg/kg/day)			
Weeks	0	0.1	0.5	3.5
		Males		
Pre-experimental	4.63	4.67	4.85	4.30
4	4.83	4.77	4.82	4.69
13	4.52	4.55	4.62	4.58
26	4.80	5.07	4.84	4.74
39	4.59	4.58	4.37	4.25*
52	4.55	4.49	4.40	4.25*
		Females		
Pre-experimental	4.58	4.60	4.63	4.58
4	4.42	4.62	4.50	4.54
13	4.55	4.60	4.60	4.85
26	4.87	5.17	4.78	4.98
39	4.34	4.48	4.49	4.16
52	4.48	4.62	4.45	4.50

*Statistically significantly different from controls ($p < 0.05$)

Intergroup Comparison of Plasma Calcium (mg/100 ml)

	Treatment (mg/kg/day)			
Weeks	0	0.1	0.5	3.5
		Males		
Pre-experimental	11.5	11.7	11.3	11.5
4	11.1	11.2	11.1	11.1
13	10.6	10.8*	10.7	10.6
26	10.7	10.8	10.7	10.6
39	10.5	10.4	10.5	10.5
52	10.4	10.4	10.4	10.2
		Females		
Pre-experimental	11.2	11.5	11.3	11.5
4	11.2	11.1	11.3	10.9
13	10.9	10.9	10.9	10.8
26	10.9	11.0	11.0	10.7
39	10.5	10.6	10.6	10.5
52	10.5	10.5	10.5	10.2

*Statistically significantly different from controls ($p < 0.05$)

Intergroup Comparison of Urine Biochemistry

	Dose Level (mg/kg/day)			
Urine pH	0	0.1	0.5	3.5
Males				
Pre-Experimental	6.93	6.46	6.85	6.76
Week 25	6.94	6.83	6.88	7.04
Week 51	7.67	7.18	7.38	7.25
Females				
Pre-Experimental	6.47	6.50	6.67	6.49
Week 25	6.77	6.86	6.58	6.87
Week 51	7.37	7.38	7.31	7.14
Urine Specific Gravity				
Males				
Pre-Experimental	1.032	1.029	1.028	1.033
Week 25	1.039	1.039	1.042	1.034
Week 51	1.040	1.039	1.043	1.041
Females				
Pre-Experimental	1.032	1.026	1.029	1.033
Week 25	1.041	1.040	1.035	1.034
Week 51	1.038	1.039	1.040	1.044

Intergroup Comparison of Absolute Organ Weights (g)

	Treatment (mg/kg/day)			
Organ	0	0.1	0.5	3.5
	Males			
Kidney	59.1	58.9	60.3	67.9*
Liver	389	401	408	445
Testes	30.2	30.2	29.1	28.0
Adjusted for bodyweight	30.8	31.4	28.1	26.8
	Females			
Liver	357	373	380	406

*Statistically significantly different from controls ($p < 0.05$).

Intergroup Comparison of Microscopic Findings - Males

Observation	Treatment (mg/kg/day)			
	0	0.1	0.5	3.5
Kidney				
# Examined	6	6	6	6
Unilateral pyelitis	0	0	1	1
Liver				
Congeries of pigment laden Kupffer cells	0	0	4	1
Testes				
Atrophy of seminiferous epithelium	0	0	1	0
Orchitis - unilateral	0	0	0	1

Intergroup Comparison of Microscopic Findings Females

Observation	Treatment (mg/kg/day)			
	0	0.1	0.5	3.5
Kidney				
# Examined				
Unilateral pyelitis	0	0	2	1
Bilateral pyelitis	0	2	0	1
Liver				
Congeries of pigment laden Kupffer cells	4	3	3	3
Mammary Gland				
Hemorrhage	0	0	1	0

Appendix II: Discussion of Fluid Feces in Dogs With Pyrethroid Chemicals

Incidence of Fluid Feces

An increased incidence of fluid feces is not an uncommon clinical observation in response to dosing with pyrethroids. This change, which was also seen in the control beagles should be differentiated from true diarrhea because

a) the dogs often also pass normal feces on days when liquid feces are observed and

b) there is no increased frequency of defecation observed which would be expected with a true diarrhea.

The observation arises from one or two probable causes which could occur together or independently. These are

a) a decreased water absorption from the colon or

b) a decreased intestinal transit time.

The former is driven by active absorption of sodium with water following passively. Thus any local effect which might cause a reduction in the ability to concentrate ions against a concentration gradient could result in reduced absorption of water and hence increased fluidity of feces (Billich and Levitan 1969).

Gut motility (peristalsis) is under control of the autonomic nervous system. Modification of the conductivity of nerves involved in this process will alter gut motility and hence bowel transit time. For example some drugs used in the treatment of constipation will directly stimulate the nerve endings of the mucosa which causes the increase of muscle tone of the intestine (Hubacher and Doernberg 1964). This is a local effect which depends on continued presence of the stimulant.

The pyrethroid class of chemicals is known to change sodium permeability, at least in nerve membranes and possibly more generally (Bradbury et al 1983, Gray and Rickard 1982). Thus, it is probable that the ability of the pyrethroids to induce fluid feces under some circumstances can be explained by either a local effect on the nerve endings in the gut mucosa and/or by increasing sodium permeability in the colon. It should be noted that other pyrethroids, deltamethrin and cypermethrin, given by gavage over a 13 week period produced liquid feces inter alia. However, these changes were not seen in subsequent studies with dietary administration. (Buckwell and Butterworth, 1977; Kalinowski et al. 1982; FAO 1982).

This latter observation provides a probable explanation for the variable incidence seen. The compound was administered in a gelatine capsule shortly prior to the daily feed. It is predicted that dissolution of the capsule will not occur until after the dog has consumed its normal meal. Under these circumstances the test compound will be distributed through a relatively large volume of stomach contents. If, however, due to sporadic early dissolution or delayed feeding behavior, the capsule dissolves prior to the dog consuming its full daily feed, then the pyrethroid may well pass through the intestines as a bolus rather than as a more dilute form. In this latter case local pharmacological actions of the type described above are more probable because of the high localized concentration of the test compound within the gastrointestinal tract.

More detailed consideration of the findings in the lambda cyhalothrin study shows that as expected the major incidence of fluid feces was seen in the high dose group. The slightly increased incidence in the mid dose group was substantially attributable to one female(F33) with the other females and the males showing individual incidences similar to the control range. This pattern of response might be expected if feeding behavior was the major determinant, though it is notable that this dog also showed a higher incidence of fluid feces pre-study. There was no individual or group increase at the low dose.

In summary the phenomenon is believed to be due to a localized pharmacological reaction to a high concentration of a test compound and this would account for the apparent dose-response relationship observed in the study. As the observation is also made in control dogs it is not compound specific. It is readily reversible as demonstrated by the sporadic incidence in individual dogs and, as with all such pharmacological type reactions, it is without histological change, indicating that no permanent structural or functional change is induced. For these reasons the observation is considered to be of no toxicological significance.

011241

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3. Bradbury JE, Forshaw PJ, Gray AJ and Ray DE (1983). The action of mephenesin and other agents on the effects produced by two neurotoxic pyrethroids in the intact and spinal rat. Neuropharmacol. 22, 907.

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Appendix III: Discussion on the Incidence of Convulsions in 2 Dogs at 0.5 mg/kg/day in 1-Year Dog Study

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Lambda-cyhalothrin
1-Year Dog Study
Guideline No. 83-1(b)

Incidence of Convulsions

Towards the end of the study, two males in the mid-dose group (0.5mg/kg/day) convulsed shortly after being transported. Dog M26 convulsed briefly in week 52 of the study while being carried to the room in which clinical examinations were performed by the Veterinary Officer. The next week, this dog again convulsed briefly while being carried to the clinical examination room, for its final examination prior to termination at the end of the study. Dog M27 convulsed twice, shortly after being put into a metabolism cage, in week 51, and again on the next day when it was removed from the metabolism cage. No other convulsions had been recorded in any dog in this dose group at any other time. Since on each of these occasions the dogs were being subjected to manipulative procedures, the Study Director concluded that these episodes were unrelated to compound, being induced by the stress and noise associated with handling. The following text gives further information to support this conclusion.

Convulsions are a rare event in dogs, but are known to occur in laboratory beagles. Examination of the clinical observation records at CTL have shown two instances of control dogs convulsing during manipulative procedures - one male dog convulsed during bone marrow sampling and a female dog (on another study) convulsed on being taken in to the clinical examination room, on week 53 of the study, just prior to termination. The situation with this latter dog is clearly directly comparable with that of M26 on the lambda-cyhalothrin study.

In addition, convulsions have been observed in a dog being dosed with a compound known NOT to be neurotoxic, as evidenced by unequivocal negative findings in acute and sub-chronic neurotoxicity studies in rats. In this case a single dog convulsed on six seperate occassions when taken to the clinical examination room for ophthalmoscopy. As with the other dogs, these convulsions came on later in the study (occurring between weeks 24 and 52). In this case, the relationship to the stress of being taken into the clinical examination room was amply demonstrated when the dog was examined at its pen-side, when it did not convulse.

Zeneca are confident that the conclusion of the Study Director was correct and that the two occasions of convulsions in two dogs in the lambda cyhalothrin study were unrelated to compound, being induced by the manipulative procedures, described above.

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

006004

DATA EVALUATION REPORT

STUDY TYPE: Chronic dog study (83-1) TOX. CHEM. NO.: 725C

ACCESSION NUMBER: 400279-02

TEST MATERIAL: PP321

SYNONYMS: Karate

STUDY NUMBER(S): PDO583

REPORT NUMBER: CTL/P/1316

SPONSOR: ICI Americas Inc., Macclesfield, England

TESTING FACILITY: ICI, PLC Central Toxicology Laboratory, Alderly, Park, Macclesfield, UK

TITLE OF REPORT: PP321: 1 Year Oral Dosing Study in Dogs

AUTHOR(S): Hext PM, Brammer A, Chalmers DT, Chart IS, Gore CW, Pate I, Banham PB

REPORT ISSUED: 1/22/86

IDENTIFYING VOLUME: Vols. 1 and 2

CONCLUSION: The NOEL for chronic effects is 0.5 mg/kg/day in beagle dogs, based upon clinical signs of neurotoxicity, including ataxia, convulsions and muscle tremors. There was an increase in fluid feces in all animals at 3.5 mg/kg/day and in one animal at 0.5 mg/kg/day (the latter was not considered to be toxicologically significant). The dose levels tested were 0.1, 0.5 and 3.5 mg/kg/day.

Classification: CORE GUIDELINE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: (Z)-(1R, 3R), S-ester and (Z)-(1S, 3S), R-ester of alpha-cyano-3-phenoxybenzyl,3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane carboxylate
Description: buff-colored powder
Batch #(s), Other #(s): batch ref. P13, CTL Ref. YO2537/001/005
Purity: 96.5% w/w PP321
Source: ICI, PLC, Plant Protection Div., Jealotts Hill, Berkshire, UK
Vehicle (if applicable): corn oil

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): male and female beagle dogs
Age: 16-21 weeks (20-25 weeks at start)
Source(s): ICI, PLC, Alderly Park, Macclesfield, UK

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3. Procedure:

a. Dosing Preparation : Animals administered the compound orally via gelatin capsule. Quantities corrected for purity and dissolved in corn oil. 0.25 ml/kg administered daily. Animals fed standard laboratory diet.
Frequency of preparation: 5 week intervals
Storage conditions: In the dark at room temperature
Stability Analyses: Stability studies done in previous studies; stable over a period of 6-7 weeks
Concentration Analyses: all solutions analyzed for PP321 content prior to use in study

b. Basis For Selection of Dosage Levels: Based upon a six-week dose-range finding study. Clinical signs of neurotoxicity and fluid feces seen at 2.5 mg/kg/day and above.

c. Animal Assignment and Dose Levels:

Test Group	Dose Administered mg/kg/day	Main Study 12 months male	female
Contr.	0	6	6
1	0.1	6	6
2	0.5	6	6
3	3.5	6	6

d. Clinical Observations and Mortality: All animals observed routinely 3 times daily during the week and 2 times daily on weekends and holidays. Full clinical exams at pre-study and at 3-monthly intervals. Exams included cardiac and pulmonary auscultation and indirect ophthalmoscopy.

e. Body Weight Determinations: Weekly

f. Food and/or Water Consumption: Daily

g. Ophthalmological Examinations (if applicable): 3-monthly intervals

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h. Clinical Pathology: (*) recommended by Guidelines

1) Hematology:

Collection times for blood (including # of animals):
prestudy, weeks 4, 13, 26, 39 and 52

The following CHECKED (X) parameters were examined:

X		X	
x	Hematocrit (HCT)*	x	Mean corpustular HGB (MCH)
x	Hemoglobin (HGB)*	x	Mean corpustular HGB conc.(MCHC)
x	Leukocyte count (WBC)*	x	Mean corpustular volume (MCV)
x	Erythrocyte count (RBC)*	x	Kaolin-cephalin
x	Platelet count*	x	Prothrombin times
	Total plasma protein (TP)		
x	Leukocyte differential count*		

2) Clinical Chemistry:

The following CHECKED (X) parameters were examined:

X	Electrolytes:	X	Other:
x	Calcium*	x	Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
	Phosphorus*	x	Cholesterol*
x	Potassium*		Globulins
x	Sodium*	x	Glucose*
	Enzymes:		Total bilirubin*
x	Alkaline phosphatase	x	Total protein*
	Cholinesterase	x	Triglycerides
	Creatinine phosphokinase*		
	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		
x	Plasma creatine kinase		

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3) Urinalysis:

Collection times for urine (including # of animals): pre-experimentally and weeks 25 and 51

The following CHECKED (X) parameters were examined:

X		X	
	Appearance*	x	Glucose*
	Volume*	x	Ketones*
x	Specific gravity*	x	Bilirubin*
x	pH	x	Blood*
x	Sediment (microscopic)*		Nitrate
x	Protein*	x	Urobilinogen

i. Gross Necropsy:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to end of exposure period and were subjected to complete gross pathological examinations:

All

Animals (groups) sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations:

All

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j. Histopathology:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to the end of the exposure period and were subjected to microscopic examination:

All

Animals (groups) which were sacrificed at the end of the treatment/observation period and were subjected to microscopic examination:

All

CHECKED (x) tissues were preserved for histopathological examination and (xx) tissues were weighed upon removal from the animal. The (*) tissues were recommended by the Guidelines.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	x	Aorta*	xx	Brain*
x	Salivary glands*	xx	Heart*	x	Periph. nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	x	Spleen*	x	Eyes (optic n.)*
x	Jejunum*	x	Thymus*		Glandular
x	Ileum*		Urogenital	xx	Adrenals*
x	Cecum*	xx	Kidneys*		Lacrimal gland
x	Colon*	x	Urinary bladder*	x	Mammary gland*
x	Rectum*	xx	Testes*	x	Parathyroids*
xx	Liver*		Epididymides	xx	Thyroids*
x	Gall bladder*	x	Prostate		Other
x	Pancreas*		Seminal vesicle	x	Bone*
	Respiratory	xx	Ovaries	x	Skeletal muscle*
x	Trachea*	x	Uterus*	x	Skin
x	Lung*			x	All gross lesions and masses
				x	Bone marrow smears
				x	Epididymides
				x	Tibia/femur (stifle joint)

k. Statistical Analyses: Body weight gains were considered by analysis of variance. Hematological and biochemical data were considered by analysis of covariance on pre-experimental values. Organ weights were considered by analysis of variance and analysis of covariance on final body weight. Student's t-test was also used.

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006004

B. RESULTS:

1. Dosing Preparation: 11 samples were analyzed for PP321 concentration. The mean values were as follows: for the 0.4 mg/ml concentration, the mean concentration range was 0.37-0.43 mg/ml; for the 2.0 mg/ml concentration, the mean concentration range was 1.85-2.08 mg/ml and for the 14.0 mg/ml concentration, the mean concentration range was 12.6-15.2 mg/ml. The concentrations were within 10% of nominal for all preparations. The mean concentrations of dosing solutions administered over the whole of the study were within 5% of the intended concentrations.

2. Clinical Observations and Mortality: In week 46, 1 male from the highest dose level (3.5 mg/kg/day) was killed because of severe ataxia and convulsions which persisted over a period of 2 days, even though dosage was withheld during this period. No other animals either died or were killed in extremis during the study.

   At 3.5 mg/kg/day, the principal clinical observations following dosing were neurological effects. These included ataxia, muscle tremors and convulsions (see attached table). Subdued behavior was also observed in many of these animals. For individual animals, usually on single days only, dosing at this level was suspended to allow recovery from the neurotoxic effects. Worn, broken or bleeding claws were observed in 3 dogs, and on 3 occasions appeared to be associated with the signs of neurotoxicity. On 3 other occasions with 1 female dog, it was unknown whether or not this accompanied neurotoxic effects. Regurgitation of food was seen occasionally during the first 2 weeks of the study from 7/12 dogs. Thereafter, there was only a moderate incidence in this group. An increased incidence in fluid feces was observed in all the dogs from this dose group thoughout the study.

   At 0.5 mg/kg/day, 2 dogs were observed to have gait abnormalities (2 times in 1 animal and 4 times in the other animal). Convulsions were observed in 2 other dogs (both males); the convulsions appeared to be precipitated by the stress of handling or noise. Blood stains on the pen floor with no obvious cause were seen in 2 dogs. The frequency of fluid feces was clearly increased in 1 dog at this dose level and the overall incidence in this group suggested a slight treatment-related effect.

   On a single occasion, 1 male dosed at the lowest dose level, 0.1 mg/kg/day had slight ataxia. Blood stains on the pen floor with no obvious cause was seen with 1 female dog in week 27. The incidence of vomiting in this dose group was comparable to controls and there was no increase in either the frequency or incidence in fluid feces over the control values.

   Other clinical findings in all dose groups were considered to be incidental.

3. Body Weight Determinations: There was no evidence of any treatment-related effects on body weight gain in either sex.

4. Food and/or Water Consumption: 5/12 dogs at the highest dose level showed a slight reduction in food intake on a very small number of occasions. Since reduction in food intake, particularly for males, was a rarity for the testing laboratory, this reduction was considered to be due to PP321. There was no apparent correlation with the occurrence of neurological effects. A total of 2 dogs in the remaining 3 groups (including controls) left food uneaten.

5. Ophthalmological Examinations: No treatment-related effects were observed.

6. Hematology: Statistically significant differences in various parameters were observed during the treatment period. The majority of the findings were noted in the highest dose group. The authors considered these observations to be minor and not to be of biological or toxicological significance.

7. Clinical Chemistry: There was evidence of slightly increased plasma triglycerides accompanied by a slight decrease in plasma cholesterol in the high dose animals throughout the dosing period. Other observed changes were considered to be incidental.

8. Urinalysis: No treatment-related effects were observed.

9. Gross Pathology: No treatment-related lesions were observed.

10. Organ Weights: In the highest dose group, mean testes weights were slightly reduced after adjustment for final body weight. This was particularly evident in 2 dogs. There were also slight dose-related increases in mean liver weights at this dose level for both sexes and evidence of increased kidney weights in males, although this was mainly due to 1 animal.

11. Histopathology:

    a. Nonneoplastic lesions: No treatment-related lesions were observed.

    b. Neoplastic lesions: No treatment-related lesions were observed.

12. Quality Assurance Measures: Appropriate inspections were conducted and reports were written. As could be reasonably established, the methods described and the results given in the report accurately reflect the data produced during the study.

006004

C. DISCUSSION:

This study appears to have been properly conducted according to the EPA Guidelines. The only significant signs of toxicity that were observed were the clinical signs of neurotoxicity and liquid feces at the highest dose level. These signs were not supported by any microscopic indications. The clinical signs of neurotoxicity were especially evident at the highest dose level, 3.5 mg/kg/day. At 0.5 mg/kg/day, the clinical signs could not be clearly attributed to neurotoxicity. Four of twelve dogs at this dose level showed some signs possibly relating to neurotoxic effects. Of the four, two animals showed slight ataxia (one time for one dog and four times during one week for another dog). The signs were so slight that little description was written of them in the individual animal data. The other two animals displayed convulsions of short duration (lasting 30 seconds to 3 minutes), one time for one animal and two times for the other animal. These convulsions occurred while the animals were either being carried or being placed in a metabolism cage. No other clinical signs of this type were observed either in these animals or in any of the other animals at this dose level throughout the duration of the study. From the clinical observation data, the NOEL for neurotoxic effects is probably very close to 0.5 mg/kg/day. The authors of the report used this dose level as the NOEL for the study. Since the data do not indicate a clear effect, 0.5 mg/kg/day is accepted as the NOEL for neurotoxic effects in dogs. The study is classified as CORE GUIDELINE.

_____

Page _____ is not included in this copy.

Pages 114 through 117 are not included in this copy.

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.

_____ Internal deliberative information.

_____ Attorney-client communication.

_____ Claimed confidential by submitter upon submission to the Agency.

_____ Third party confidential business information.

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.

US EPA ARCHIVE DOCUMENT

H

EPA Reviewer: Pamela M. Hurley
Registration Action Branch 2 (7509C)
TXR No. 0050580

Pamela M Hurley, Date 03/26/2004

DATA EVALUATION RECORD
Supplement to DER for MRID No. 00150842 Cyhalothrin: Chronic Feeding/Oncogenicity Study in Mice. TXR Nos. 005100, 011241

STUDY TYPE: Chronic Feeding/Oncogenicity Study in Mice
OPPTS Number: 870.4300 OPP Guideline Number: §83-5

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (89.25% a.i.)

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

CITATION: Colley, J.; Dawe, S.; Heywood, R.; et al. (1984) Cyhalothrin: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Mice: Final Report Vol. 3.: Rept No. ICI/395. Unpublished study prepared by Huntingdon Research Centre. 553 p. MRID 00150842

Colley, J.; Dawe, S.; Heywood, R.; et al. (1984) Cyhalothrin: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Mice: Addendum to Final Report: No. CTL/C/1260: No. ICI/395/83668. Unpublished study prepared by Imperial Chemical Industries, PLC. 70 p. MRID 00153035

Colley, J.; Dawe, S.; Heywood, R.; et al. (1984) Cyhalothrin: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Mice: (Final Report): Report No. ICI 395/83668. Unpublished study prepared by Huntingdon Research Centre. 849 p. MRID 00154804

Athis, J. (1994) Comments on February 1993 EPA Rfd/Peer Review of Cyhalothrin Oncogenicity/Chronic Feeding Study in Mice (Accession Number 073214-073216). Unpublished study prepared by Zeneca Agrochemicals. 12 p. MRID 43241902

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: Groups of 52/sex CD-1 mice were fed technical cyhalothrin (89.25%) in the diet at 0, 20, 100 or 500 ppm (approximately 0, 3, 15 or 75 mg/kg/day) for 104 weeks. In addition, 4 satellite groups of 12 mice/sex were fed the same dietary concentrations and terminated at week 52.

No treatment-related effects were observed at 3 mg/kg/day. At 15 mg/kg/day, an increased incidence of piloerection was observed in males between weeks 13 and 52. This was the only observed effect at 15 mg/kg/day. After week 52, the incidences of piloerection were comparable to the control group. At 75 mg/kg/day, an increased incidence of piloerection was observed in both sexes and hunched posture was observed up to 78 weeks, particularly in males. After 78 weeks, the incidences of hunched posture were similar between treated and control groups. Decreased body weight gain was also observed in males during the first 13 weeks (54% of the control group). Mean body weight was 10 percent lower than the controls at week 13. For the entire two years, body weight gain in males was 77% of the control value.

On 2/12/93 and 6/16/94, the HED RfD/Peer Review Committee concluded that cyhalothrin was not tested at a sufficiently high dose level for an adequate carcinogenicity study in mice. Following the decision by the Committee, Toxicology Branch 1 (TB-1) determined that there was not enough toxicological concern to warrant a requirement for a new carcinogenicity study in the mouse at that time. However, there was sufficient concern about the adequacy of dosing in this study that additional testing may be required in the future. This decision was based on data from the mouse chronic feeding/oncogenicity study, the 28-day range finding study in the mouse and the results from mouse and rat carcinogenicity studies conducted with similar pyrethroids.

The 2/12/93 RfD/Peer Review Committee also had concern over the increased incidences of mammary tumors in females (1/52, 0/52, 7/52, 6/52). **On 6/16/94, the HED RfD/Peer Review Committee evaluated the study in more detail and noted that the concurrent control value was low when compared to historical control values. Because of the equivocal nature of the findings, and in view of the inadequacy of the dose levels tested, the Committee concluded that the chemical should be classified as a Group D chemical.**

The LOAEL for systemic chronic toxicity is 75 mg/kg/day based on an increased incidence of piloerection and hunched posture and decreased mean body weight gain in males and the NOAEL is 15 mg/kg/day.

Under the conditions of the study, cyhalothrin is not considered to be oncogenic in mice. However, there is concern over the adequacy of the dosing in the study and additional testing may be required in the future, particularly if new uses result in significantly higher residues in human foods and/or there is significantly higher occupational (or future residential) exposure due to changes in parameters such as the method of application.

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a chronic feeding/oncogenicity study (**§83-5**) in the mouse.

Detailed Discussion on the Adequacy of the Dosing

On February 12, 1993, the HED RfD/Peer Review Committee met to evaluate cyhalothrin / lambda-cyhalothrin and questioned whether or not the mouse carcinogenicity study was tested at sufficiently high dose levels. The Committee stated that "generally, the highest dose tested in the mouse carcinogenicity study appears to be approaching an adequate dose for carcinogenicity testing in males based upon decreased body weight gain. On the other hand, several questions were raised concerning the adequacy of doses tested....in females." The Registrant submitted a response to the question concerning the dose levels tested and a 28-day range-finding study in the mouse.

In their response, the Registrant stated that the 2-year mouse study was started in 1980, before records were kept on selection of dose levels. Therefore, they had to reconstruct the reasoning from the 28-day mouse study. They also stated that hypertrophy of the liver was not established to be of no toxicological significance at that time. In addition, the highest dose to be tested was set on the response of the most sensitive sex. "It was considered good practice not to have too wide a divergence in the dosing regimes used with the different species, since to do so was considered to impact adversely on extrapolations between species."

In the 28-day mouse study, cyhalothrin (technical, no purity available) was tested in an oral feeding study in CD-1 mice as a range-finding study for the carcinogenicity study. Twelve mice/sex/dose level were tested at 0, 5, 25, 100, 500 or 2000 ppm in the diet (0, 0.65, 3.30, 13.5, 64.2 or 309 mg/kg/day for males and 0, 0.80, 4.17, 15.2, 77.9 or 294 mg/kg/day for females).

At 2000 ppm, piloerection, abnormal gait (walking on toes), hunched posture, increase in respiration rate and emaciated appearance were observed. Six males and 3 females died during the study. Both males and females had a significant decrease in body weight gain over the treatment period when compared to controls (-1g versus 5 g in controls for males ($p < 0.001$) and 0g versus 3 g in controls for females ($p < 0.001$)). A decrease in food consumption was observed in both sexes during the first week (60.8% of controls for males and 62.5% of controls for females) and in females for the remainder of the study (82% of controls, $p < 0.05$). Males had a slightly lower mean total white blood cell count (68%). The differential white cell count revealed lower lymphocyte counts (58.7%) and higher neutrophil counts (62.5% above controls), $p < 0.01$ for all hematological values in males at this dose level. Significantly higher APDM activity was observed in both sexes (61.9% above controls for males and 77.8% above controls for females). Slight increases in kidney weights (28.8% over controls for males, $p < 0.001$) and liver weights (17% over controls for males ($p < 0.05$) and 3.1 % over controls for females) were observed. In females, the differences were not statistically significant. Slightly lower heart weights were also observed in females (87.7% of controls, $p < 0.05$)). Minimal centrilobular hepatocyte enlargement was observed in 2/12 females.

At 500 ppm, piloerection was observed in several mice, several males had low white blood cell counts (not statistically significant) as well as marginally lower lymphocyte numbers (80%). Significantly higher APDM activity was observed in females (26.2% over controls). Slightly higher kidney weights were observed in males (13.5% over controls, $p < 0.01$)) and slightly lower heart weights were observed in females (93.0%, $p < 0.05$).

At 100 ppm, piloerection was also observed in several mice. One female had an emaciated appearance. Marginally lower lymphocyte numbers were noted for males (79% of controls). Significantly higher APDM activity was observed in females (24.8% over controls). Slightly higher kidney weights were observed in males (13.0% over controls, $p < 0.01$) and marginally lower heart weights were observed in females (87.7%, $p < 0.01$).

The NOAEL is 500 ppm and the LOAEL is 2000 ppm based on mortality, clinical signs of toxicity, decreases in body weight gain and food consumption, changes in hematology and organ weights and minimal centrilobular hepatocyte enlargement. The minimal effects observed at 500 and 100 ppm are not considered to be toxicologically significant.

Thus, from this study, it is evident that 2000 ppm was above the MTD (mortality). The effects at 500 ppm were minimal. Therefore, it appears that the MTD for the mouse study is somewhere between 500 and 2000 ppm.

Provided with the newly submitted range-finding study and the Registrant response above, the HED RfD/Peer Review Committee reconvened on June 16, 1994 concerning the mouse carcinogenicity study conducted with cyhalothrin. At that meeting they "concluded that the chemical was not tested at a sufficiently high dose level for carcinogenicity testing in mice." Subsequent to the meeting, the respective Toxicology Branch reviewing cyhalothrin determined that "there was not enough toxicological concern to warrant a requirement for a new carcinogenicity study in the mouse at this time" (memorandum from P. Hurley to G. Ghali, dated 8/6/94). However, there was sufficient concern about the adequacy of dosing in this study that additional testing may be required in the future.

Detailed Discussion of the Incidences of Mammary Adenocarcinomas

On February 12, 1993, the HED RfD/Peer Review Committee had questions concerning the significance of the mammary adenocarcinomas in female mice. The incidences were reported in the Data Evaluation Record (DER) as follows:

Incidences of Mammary Adenocarcinomas in Female Mice Dosed With Cyhalothrin

0 ppm	20 ppm	100 ppm	500 ppm
1/52	0/52	7/52 (13.5%)	6/52 (11.5%)

In the paragraphs summarizing the data, the DER states that the incidences were statistically significant at 100 ppm (p = 0.03) and 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 at 100 ppm (13.5%) was only slightly higher than the laboratory's historical range (2-12%; average of 17 studies was 81/1156 or 7.0%). The incidence at 500 ppm (11.5%) was within the historical control range. In addition, as can be seen from the historical control data, the concurrent control was among the lowest of the historical control range, and the incidence of 0/53 tumors at the low dose of 20 ppm is lower than the lowest value observed in the historical control range. Neither the incidence at 100 ppm nor that at 500 ppm are statistically significant when compared to the historical control mean (Fishers Exact, p = 0.16, p = 0.37; statistics provided by Registrant).

The following table shows the historical control data on the incidence of mammary adenocarcinoma in studies performed on female CD-1 mice at the Huntingdon Research Centre for animal delivery dates between May 1978 and November 1980. Also included is the incidence of mammary adenocarcinoma in control female mice in this study (ICI 395).

Historical Control Data on the Incidence of Mammary Adenocarcinoma				
Study	Date of Animal Receipt	Duration (Weeks)	Incidence*	
1	24/05/78	104	3/60	5.0%
2	31/05/78	104	7/60	11.7%
3	05/07/78	104	6/100	6.0%
4	30/08/78	108	3/51	5.9%
5	13/12/78	107	6/52	11.5%
6	14/02/79	104	1/55	1.8%
7	25/04/79	115	10/104	9.6%
8	04/07/79	121	9/104	8.7%
9	18/07/79	107	2/52	3.8%
10	29/08/79	104	3/52	5.8%
11	19/09/79	104	3/52	5.8%
12	05/03/80	108	3/52	5.8%
13	19/03/80	104	1/50	2.0%
14	19/03/80	111	5/104	4.8%
15	26/03/80	109	11/104	10.6%
16	18/06/80	108	5/52	9.6%
17	12/11/80	104	3/52	5.8%
Total			81/1156	7.0%
ICI 135	12/3/80	104	1/52	1.9%

*Incidence is expressed as the number of mice with mammary adenocarcinoma over the number

of control mice in the main group (excluding satellite group animals) and as a percentage.

The Registrant provided the following summary table on mouse adenocarcinomas in the mouse study:

Incidence at 2 Years of Mouse Adenocarcinoma

Dose (ppm)	0	20	100	500
Interim	0/12	0/11	0/11	0/10
Intercurrent	0/27	0/33	5/28 p=0.03	3/34 p=0.17
Terminal	1/25	0/20	2/25 p=0.50	3/20 p=0.22
Total	1/64	0/64	7/64 p=0.03	6.64 p=0.06
*Corrected			*p=0.03	*p=0.04
Intercurrent Plus Terminal	1/52	0/53	7/53 p=0.03	6/54 p=0.06
Trend Test (Total)	*p=0.016			

P values quoted are for a Fishers Exact comparison with concurrent control values unless otherwise designated.

P values marked with an asterisk are from analyses corrected for inter-group differences in mortality and context of observation.

The Registrant also provided the following comments concerning the mammary adenocarcinomas in this study.

"Zeneca believes that there is a compelling pathological case which demonstrates that the tumors are not treatment-related.

The morphology of the tumors in the treated mice is identical to that of the mammary adenocarcinomas seen in the control mice in this and other studies. A difference in morphology might have been expected if the tumors were compound-related.

All tumors occurred as single lesions in individual mice. There was no evidence of multiplicity of tumors with increasing dosage which might have been expected if they were compound-

related.

None of the tumors in treated animals showed evidence of metastases. The only tumor that had metastasized in this study was that in a control animal.

There was no evidence of pre-neoplastic change in the mammary gland.

All tumors were self-evident (first seen as palpable masses) which permits good analysis of their onset. There was however no evidence of decreased latency or time of onset of the mammary tumors in comparison with controls.

The findings were restricted to one sex (female) and one species (mouse). Furthermore there is no published evidence that other pyrethroids induce mammary adenocarcinmoas in any species (Bradbury & Coats, 1989). **[Note: TB-1 checked the Division's Carcinogenicity Peer Review files on pyrethroids and verifies that there are no data at this time which indicate that this class of chemicals induces mammary tumors in mice.]**

In summary, Zeneca is led to conclude that there is no treatment-related effect on the incidence of mammary adenocarcinomas in this study based on the following:

(i) the absence of a dose-response relationship;

(ii) the low concurrent control incidence;

(iii) the incidence at a single intermediate dose is only marginally in excess of the historical control range and is not statistically significant when compared to historical controls;

(iv) the pathology of the lesion is entirely consistent with control (spontaneous) tumors. Zeneca concludes that the mouse mammary adenocarcinoma is not treatment-related."

Ref.: Bradbury S.P. and Coats J.R. (1989) Comparative Toxicology of the Pyrethroid Insecticides. Reviews of Environmental Contamination and Toxicology. Vol. 108 pp 133-177. Springer-Verlag Publishers, New York.

On 6/16/94, the HED RfD Committee reconvened and evaluated the study in more detail in light of the response and additional data provided by the Registrant. The Committee noted the following:

- Incidences of mammary adenocarcinomas appeared to be increased in females at both the mid- ($p = 0.03$) and high dose levels ($p = 0.04$). There was also a positive dose-related trend.

- There was a lack of a consistent dose-related response and the incidence at the mid-dose level was slightly higher than the historical control range. The incidence at the high-dose level was within the historical control range.

- The concurrent control was relatively low and was among the lowest of the historical control range.

- There was no evidence of decreased latency or time of onset of the mammary tumors when compared to the control group.

Therefore, because of the equivocal nature of the findings, and in view of the inadequacy of the dose levels tested, the Committee concluded that the chemical should be classified as a Group D chemical.

Appendix IV: Registrant Response to Dose Setting for Two Year Mouse Study

2. DOSE SETTING FOR TWO YEAR MOUSE STUDY

This study was started in 1980 before the universal practice of archiving a dose setting rationale with the raw data. Nevertheless with knowledge of the philosophy behind the then current practices and the results obtained in the 28 day study it is possible to reconstruct the logic used in the dose selection for the chronic study.

Background information

28 day studies were commonly used to set doses for life time studies in mice. These studies essentially posed the question, "Are the effects seen in the mouse qualitatively similarly to those in the rat?" If the answer was in the affirmative then additional information on progression of the toxic responses seen could be gained from the 90 day rat study, with the 28 day mouse study supplying essentially quantitative information to allow doses for the chronic study to be set.

Adaptive hypertrophy of the liver was not then unequivocally established as of no toxicological significance. It was therefore taken into account when setting doses although it was generally not regarded as the sole determinant of the highest dose.

It was usual practice to treat both sexes equally. Thus the highest dose would be set with reference to the sex showing the greater response. This remains laboratory practice unless the difference between the sexes is very large.

It was considered good practice not to have too wide a divergence in the dosing regimes used with the different species, since to do so was considered to impact adversely on extrapolations between species.

Results in the 28 Day Range-Finding Study

The mouse 28 day study showed significant mortality (50% in males and 25% in females) at 2000 ppm in diet and the animals gained no weight at all.

The next dose tested was 500 ppm in diet where the response was limited to pilo-erection in the males (also seen at lower doses) with a slightly reduced weight gain, compared to the lower dose groups, though not the controls (which showed an atypically small gain for male mice). In addition there was a small increase in kidney weight in males at this dose level together with some signs of increased amino-pyrene demethylase activity (APDM-a marker for some isoenzymes of cytochrome P_{450}) in the liver. By contrast females showed a clear and statistically significant increase in APDM activity at both 500 and 100 ppm.

These effects were qualitatively similar to those seen in the 90 day rat study, endorsing the approach that predictions for the progression of toxicity could be based on the rat data with those in the 28 day mouse study being used to determine dose levels. It should be noted that in the rat study body weight continued to diverge from controls after the initial 4 week period, albeit at a slow rate.

Conclusions from the 28 day Mouse study

It was evident that 2,000 ppm would be too high a dose for the chronic study, and that 500 ppm produced minimal responses in a 28 day period. In the absence of any additional information on the dose response relationships between these two doses and given their proximity it would have been considered imprudent to exceed the 500 ppm dose rate to any significant extent, especially as significant changes would be expected to develop further over the course of the chronic study. The expectation would have been that the sensitivity afforded by the increased numbers of animals used in a chronic study would be sufficient to establish 500 ppm as at or close to an MTD (as defined by OECD) probably in terms of body weight (a conclusion born out for males in the chronic study) and certainly in terms of increased liver (and possibly kidney) weight and increased APDM activity.

The low dose was selected at 20 ppm on the basis of increased APDM activity in females where it was considered that this would represent a no effect level. The mid dose (100 ppm) was selected as the geometric mean between 20 and 500 ppm.

It should be noted that these doses are exactly twice the inclusion rate of those used in the rat study. This means that the dose rates in (mg/kg/day) received by the mice were some five times greater than those for the rats.

Conclusions

Given the combination of factors detailed above, and the experience with contemporary studies, the information generated would have been considered sufficient for dose selection and we believe no other course of action would have been taken.

In the event, it is clear that an MTD, as defined in 1980, was achieved for male mice and that female mice were close to this level (by less than a four-fold factor).

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

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. 073214-073216.

APPROVED BY:

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

Signature: I. Cecil Felkner

Date: 11-14-86

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:

William L. McLellan, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: William L. McLellan
Date: Nov. 14, 1985

Robert J. Weir, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Robert J. Weir
Date: Nov. 14, 1985

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
Chronic Toxicity/Oncogenicity
Technical Quality Control
Dynamac Corporation

Signature: I. Cecil Felkner
Date: 11-19-85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela Hurley
Date: 1/23/86

Edwin Budd
EPA Section Head

Signature: John Schmitz
Date: 5/15/86

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 1.

11. MATERIALS AND METHODS (PROTOCOLS):

See Appendix A for details.

A. Materials and Methods:

1. The test material, cyhalothrin, batch No. Y00 102/010/005, was described as a brown viscous liquid. The purity was not specified. The dosed 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 analyzed for cyhalothrin concentration.

2. Four main groups of 52 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). In addition, four satellite groups of 12 mice of

[1]Only 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 21.5 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	19.3 ± 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 $p < 0.01$.

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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 100 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)				Female/Dose Level (ppm)			
	0	20	100	500	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.

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APPENDIX A

Materials and Methods

US EPA ARCHIVE DOCUMENT

_____

Page _____ is not included in this copy.

Pages 145 through 154 are not included in this copy.

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.

_____ Internal deliberative information.

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EPA Reviewer: Pamela M. Hurley Pamela M Hurley , Date 3/26/2004
Registration Action Branch 2 (7509C)
TXR No. 0050580

DATA EVALUATION RECORD
Supplement to DER for MRID No.: 00154802 Cyhalothrin: Multigeneration Reproduction Study in the Rat. TXR Nos. 005100, 005161, 009957

STUDY TYPE: Multigeneration Reproduction Study in the Rat
OPPTS Number: 870.3800 OPP Guideline Number: §83-4

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (89.2% a.i.)

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

CITATION: Milburn, G.; Banham, P.; Godley, M, et al. (1984) Cyhalothrin: Three-Generation Reproduction Study in the Rat: Report No: CTL/P/906. Unpublished study prepared by Imperial Chemical Industries PLC. 1916 p. MRID 00154802.

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: In the three-generation reproduction study, groups of 15 male and 30 female SPF Wistar-derived rats/dose were fed technical cyhalothrin (89.2%) in the diet at 0, 10, 30 or 100 ppm (approximately 0, 0.5, 1.5 or 5.0 mg/kg/day) (MRID 00154802). The premating periods were 12 weeks for the F_0 animals and 11 weeks for the F_1 and F_2 animals.

Parental toxicity was observed as decreased mean body weight and body weight gain during the premating and gestation periods at 5.0 mg/kg/day. There were no other treatment-related effects. Offspring toxicity was observed as reduced mean pup weight and pup weight gains during lactation, again at 5.0 mg/kg/day. No other treatment-related effects were observed.

The parental/offspring systemic NOAELs are 1.5 mg/kg/day and the parental/offspring systemic LOAELs are 5.0 mg/kg/day based on decreased mean body weight and body weight gain during the premating and gestation periods and reduced mean pup weight and pup weight gain during lactation. The reproductive NOAEL is 5.0 mg/kg/day (highest dose tested).

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a multigeneration reproduction study (**§83-4**) in the rat.

RfD/Peer Review Committee Changes to Original DER

Parental/Systemic Toxicity:

The original NOAEL and LOAEL for parental toxicity were 0.5 and 1.5 mg/kg/day, respectively based on decreased body weights and body weight gains during the pre-mating and gestation periods. There were no treatment-related mortalities or clinical signs of toxicity. The original Data Evaluation Record (DER) essentially stated that with the exception of those at the lowest dose level, all the decreases in mean body weights and body weight gains that were statistically significant when compared to controls were toxicologically significant. On February 12, 1993, the RfD/Peer Review Committee reconsidered the body weight gain data and raised the parental systemic toxicity NOAEL from 0.5 mg/kg/day to 1.5 mg/kg/day based on decreased parental body weight gains observed at the LOAEL of 1.5 mg/kg/day.

Reproductive Toxicity:

The original NOAEL for reproductive effects was based on decreases in pup weight gain during lactation, decreases in litter size and decreases in live-born index. These are considered to be offspring effects rather than reproductive effects. There were no treatment-related effects on parental fertility, on precoital interval, on the length of gestation or on maternal neglect. The reproductive NOAEL is therefore re-determined to be 5 mg/kg/day (HDT).

Offspring Toxicity:

The original NOAEL and LOAEL for offspring systemic toxicity (referred to as reproductive toxicity) were less than 0.5 and 1.5 mg/kg/day, respectively based on decreased mean pup weight gain during the lactation period. The NOAEL and LOAEL were raised to 0.5 and 1.5 mg/kg/day, respectively by Toxicology Branch I (memorandum from P. Hurley to G. LaRocca, dated 5/22/86; HED document number 005161) due to lack of consistency in decreased body weight gains at 0.5 mg/kg/day. On February 12, 1993, the RfD/Peer Review Committee raised the offspring systemic NOAEL a second time from 0.5 mg/kg/day to 1.5 mg/kg/day based on decreased mean pup weight gain during the lactation period.

The original DER stated that there were statistically significant reductions in litter size for the high dose litters of the F_2A (80% of controls, days 5-29 of lactation) and F_3B (87% of control, days 11-29 of lactation) generations. However, this reduction in litter size was not seen in litters F_2B or in F_3A. It was not consistent. Since the values were between 80-87% of control values, it is possible that the high dose is close to the LOAEL for litter size.

The original DER also stated that there was a decrease in the percentage of live-born pups in the low-dose F_1B and in the mid- and high dose F_3B litters. Again, there was no consistency across other generations or across the other mating groups. In addition, these percentages were still within 90% of the control percentages.

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

005161

OFFICE OF
PESTICIDES AND TOXIC SUBSTANC

MEMORANDUM

SUBJECT: 53218-EUP-1;2. 5G3204. Cyhalothrin (Grenade™). Application for Experimental Use Permit and Temporary Tolerance to Support Use on Cattle.

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

Budd 5/19/86
5/22/86

Background:

Coopers Animal Health, Inc. requested an Experimental Use Permit (EUP) for Grenade™ (Cyhalothrin active ingredient) insecticide on cattle. In a memorandum to George LaRocca dated May 5, 1986, Toxicology Branch (TB) responded to the request. In the section entitled, "Comments on the Toxicity Data Base for Cyhalothrin", the TB comment on the three-generation reproduction study in rats was inadvertantly omitted. The following paragraphs state TB's position on this key study.

The rat three-generation reproduction study on cyhalothrin was reviewed by EPA's Contractor and was assigned a classification of SUPPLEMENTARY on the basis of "compound-related toxicity" in the offspring at all dose levels and on the basis of discrepancies between the summary tables and the individual animal data. TB has reviewed the data and has determined that the study should be reassigned a classification of CORE GUIDELINE for the following reasons:

1. The effect noted by the Contractor in the offspring at all dose levels was decreased body weight gain during the weaning period. The data indicate that at the lowest dose level (10 ppm), there was a decrease in body weight gain in the F_1A females on postnatal day 5, but at none of the succeeding days on which the animals were weighed (days 11, 22, and 29). Only one other group at this dose

005161

level showed this effect. F_3A males displayed a significantly decreased bodyweight gain and postnatal days 11 and 22. None of the other data points at this dose level were less than control values. TB believes that since there was no consistency in this response at this dose level, the data do not indicate a meaningful toxicologic response. Therefore, the NOEL and LOEL for offspring toxicity are determined to be 10 ppm and 30 ppm, respectively. The NOEL and LOEL for parental toxicity remain at 10 ppm and 30 ppm, respectively.

2. The discrepancies between the summary tables and the individual animal data are minor and do not affect the outcome of the study.

3. The study is determined to be CORE GUIDELINE because the design and conduct reflect modern-day standards.

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005100

EPA: 68-02-4225
DYNAMAC No. 1-029-C
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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.

5. REVIEWED BY:

Michael J. Norvell, Ph.D., D.A.B.T.
Principal Reviewer
Dynamac Corporation

Signature: G Millcovsky for
Date: 13 Jan 86

Michael A. Gallo, Ph.D., D.A.B.T.
Independent Reviewer
Dynamac Corporation

Signature: G Millcovsky for
Date: 13 Jan 86

6. APPROVED BY:

Guillermo Millicovsky, Ph.D.
Teratogenicity and Reproductive Effects
Technical Quality Control
Dynamac Corporation

Signature: G Millcovsky for
Date: 13 Jan 86

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela Hurley
Date: 4/23/86

Edwin Budd, M.S.
EPA Section Head

Signature: Edwin Budd
Date: 5/5/86

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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.

8. RECOMMENDATIONS:

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.

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

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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.

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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 ($p \leq 0.01$).

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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	129.6	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 ($p \leq 0.01$).

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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

	Dose Level (ppm)			
Litter	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.

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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 ($p \leq 0.05$).

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TABLE 5. Effect of Cyhalothrin on Mean Litter Size in Rats (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

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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

	Dose Level (ppm)			
Litter	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

	Dose Level (ppm)			
Weight Gain	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 ($p \leq 0.05$).

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TABLE 8. Effects of Cyhalothrin on Mean Initial Pup Body Weight (g) and Weight Gain (g) in Rats (Continued)

	Dose Level (ppm)			
Weight Gain	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 ($p \leq 0.05$).

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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.

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APPENDIX A

Materials and Methods

US EPA ARCHIVE DOCUMENT

_____

Page _____ is not included in this copy.

Pages 189 through 199 are not included in this copy.

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.

_____ Internal deliberative information.

_____ Attorney-client communication.

_____ Claimed confidential by submitter upon submission to the Agency.

_____ Third party confidential business information.

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.

EJ

EPA Reviewer: Pamela M. Hurley Pamela M Hurley Date 3/26/2004
Registration Action Branch 2 (7509C)
TXR No. 0050580

DATA EVALUATION RECORD
Supplement to DER for MRID No.: 00154803 Cyhalothrin:
Chronic/oncogenicity study in the rat. TXR No. 005100

STUDY TYPE: Chronic feeding/oncogenicity study in the rat
OPPTS Number: 870.4300 OPP Guideline Number: §83-5

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (total pyrethroid content 92.2% of which 96.8% cyhalothrin or 89.2%)

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

CITATION: Pigott, G.; Chart, I.; Godley, M., et al. (1984) Cyhalothrin: Two Year Feeding Study in Rats: Report No: CTL/P/980: and Individual Animal Data Supplement: Report No: CTL/P/980Sσ. Unpublished study prepared by Imperial Chemical Industries. 2687 p. MRID 00154803

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: In a chronic feeding/carcinogenicity study in rats, groups of 52 male and 52 female Alpk/AP strain rats were fed 0, 10, 50 or 250 ppm (0, 0.5, 2.5 or 12.5 mg/kg/day) cyhalothrin (89.2%) in the diet for 2 years (MRID 00154803). Additional groups of 20 males and females were added to each dose level as extras and for the purpose of interim sacrifice.

No treatment-related effects were observed at either 0.5 or 2.5 mg/kg/day. At 12.5 mg/kg/day, decreased mean body weight (11% for males and 8.5% for females) and food consumption in both sexes were observed. There were no neurological effects noted. **The LOAEL for chronic toxicity in rats is 12.5 mg/kg/day and the NOAEL is 2.5 mg/kg/day based on decreases in mean body weight. Under the conditions of the study, there was no indication of oncogenic activity for this chemical.**

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a chronic feeding/oncogenicity study (**§83-5**) in the rat.

Notes: On February 12, 1993 (memorandum from G. Ghali to G. LaRocca, dated 8/25/93), the HED RfD/Peer Review Committee reassessed the RfD for cyhalothrin. At that meeting, the

Committee decided that the high dose tested in the rat carcinogenicity study was approaching an adequate dose. Based on the range finding study in the same strain of rat, it was evident that the animals could have tolerated higher doses. Data from the range finding study indicated that body weight gain in males and females was reduced by 10 and 6%, respectively.

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

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

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.

5. REVIEWED BY:

Robert J. Weir, Ph.D.
Principal Author
Dynamac Corporation

Signature: Robert J. Weir
Date: 9/3/85

Finis L. Cavender, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Finis Cavender
Date: 9/5/85

6. APPROVED BY:

William McLellan, Ph.D.
Oncogenicity and Chronic Effects
Technical Quality Control
Dynamac Corporation

Signature: William J. McLellan
Date: Sept. 3, 1985

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

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 ($p \leq 0.05$).

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 ($p \leq 0.01$).

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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	50.6	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	164*
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.

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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)

	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
Pathologic Findings	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)

	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
Pathologic Findings	0	10	50	250	0	10	50	250
Colon - Number Examined	21	23	24	27	22	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

	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
Pathologic Findings	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

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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.

B. 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

US EPA ARCHIVE DOCUMENT

_____

Page _____ is not included in this copy.

Pages 219 through 231 are not included in this copy.

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.

_____ Internal deliberative information.

_____ Attorney-client communication.

_____ Claimed confidential by submitter upon submission to the Agency.

_____ Third party confidential business information.

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.

EPA Reviewer: Pamela M. Hurley Pamela M Hurley . Date 3/26/2004
Registration Action Branch 2 (7509C)
TXR No. 0050580

DATA EVALUATION RECORD
Supplement to DER for MRID No. 00154800 Cyhalothrin:
Developmental toxicity study in the rat. TXR No. 005100

STUDY TYPE: Developmental Toxicity Study in the Rat
OPPTS Number: 870.3700 OPP Guideline Number: §83-3

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (89.25% a.i.)

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

CITATION: Killick, M. (1981) Cyhalothrin: Oral (Gavage) Teratology Study in the Rat: CTL Study Number RR 0170: Report No. 2661-72/208. Un published study prepared by Hazleton Laboratories Europe Ltd. 171 p. MRID 00154800.

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: In a developmental toxicity study, technical cyhalothrin (89.25%) was administered by gavage to 24 SPF CD rats/dose at the following dose levels: 0, 5, 10, 15 mg/kg/day during the gestation period (days 6 through 15) (MRID 00154800). Maize oil was used as the vehicle.

No treatment-related effects were observed in the dams at dose levels of either 5 or 10 mg/kg/day. At 15 mg/kg/day, uncoordinated movements in the limbs were observed in two dams, one from gestation days 8-10 and the other from gestation days 12-18. In addition, a statistically significant reduction in mean body weight gain was observed, both during dosing (70% of control value) and throughout the entire gestation period (88% of control value). The adjusted mean gestational body weight gain was 67% of the control value. Mean body weight gain was comparable to the control group during the post-dosing period. Food consumption was also significantly reduced during gestation days 6-12 (77-91%). No treatment-related developmental effects were observed at any dose level.

The maternal NOAEL is 10 mg/kg/day and the maternal LOAEL is 15 mg/kg/day based on uncoordinated movements in the limbs starting on gestation day 8 and reduced body weight gain and food consumption during the dosing period. The developmental NOAEL is greater than 15 mg/kg/day (HDT). No developmental effects were observed.

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a study (**§83-3**) in the rat.

Note: The original Contractor DER classified this study as Core Supplementary, based on high incidences of dilated ureters and the method of sacrificing the rat pups by intracardiac injection. In a memorandum from P. Hurley to G. LaRocca, dated May 5, 1986 (relevant page attached from HED document number 005100), HED reclassified this study as Core Minimum. The higher incidences of dilated ureters was not considered to be a treatment-related effect. In addition, a comparison of the current control incidences with the historical control incidences indicated that the current controls had a low incidence of dilated ureters. The treated groups had incidences that were similar to the historical control incidences. The use of the intracardiac injection method to sacrifice the fetuses was not considered by HED to so seriously compromise the study to justify the supplementary (and thus, unacceptable) classification. The procedure was a standard practice in European laboratories at the time. In addition, there are no indications of malformations in the hearts of the pups in this study.

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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.

005180

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

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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: Krystyna Locke for
Date: 1/17/86

Edwin Budd
EPA Section Head

Signature: John Schaeffer
Date: 5/5/86

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.

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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.

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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.

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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 ($p < 0.01$).

TABLE 3. Effects of Cyhalothrin on Fertility Incidences in Rats

	Dose (mg/kg/day)			
Parameter	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

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

	Dose (mg/kg/day)			
Parameter	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.

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APPENDIX A

Materials and Methods

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Page _____ is not included in this copy.

Pages 250 through 268 are not included in this copy.

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.

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US EPA ARCHIVE DOCUMENT

L

EPA Reviewer: Pamela M. Hurley
Registration Action Branch 2 (7509C)
TXR No. 0050580

Pamela M Hurley , Date 3/26/04

DATA EVALUATION RECORD
Supplement to DER for MRID No. 00154801 Cyhalothrin:
Developmental toxicity study in the rabbit. TXR No. 005100

STUDY TYPE: Developmental Toxicity Study in the Rabbit
OPPTS Number: 870.3700 OPP Guideline Number: §83-3

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (89.25% a.i.)

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

CITATION: Killick, M. (1981) Cyhalothrin: Oral (Gavage) Teratology Study in the New Zealand White Rabbit: CTL Study Number RB 0169: Report No. 2700-72/211. Unpublished study prepared by Hazleton Laboratories Europe Ltd. 173 p. MRID 00154801.

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: In a developmental toxicity study, technical cyhalothrin (89.25%) was administered by gavage to 18-22 New Zealand White rabbits/dose at the following dose levels: 0, 3, 10, 30 mg/kg/day during the gestation period (days 6 through 18) (MRID 00154801). Corn oil was used as the vehicle.

No treatment-related effects were observed in the does at dose levels of either 3 or 10 mg/kg/day. At 30 mg/kg/day, a statistically significant reduction in mean body weight gain was observed from gestation days 6-9 when compared to the control group. Mean body weight gain was 48% of the control value during the dosing period. It was 122% of the control value during the post-dosing period and 88% of the control value for the entire gestation period (days 0-28). The % adjusted mean gestational body weight gain was 59% of the control value. Food consumption was also significantly reduced during gestation days 6-15 (71-77%). No treatment-related developmental effects were observed at any dose level.

The maternal NOAEL is 10 mg/kg/day and the maternal LOAEL is 30 mg/kg/day based on decreased body weight gain during the dosing period. The developmental NOAEL is 30 mg/kg/day (HDT). No effects were observed.

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a study (**§83-3**) in the rabbit.

Note: The original Contractor DER classified this study as Core Supplementary (unacceptable under the current classification), based on high incidences of maternal deaths in all groups. They also questioned the method of sacrificing the rabbit pups by intracardiac injection. In a memorandum from P. Hurley to G. LaRocca, dated May 5, 1986 (relevant page attached from HED document number 005100), HED reclassified this study as Core Minimum. HED determined that although there were high incidences of maternal deaths due to pulmonary disorders, the final number of does per dose group was still within acceptable limits for an acceptable study. The use of the intracardiac injection method to sacrifice the fetuses was not considered by HED to so seriously compromise the study to justify the supplementary (and thus, unacceptable) classification. The procedure was a standard practice in European laboratories at the time. In addition, there are no indications of malformations in the hearts of the pups in this study.

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.

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., Harrogate, 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: 11-26-85

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: I 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

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 Supplemental; it did not provide adequate information for assessing the potential teratogenicity of the test material.

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.

11. 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. YO0102/010/005. 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).

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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

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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%]

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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 ($p < 0.01$).

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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.

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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.

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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

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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.

B. 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

20

_____

Page _____ is not included in this copy.

Pages 289 through 308 are not included in this copy.

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.

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_____ The product confidential statement of formula.

_____ Information about a pending registration action.

__X___ FIFRA registration data.

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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.

US EPA ARCHIVE DOCUMENT

M

EPA Reviewer: Pamela M. Hurley
Registration Action Branch 2 (7509C)
TXR No. 0050580

Pamela M Hurley, Date 3/26/2004

DATA EVALUATION RECORD
Supplement to DER for MRID No.: 00154805 Cyhalothrin: 90-Day Feeding Study in the Rat. TXR No. 005100

STUDY TYPE: 90-Day Feeding Study - Rat
OPPTS Number: 870.3100 OPP Guideline Number: §82-1

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (92.2% a.i.)

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

CITATION: Lindsay, S.; Chart, I.; Godley, M.; et al. (1981) Cyhalothrin: 90-Day Feeding Study in Rats: Report No: CTL/P/629. Unpublished study prepared by Imperial Chemical Industries PLC. 539 p. MRID 00154805

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: In a 90-day feeding study in male and female SPF Alderley Park Wistar-derived rats, technical cyhalothrin (92.2% w/w pyrethroids of which 96.8% was cyhalothrin) was fed in the diet at levels of 0, 10, 50 or 250 ppm (estimated to be 0, 0.5, 2.5, 12.5 mg/kg/day) (MRID 00154805). Twenty rats/sex/dose level were assigned. The animals were examined for clinical signs of toxicity. Bodyweights, food consumption, hematological and clinical chemistry parameters, urinalysis parameters, organ weights, and macroscopic and microscopic observations were recorded. In addition, hepatic aminopyrine-N-demethylase activity was measured.

No significant treatment-related effects were observed at 0.5 or 2.5 mg/kg/day. At 12.5 mg/kg/day, mean body weight (10-16% less than controls) and body weight gain (13% less than controls) were significantly reduced in males (p less than or equal to 0.01). Mean body weight was also significantly reduced in females at this level, but only during the first week (p less than or equal to 0.05). This decrease in body weight gain was accompanied by a decrease in food consumption; however, there was no effect on food utilization at any dose level. Dietary palatability and food refusal with concurrent reduced body weight may be a factor. A dose-related reduction in mean red cell volume values was observed in both sexes at all dose levels at week 13; 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 selected clinical chemistry parameters; however

they were not dose related or recurring on the time basis, nor were they supported by microscopic findings. Hence, neither the hematological nor the clinical chemistry changes are considered compound-related. Hepatic aminopyrine-N-demethylase activity was increased in both sexes at 12.5 mg/kg/day and in the males at 2.5 mg/kg/day. This is a reversible, compensatory change usually considered to be adaptive rather than an adverse toxicological response.

The NOAEL is 2.5 mg/kg/day and the LOAEL is 12.5 mg/kg/day based on decreased bodyweight gain in males.

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a subchronic oral study (**§82-1**) in the rat.

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

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

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
Dynamac Corporation

Signature: Robert Weir
Date: 9/3/85

Finis Cavender, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Finis Cavender
Date: 9/3/85

6. APPROVED BY:

William L. McLellan, Ph.D.
Subchronic Toxicity
Technical Quality Control
Dynamac Corporation

Signature: William L. McLellan
Date: 9/3/85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pam Hurley
Date: 4/23/86

Edwin Budd
EPA Section Head

Signature: _____
Date: _____

5

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 (ADM/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.

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

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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 ($p \leq 0.01$).

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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]

	Dietary Concentration (ppm)															
	0				10				50				250			
Weeks	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	13.42	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
4	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
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	15.43	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 ($p \leq 0.01$).

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

Weeks	Dietary Concentration (ppm) 0 Alan[b] trans (mU/ml)	Aspart trans (mU/ml)	Chol (mg/dl)	TrlG (mg/dl)	P Urea (mg/dl)	10 Alan trans (mU/ml)	Aspart trans (mU/ml)	Chol (mg/dl)	TrlG (mg/dl)	P Urea (mg/dl)	50 Alan trans (mU/ml)	Aspart trans (mU/ml)	Chol (mg/dl)	TrlG (mg/dl)	P Urea (mg/dl)	250 Alan trans (mU/ml)	Aspart trans (mU/ml)	Chol (mg/dl)	TrlG (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	54.5	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; TrlG = triglycerides; ? Urea = Plasma urea.

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

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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.

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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.

APPENDIX A

MATERIALS AND METHODS

_____

Page _____ is not included in this copy.

Pages 325 through 333 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

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US EPA ARCHIVE DOCUMENT

N

EPA Reviewer: Pamela M. Hurley Pamela M Hurley Date 3/26/2004
Registration Action Branch 2 (7509C)
TXR No. 0050580

DATA EVALUATION RECORD
Supplement to DER for MRID No.: 00153029 Cyhalothrin: 28-Day Feeding Study. TXR Nos. 005158, 005316

STUDY TYPE: 28-Day Feeding Study in Rats
OPPTS Number: N/A OPP Guideline Number: § N/A

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (89.0% a.i.)

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

CITATION: Tinston, D.; Banham, P.; Chart, I.; et al. (1984) PP563: 28-day Feeding Study in Rats: Summary Report: CTL Study No. PR0337: Report No. CTL/P/1056. Unpublished study prepared by Imperial Chemical Industries, PLC. 79 p. MRID 00153029

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: In a 28-day feeding study in male and female SPF Alpk/AP Wistar-derived rats (16/sex/dose), cyhalothrin (PP563, 89.0%) and PP654, an isomer mixture similar to cyhalothrin which contains both cis and trans isomers (cyhalothrin contains only the cis isomer) were fed in the diet at levels of 0, 20, 100, 250, 500 or 750 ppm (estimated to be approximately 0, 2, 10, 25, 50 or 75 mg/kg/day cyhalothrin based on use of very young animals; clinical signs upon which NOAEL is based started on day 3) and 500 or 750 ppm (approximately 50 or 75 mg/kg/day PP564; MRID 00153029). The animals were examined once daily for clinical signs of toxicity. Bodyweights, food consumption, hematological and clinical chemistry parameters, ophthalmological examinations, urinalysis parameters, organ weights, and macroscopic examinations were conducted and/or measured. For cyhalothrin, livers from up to 8/sex/group were fixed in formol corrosive for microscopic examination. The remaining livers plus selected tissues (including sciatic nerves, brain and spinal cord) from 8/sex/group were fixed in formol saline for microscopic examination. The livers from the PP564 animals were included in this group. In addition, the left sciatic and posterior tibial nerves from 4 male and 4 female controls and high dose cyhalothrin groups were fixed in formol glutaraldehyde for microscopic examination. With all remaining animals, only abnormal appearing tissues were examined microscopically. Livers from 6/sex/group were taken for measurement of hepatic aminopyrine-N-demethylase (APDM) activity and electron microscopy. Smooth endoplasmic reticulum (SER) was quantified.

At 20 ppm and above, a dose-related increase in APDM activity was observed in males. At 20 ppm, the increase was only slight (26.00 versus 22.30 micromoles HCHO/hr/g liver). Slight hypersensitivity to touch was observed in 4 females starting on day 2; however, this had a variable dose-response. At 100 ppm and above, a dose-related increase in APDM activity was observed in females. At 100 ppm, the increase was only slight (14.21 versus 12.03 micromoles HCHO/hr/g liver). Clinical signs included high stepping gait in 1 male on day 3 and slight hypersensitivity to touch (2 males on days 2-4, 3 females on day 2) and sound (2 males on day 23; again, variable dose-response). At 250 ppm, 1 male and 2 females had high-stepping gait starting on day 2, 2 males had ataxia starting on day 3, 3 males had hunched posture starting on day 4 and 5 females had increased activity starting on day 4. In addition, significant decreases in mean body weight gain and food consumption (both sexes), increases in mean relative liver weights and decreases in mean heart weights were observed at 250 ppm and above. At 500 ppm and above, high stepping gait, ataxia, hunched posture, tail erect, increased activity, lack of grooming and salivation were the major dose-related clinical signs with cyhalothrin. Reductions in serum plasma triglyceride levels and protein excretion levels in urine were observed in males. At higher dose levels, the reductions in serum plasma triglyceride levels were observed in both sexes. With PP564, high stepping gait, ataxia, hunched posture and increased activity in females were observed, but to a lesser extent. Reductions in serum plasma triglyeride levels were also observed. At 750 ppm an additional clinical sign of loss of stability was observed in 1 male and 3 females. With PP564, similar clinical signs were observed as with cyhalothrin, but to a lesser extent. Loss of stability was not observed.

The NOAEL for cyhalothrin is 20 ppm (2 mg/kg/day) and the LOAEL is 100 ppm (10 mg/kg/day) based on clinical signs of neurotoxicity. At higher dose levels, decreases in body weight gain and food consumption and changes in organs weights were also observed. The NOAEL for PP564 is less than 500 ppm (50 mg/kg/day).

This study is classified as **acceptable nonguideline** and does not satisfy any particular guideline requirement.

Incidence of Selected Clinical Observations								
		PP563: Cyhalothrin					PP564	
Dose (ppm) Observation	Control	20	100	250	500	750	500	750
Males								
Convulsions								
High-stepping gait	0/0[a]	0/0	1/1	1/1	46/8	69/8	5/3	33/8
Ataxia	0/0	0/0	0/0	2/2	63/8	133/8	2/1	66/8
Piloerection	22/5	25/5	15/4	31/9	62/8	101/8	31/5	42/8
Hypersensitivity to touch	0/0	0/0	2/2	0/0	6/5	15/4	1/1	1/1
Hypersensitivity to sound	0/0	0/0	2/2	13/9	17/8	82/8	4/4	33/8
Hunched	0/0	0/0	0/0	5/3	51/7	51/8	8/4	51/7
Loss of stability	0/0	0/0	0/0	0/0	0/0	1/1	0/0	0/0
Tail erect	0/0	0/0	0/0	0/0	3/3	23/8	0/0	0/0
Increased activity	0/0	0/0	0/0	0/0	33/8	23/5	0/0	8/3
Decreased activity	0/0	0/0	0/0	0/0	9/4	1/1	0/0	7/6
Ungroomed, stained tail, staining of ventral fur	0/0	0/0	0/0	0/0	4/4	10/4	0/0	0/0
Salivation	0/0	0/0	0/0	0/0	3/2	19/7	0/0	4/1
Weak	0/0	0/0	0/0	0/0	0/0	4/1	0/0	0/0

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Incidence of Selected Clinical Observations								
		PP563: Cyhalothrin					PP564	
Dose (ppm) Observation	Control	20	100	250	500	750	500	750
Females								
Convulsions					0/0	6	0/0	0/0
High-stepping gait	0/0	0/0	0/0	4/2	50/8	81/8	1/1	28/8
Ataxia	0/0	0/0	0/0	0/0	23/8	118/8	2/2	26/8
Piloerection	11/5	9/3	10/4	17/4	33/8	98/7	9/4	12/6
Hypersensitivity to touch	0/0	4/4	3/3	16/8	13/5	11/6	2/2	8/3
Hypersensitivity to sound	0/0	0/0	0/0	16/8	6/4	53/6	0/0	18/6
Hunched	0/0	3/1	0/0	0/0	16/6	87/8	4/2	16/5
Loss of stability	0/0	0/0	0/0	0/0	0/0	6/3	0/0	0/0
Tail erect	0/0	0/0	0/0	0/0	1/1	21/8	1/1	15/8
Increased activity	0/0	0/0	0/0	9/5	55/8	15/4	22/4	22/8
Decreased activity	0/0	0/0	0/0	0/0	1/1	5/4	0/0	0/0
Ungroomed, stained tail, staining of ventral fur	0/0	0/0	0/0	0/0	0/0	59/5	0/0	0/0
Salivation	0/0	0/0	0/0	0/0	0/0	33/6	0/0	0/0
Weak	0/0	0/0	0/0	0/0	0/0	33/4	0/0	0/0

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Incidence of Selected Clinical Observations								
		PP563: Cyhalothrin					PP564	
Dose (ppm) Observation	Control	20	100	250	500	750	500	750
Depressed respiration	0/0	0/0	0/0	0/0	0/0	4/4	0/0	0/0

[a]Total number of observations in x number of animals

Overall Group Mean Bodyweight Gain (g), Food Consumption and Food Utilization[a]								
		PP563: Cyhalothrin					PP564	
Dose (ppm)	Control	20	100	250	500	750	500	750
Males								
Mean Body Weight Gain/Group	194.1	194.4	192.8	174.9* (90)	147.4* (76)	72.9** (38)	169.4	131.5** (68)
Mean Total Body Weight Gain/Cage	776.5	777.5	771.0	699.8	569.0*	384.0**	657.0	546.5**
Mean Food Consumption/Cage	2516.0	2637.5	2540.7	2233.7* (89)	1947.0* (77)	1148.0** (46)	2311.5 (92)	1886.0** (75)
Mean Food Utilization	3.2	3.4	3.3	3.2	3.4	3.0	3.5	3.5

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Overall Group Mean Bodyweight Gain (g), Food Consumption and Food Utilization[a]								
		PP563: Cyhalothrin					PP564	
Dose (ppm)	Control	20	100	250	500	750	500	750
Females								
Mean Body Weight Gain/Group	102.9	101.5	102.9	87.9** (85)	73.9** (72)	42.6** (41)	84.8* (82)	71.0** (69)
Mean Total Body Weight Gain/Cage	411.5	406.0	411.5	351.8*	287.5*	17.2**	332.5	290.5*
Mean Food Consumption/Cage	2035.0	1992.2	1980.2	1726.7* (85)	1591.0** (78)	886.0** (44)	1848.5* (91)	1638.0* (80)
Mean Food Utilization	4.9	4.9	4.8	4.9	5.5	5.2	5.6	5.6

* $p < 0.05$
**$P < 0.01$
[a]Food utilization = Mean food intake per g body weight gained
( ) = % of control

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Mean Plasma Triglyceride Levels (mg/100 ml)								
		PP563: Cyhalothrin					PP564	
Dose (ppm)	Control	20	100	250	500	750	500	750
Males								
Value Std. Dev.	185 41	203 60	168 67	142 60	75 20	37 9	115 30	93 44
Females								
Value Std. Dev.	139 31	129 53	143 35	149 36	101 36	45 13	119 49	121 40

Mean Protein Levels in Urine (mg/rat)								
		PP563: Cyhalothrin					PP564	
Dose (ppm)	Control	20	100	250	500	750	500	750
Males								
Value Std. Dev.	24.4 3.7	28.5 7.6	27.8 3.2	23.7 3.6	18.0 5.9	8.7 3.2	24.8 3.0	20.7 6.5
Females								
Value Std. Dev.	1.5 1.3	1.1 0.2	1.2 0.6	1.2 0.3	0.6 0.1	0.9 0.2	0.9 0.2	1.3 0.7

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Means of Selected Organ Weights								
		PP563: Cyhalothrin					PP564	
Dose (ppm)	Control	20	100	250	500	750	500	750
Males								
Liver								
Absolute	15.3	15.6	15.9	15.4	14.1*	9.4**	14.6	12.7**
Relative	14.3	14.3	14.4	15.1**	15.2**	13.8	14.7	15.0**
Heart								
Absolute	1.07	1.03	1.02	0.95**	0.86**	0.64**	0.90**	0.85**
Relative	1.03	0.98	0.97	0.93*	0.88*	0.76**	0.89**	0.91*
Kidney								
Absolute	2.39	2.33	2.34	2.21*	2.08**	1.63**	2.12**	1.97**
Relative	2.22	2.17	2.17	2.12	2.16	2.08	2.08	2.19
Spleen								
Absolute	0.81	0.75	0.75	0.71*	0.60**	0.40**	0.69**	0.57**
Relative	0.74	0.68	0.68	0.67	0.63*	0.59*	0.67	0.66
Testes								
Absolute	2.86	2.90	2.86	2.87	2.86	2.74	2.73	2.76
Relative	2.71	2.75	2.70	2.80	93*	3.14**	2.69	2.96*
Brain								
Absolute	1.93	1.89	1.92	1.94	1.91	1.83*	1.92	1.84*
Relative	1.88	1.85	1.88	1.92	1.93	1.95	1.91	1.90

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Means of Selected Organ Weights								
		PP563: Cyhalothrin					PP564	
Dose (ppm)	Control	20	100	250	500	750	500	750
Females								
Liver								
Absolute	9.2	9.2	9.6	9.4	8.8	7.3**	8.8	8.8
Relative	8.7	8.6	9.1	9.6*	9.4	9.6	9.1	9.7*
Heart								
Absolute	0.72	0.74	0.75	0.73	0.70	0.52**	0.74	0.66
Relative	0.68	0.70	0.71	0.74	0.72	0.65	0.74	0.70
Kidney								
Absolute	1.58	1.63	1.63	1.57	1.49	1.35*	1.52	1.53
Relative	1.51	1.53	1.56	1.58	1.52	1.61	1.52	1.62*
Spleen								
Absolute	0.47	0.46	0.51	0.44	0.45	0.28**	0.45	0.49
Relative	0.46	0.44	0.49	0.44	0.46	0.33*	0.45	0.50
Ovaries								
Absolute	0.129	0.145	0.124	0.107	0.116	0.072**	0.102*	0.090**
Relative	0.125	0.141	0.121	0.108	0.119	0.086*	0.103	0.094*
Brain								
Absolute	1.76	1.78	1.76	1.77	1.80	1.56**	1.77	1.78
Relative	1.75	1.76	1.75	1.77	1.80	1.60*	1.77	1.79

* $p < 0.05$. **$p < 0.01$. ( ) = % of control

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

005316

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Oral (82-1) rat TOX. CHEM. NO.: 271F

ACCESSION NUMBER: 073980

TEST MATERIAL: (RS)alpha-cyano-3-phenoxybenzyl (Z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoro-prop-1-enyl)-2,2-dimethylcyclopropane-1-carboxylate and (RS)alpha-cyano-3-phenoxybenzyl (EZ)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-1-carboxylate

SYNONYMS: Cyhalothrin, PP563 (active ingredient of Grenade) for first test chemical and PP564 for second test chemical

STUDY NUMBER(S): PRO337

REPORT NUMBER: CTL/P/1056

SPONSOR: ICI PLC Plant Protection Division, UK

TESTING FACILITY: ICI PLC, Cntrl. Tox. Lab., Alderly Park, Macclesfield, UK

TITLE OF REPORT: PP563: 28-Day Feeding Study in Rats - Summary Report

AUTHOR(S): Tinston DJ, Banham PB, Chart IS, Gore CW, Pratt I, Scales MDC, Weight TM.

REPORT ISSUED: 7/12/84

IDENTIFYING VOLUME: Volume II, Book 1 of 2, Section C, Tab Ref. 9C

CONCLUSION: For male rats effects were noted at the lowest dose level PP563, 20ppm. For females, the NOEL was 20 ppm. PP564 was less toxic than PP563, indicating that the cis isomer is more toxic than the trans isomer.

Classification: Not Core Guideline, but acceptable for the purposes for which it was performed.

MATERIALS AND METHODS:

Chemical:

PP563 was given the following references: CTL - Y00102/006/001 and Plant Protection Batch P5. It had a purity of 89.0% w/w (100% cis isomer). PP564 was given the following references: CTL - Y00102/001/001 and Plant Protection Batch P5. It had a purity of 84.0% w/w (50:50 cis:trans isomers). Both were viscous, pale yellow liquids.

Animals:

Male and female Alpk/AP (Wistar-derived) rats were obtained from the Animal Breeding Unit at ICI PLC, Alderly Park, Macclestield, Cheshire, UK. The rats were 3 weeks old and were acclimated for one week. The animals were supplied in two groups, one group arriving a week ahead of the other group.

Protocol:

Six groups of 16 male and 16 female rats were fed the experimental diets at the following dose levels for 28 days: 0, 20, 100, 250, 500, and 750 ppm (PP563); and 500 and 750 ppm (PP564). All rats were observed once daily throughout the experimental period for any clinical signs of toxicity. The eyes of all rats from the control, 500 and 750 ppm groups (PP563) were examined pre-experimentally and during the week prior to termination with an ophthalmoscope with and without a mydriate. Bodyweights were recorded weekly and food consumption was recorded daily for the first week and weekly thereafter.

Clinical Chemistry:

The following clinical chemistry parameters were measured in up to 8 designated male and female rats per group prior to the experimental phase and at termination: plasma urea, glucose, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and triglyceride and plasma cholesterol levels (at termination only).

Urinalysis:

Urinalysis measurements were taken from up to 4 male and 4 female rats prior to the experimental phase and at termination. The rats were given an oral water load at 2.5 ml/100g bodyweight and the urinary volume, pH, specific gravity and urinary sediments were measured. The animals were then deprived of water for 18 hours during which time the urine was collected for analysis of urinary volume, pH, specific gravity, protein, glucose, bilirubin and ketones.

Hematology:

The following hematological measurements were taken pre-experimentally and terminally from up to 8 male and 8 female animals per group: hemoglobin, total white cell count, red cell count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, hematocrit, differential white cell count and platelet count. The morphological appearance of the red cells were also examined. At termination, in addition to the above, prothrombin and kaolin/cephalin time tests were conducted and 2 bone marrow smears from the right femurs of all rats were examined for any cytological abnormalities.

Pathology:

Any rats found dead or moribund during the study received a full post mortem examination and tissues were submitted for histopathological examination. The weights of the following organs were recorded from up to 8 male and females rats per group: gonads (combined), spleen, adrenals (combined), kidneys (combined), liver, thymus, heart, lungs (combined), brain and pituitary. The livers from these animals (except the PP564 livers) were fixed in formol corrosive for histopathological examination. The livers from the PP564 group along with the following tissues from 8 male and 8 female animals per group were fixed in formol saline: salivary glands (parotid, sub-maxillary and sub-lingual), cervical lymph node, mammary tissue, voluntary muscle, testes, epididymides, protate and seminal vesicles or ovaries, uterus and cervix, urinary bladder, spleen, pancreas, stomach, duodenum, jejunum, ileum, mesenteric lymph node, caecum, colon, adrenals, kidneys, liver, thyroid, aorta, trachea, esophagus, thymus, heart, lungs, eyes, sciatic nerves, brain and spinal cord. The left sciatic and posterior tibial nerves from 4 male and 4 female controls and 750 ppm PP563 groups were fixed in formol glutaraldehyde and examined. All remaining animals received a gross post mortem examination and only abnormal appearing tissues were submitted for histopathological examination. Livers from a designated 6 male and 6 female animals from all groups were taken for measurement of hepatic aminopyrine-N-demethylase activity. These livers were the same as those taken for measurement of weight and examination by electron microscope. For the electron microscopy, samples were taken from the median lobes from the preselected male and female animals from control, 20, 100 and 250 ppm groups (PP563). Smooth endoplasmic reticulum (SER) was quantified using the point counting method of Weibel.

RESULTS:

Dietary Concentrations:

Concentrations of PP563 and PP564 were within 10% of the nominal values except for the 500 ppm PP563 and 500 ppm PP564 diets where the mean concentrations were 83% and 89% respectively. PP563 was shown to be stable in the diet for up to 30 days after preparation.

Mortalities:

Three male and three female rats receiving 750 ppm PP563 in the diet were found to be either dead or moribund. As a result, a second batch of animals already scheduled to start one week later were fed 500 ppm instead (this also included a second batch of PP564 animals). At 750 ppm, 2 more female rats died, one after 14 days and one after 27 days. No other deaths occurred during the study.

Clinical Observations:

Clinical observations included high-stepping gait, severe ataxia, hypersensitivity to external stimuli, piloerection and excessive salivation at the 750 and 500 (less severe) ppm (PP563) levels and similar but transient effects at the 250 ppm level. At 100 ppm, one male showed high stepping gait on day 3. Also at the lower levels there was occasional evidence of slight hypersensitivity to external stimuli. The clinical effects observed with PP564 were comparable but less severe: the effects noted at the 750 ppm level were similar to those noted at the 500 ppm level of PP563 and the effects observed at the 500 ppm level were similar to those noted at the 250 ppm level of PP563.

Bodyweight Gain and Food Consumption:

Statistically significant decreases in bodyweight gain were noted for male and female groups receiving either PP563 or PP564 at dietary concentrations of 250 ppm or greater (except for bodyweight gains of males receiving 500 ppm PP564). Statistically significant reductions in food consumption were also observed in both male and female rats fed levels of 250 ppm or greater for both PP563 and PP564.

Clinical Chemistry and Urinalysis:

Reductions in plasma triglyceride levels were noted in males receiving either 500 or 700 ppm PP563 and to a lesser extent in females receiving 750 ppm PP563 and males receiving either 500 or 750 ppm PP564. Dose-related decreases in protein excretion levels in the urine were observed in males receiving either 500 or 750 ppm PP563.

Organ Weights:

Statistically significant increases in liver weights (after adjustments for bodyweights) were observed in the 250 and 500 ppm dose groups (PP563) and in the 750 ppm (PP564) dose group. At 750 ppm 563, the large bodyweight reduction distorted the organ weight analysis. There was some evidence of increased testes weights and decreased ovary weights at the 500 and 750 ppm levels of PP563. There was a dose-related reduction in the heart weight of males fed diets containing PP563 which was statistically significant down to 250 ppm. There was also some evidence for reduction in spleen, brain and thymus weights in groups which grew less than controls.

Histopathology:

Male and female rats dying or killed in extremis showed thymic atrophy, and enlargement, vacuolation and differential staining of the cortical cells of the adrenals. In males, incomplete spermatogenesis and reduction of seminal vesicular secretion was evident. No changes in the nervous system were present. No other changes were noted.

Hepatic Aminopyrine Demethylase Activity:

A dose-related increase in APDM activity was observed in male rats receiving 20 ppm and above (PP563), in females receiving 100 ppm and above (PP563) and in PP564 but to a lesser extent.

Electron Microscopy:

There was a statistically significant increase in SER proliferation (greater in males than in females) which did not show any dose-response effect. The effect was observed in males at dose levels of 20, 100 and 250 ppm PP563 and in females at 250 ppm PP563. One female rat receiving 250 ppm PP563 showed marked vacuolation of hepatocyte cytoplasm, as a consequence of dilatation of endoplasmic reticulum.

DISCUSSION:

The results of this study confirmed the results of another previously submitted 28-day study on cyhalothrin in rats (Moyes et al. 1984) conducted at dose levels of 1 - 250 ppm. Clinical observations indicated signs of neurotoxicity, characteristic of synthetic pyrethroid toxicity. Evidence of decreased bodyweight gain and food consumption was also noted, as well as increased ADPM activity and proliferation of SER. As evidenced by comparing the results from testing PP564 with the results from PP563, it appears that the cis component is the more toxic of the 2 isomers. It should be noted that even at the lethal dose of 750 ppm PP563, no histopathological changes were observed in the peripheral nerves, even when accompanied by neurotoxic signs. The liver hypertrophy accompanied by increases in liver weight, APDM activity and SER proliferation are characteristic of effects due to pyrethroid administration. These effects are considered to be adaptive in this case. The authors stated that the histopathological changes noted in the animals that died were due to stress rather than PP563 toxicity, especially since there was no sign of these changes in the animals that survived.

The purpose of the study was to find the highest dose useful for a longer term study and to compare the toxicity of PP563 with PP564. It was recommended that for longer term studies, dosages higher than 250 ppm should not be used. This study is not Core Guideline because the exposure time was only 28 days and only 8 of the animals per sex per dose group were examined for many of the measurements taken. However, the study is acceptable for the purpose that it was conducted.

EPA Reviewer: Pamela M. Hurley Pamela M Hurley , Date 3/26/2004
Registration Action Branch 2 (7509C)
TXR No. 0050580

DATA EVALUATION RECORD
Supplement to DER for MRID No.: 00154795 Cyhalothrin: 26-Week Oral Study in the Dog. TXR Nos. 005100, 006618.

STUDY TYPE: 26-Week Oral Capsule Study in the Dog
OPPTS Number: 870.3150 OPP Guideline Number: § 82-1

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (pyrethroid content: 92.2% w/w of which 96.8% is cyhalothrin)

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

CITATION: Chesterman, H.; Heywood, R.; Allen, T.; et al. (1981) Cyhalothrin: Oral Toxicity Study in Beagle Dogs (Final Report: Repeated Daily Dosing for 26 Weeks): Report No. ICI/326/8162. Unpublished study prepared by Huntingdon Research Centre. 210 p. MRID 00154795

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: In a 26-week oral study in male and female beagle dogs, six dogs/sex/dose level received technical cyhalothrin (pyrethroid content: 92.2% w/w of which 96.8% is cyhalothrin) via oral administration in gelatin capsules (MRID 00154795). The test chemical had been dissolved in corn oil prior to placement in the capsules. The following dose levels were tested: 0, 1.0, 2.5 or 10.0 mg/kg/day. The following parameters were measured and/or recorded: daily clinical observations, body weights, food consumption, ophthalmological examinations, neurological examinations, clinical biochemistry, urinalysis, gross necropsy and microscopic examinations.

At 1.0 mg/kg/day, a slight increase in the passage of liquid feces was observed in in both sexes combined (7% over the control group). This was the only effect observed at this dose level and it was not considered to be of toxicological significance.

At 2.5 mg/kg/day, l iquid feces were observed at an increased rate (26% over the control group, both sexes combined). No other effects were observed. At this dose level, due to the greater number of animals affected and the greater increase in incidence, the liquid feces was considered to be a toxicological effect.

At 10.0 mg/kg/day, liquid feces were observed at an increased rate over the control group (both sexes). In addition, the following effects were observed: increase in water consumption during first 4 weeks, vomiting, usually within a few hours following dosing and occasional unsteadiness and/or muscular trembling. During week 2, head shaking and excessive salivation were observed in several dogs. These signs were observed only occasionally during the subsequent test weeks. One male had more severe signs. During the second week, excessive salivation and head shaking were noted. On day 14, 3 hours post-dosing, the dog was in a state of collapse, stiff limbed and frothing at the mouth with the presence of vomitus. It recovered in 6 hours. In the following weeks with this dog, there were periods of head shaking, salivation, loss of appetite, episodes of collapse, muscular spasms, marked incoordination, vocalization and one episode of convulsive behavior (week 8).

The NOAEL is 1.0 mg/kg/day and the LOAEL is 2.5 mg/kg/day based on an increase in incidence of liquid feces. At 10.0 mg/kg/day, liquid feces and clinical signs of neurotoxicity (occasional unsteadiness and/or muscular trembling, head shaking, excessive salivation, frothing at the mouth, stiff limbed, episodes of collapse, muscular spasms, marked incoordination, vocalization and one episode of convulsive behavior (week 8)) were observed.

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a subchronic oral study **(§82-1)** in the dog.

Note: The original DER requested an analysis of the test material (HED document number 005100). The test material analysis was submitted at a later date and is reflected in this updated executive summary (HED document number 006618).

Intergroup Comparison of the Incidences of Liquid Feces
(Both Sexes Combined)

Incidences	Dose Levels (mg/kg/day)			
	0	1.0	2.5	10.0
# Observations	31	389	671	1008
# Dogs Affected	2♂; 6♀	6♂; 6♀	6♂; 6♀	6♂; 6 ♀

Initial Bodyweights and Weight Changes (g) During Dosing Period

Weight Parameter	Dosage (mg/kg/day)			
	0	1.0	2.5	10.0
	Males			
Mean Initial Bodyweight	11300	11317	11267	11433
Mean Wt. After 26 Weeks	12733	12900	13650	13233
Mean Gain (Weeks 1-26)	1433	1583	2383	1800
	Females			
Mean Initial Bodyweight	10583	10483	10467	10433
Mean Wt. After 26 Weeks	12983	13300	12567	12483
Mean Gain (Weeks 1-26)	2400	2817	2100	2050

Most dogs consumed all food offered. Small residues of remaining food was recorded. The following table summarizes food left.

Group Mean Total Quantities of Food Left During Pre-Dosing Period and During Study (Both Sexes Combined)

Group	Pre-Dose 4 Weeks	Weeks 1-26
Control	33	405
1.0 mg/kg/day	68	52
2.5 mg/kg/day	18	28
10.0 mg/kg/day	15	981*

*Statistically significant ($p < 0.05$) by Chi^2 test, based on a 2x2 contingency table. The

proportion of control and 10.0 mg/kg/day dogs leaving food during the dosing period were compared.

Group Mean Serum Electrolyte and Urinary pH and Specific Gravity Values - Both Sexes Combined								
Parameter	Dosage mg/kg/day	Results Before Dosing Commenced	Results During Week					
			4	8	12	16	20	25
			of Dosing					
Sodium (Na) mEq/l	Control	145	146	145	148	148	148	148
	1.0	143*	146	147*	149	148	145*	149
	2.5	143**	143**	148**	147	149	145*	148
	10.0	144	144*	148**	148	147	145*	149
Potassium (K) mEq/l	Control	4.7	4.6	4.6	4.6	4.5	4.4	4.5
	1.0	4.6	4.6	4.7	4.7	4.6	4.5	4.5
	2.5	4.6	4.6	4.6	4.6	4.4	4.4	4.4
	10.0	4.8	4.7	4.8	4.7	4 5	4.5	4.4
Calcium (Ca) mEq/l	Control	5.5	5.4	5.4	5.4	5.4	5.7	5.4
	1.0	5.5	5.4	5.5	5.5	5.4	5.6	5.4
	2.5	5.6	5.4	5.5	5.5	5.4	5.6	5.4
	10.0	5.5	5.5	5.6	5.4	5.3	5.7	5.6*
Chloride (Cl) mEq/l	Control	109	111	113	113	112	116	112
	1.0	108	108*	114	114	113	115	111*
	2.5	108	110	113	113	111	112***	111
	10.0	108	110	112	112	110**	112***	111
Inorganic Phosphorus (P) mEq/l	Control	3.9	3.4	3.2	3.0	2.8	2.7	2.6
	1.0	3.8	3.5	3.3	3.1	3.0	2.7	2.6
	2.5	3.7	3.3	3.1	3.0	2.8	2.6	2.5
	10.0	3.8	3.4	3.3	3.0	2.8	2.7	2.6
Urinalysis Results								
Urinary pH	Control	6.0		6.3		6.7		6.3
	1.0	6.0		6.2		6.8		6.2
	2.5	6.0		6.3		6.8		6.3
	10.0	6.0		6.5		6.6		6.4
Urinary Volume ml	Control	159		125		147		126
	1.0	138		132		132		123
	2.5	125		121		130		125
	10.0	123		97		108*		129
Urinary Specific Gravity x 10^3	Control	1041		1045		1048		1046
	1.0	1041		1043		1049		1046
	2.5	1043		1046		1049		1048
	10.0	1042		1047		1048		1046

*p < 0.05
**p < 0.01
***p < 0.001

Intergroup Comparison of Microscopic Findings - Males

Observation	Treatment (mg/kg/day)			
	0	1.0	2.5	10.0
Kidney				
# Examined	6	6	6	6
Focal nephritis	2	0	0	0
Lymphocytic pyelitis renal scarring	0	0	1	0
Liver				
# Examined	6	6	6	6
Lipid in cytoplasm of bile duct epithelial cells	5	6	6	5
Testes				
# Examined	6	6	6	6
Occasional multinucleate cells in seminiferous tubules	1	2	2	4
Brain				
# Examined	6	6	6	6
Artefactual mucocyte vacuolation in White matter	1	4	2	
Pituitary				
# Examined	6	6	6	6
Anterior lobe cysts with basophilic colloid	4	4	5	5
Spinal Cord				
# Examined	6	6	6	6
Occasional swollen myelin sheath with myelophage	2			
Solitary swollen myelin sheath with central granular eosinophilic round body	1			
Agonal hemorrhage and artefactual vacuolation in white and/or grey matter		2		
Occasional myelin sheath vacuolation			2	
Occasional swollen myelin sheath with Gitter cells			2	

Intergroup Comparison of Microscopic Findings Females

Observation	Treatment (mg/kg/day)			
	0	1.0	2.5	10.5
Kidney				
# Examined	6	6	6	6
focal nephritis	1	1	0	0
Lymphocytic pyelitis				
renal scarring	0	1	0	2
Liver				
# Examined	6	6	6	6
Lipid in cytoplasm of bile duct epithelial cells	6	6	5	5
Cervix				
# Examined	6	6	6	6
Occasional neutrophilic leucocytes in epithelium	4	0	2	1
Brain				
# Examined	6	5	6	6
Artifactual vacuolation of hypothalamic neurophil	1			
Artefactual vacuolation and/or mucocytes in white matter		6		3
Agonal hemorrhage		1		
Stem: Occasional eosinophilic swellings (neuroaxonal dystrophy) in dorsal nuclei		1		
Artefactual vacuolation				1
Pituitary				
# Examined	6	6	6	6
Anterior lobe cysts contain basophilic colloid	6	5	6	3
Spinal Cord				
# Examined	6	6	6	6
Occasional myelin sheath swelling with myelophage	1			
Solitary glial focus in white matter of 1 section	1			
Occasional myelin sheath swelling with Gitter cells	2		3	2
Artefactual vacuolation in grey and/or white matter		3		
Artefactual vacuolation				1

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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: 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:

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.

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,

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.

P

Reviewed By: Pamela M. Hurley Pamela M Hurley Date: 3/26/2004
Registration Action Branch 2
Secondary Reviewer: Roger L. Gardner Roger Gardner Date: 3/26/04
Toxicologist, BPPD
TXR No. 0050580

DATA EVALUATION REPORT
Updated DER for MRID 41387702. Lambda-cyhalothrin: 21-Day inhalation study in the rat. TXR No. 007868

STUDY TYPE: 21-day inhalation - rat (82-4)
OPPTS Number: N/A OPP Guideline Number: § N/A

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Lambda - cyhalothrin Technical (81.5% a.i.)

SYNONYMS: [(RS) α-cyano-3-phenoxybenzyl (z)-(1RS,3RS)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-carboxylate]; PP321, Karate, Commodore, Saber

CITATION: Hext, P. (1990) Lambda-Cyhalothrin Production Material: 21-day Sub-acute Inhalation Toxicity Study in the Rat: Lab Project Number: CTL/P/2772: MR0135. Unpublished study prepared by ICI Central Toxicology Laboratory. 102 p. MRID 41387702

SPONSOR: ICI Americas, Inc., Agricultural Products, Wilmington, Delaware 19897

EXECUTIVE SUMMARY: In a 21-day inhalation study, 10/sex/dose SPF Alpk:APfSD Wistar-derived) albino rats were exposed nose-only 6 hours/day, 5 days/week for 21 days to lambda-cyhalothrin (81.5% pure) at 0, 0.3, 3.3, or 16.7 micrograms/L (estimated to be approximately 0, 0.08, 0.90 or 4.5 mg/kg/day) (MRID 41387702). The MMAD ranged from 1.47 to 1.91 micrometers and the GSD ranged from 1.02 to 2.24 micrometers.

No treatment-related effects were observed at 0.3 micrograms/L. At 3.3 micrograms/L, the following was observed: salivation, lachrymation, paw flicking (males only), tail erections and splayed gait (males only); decreased body weight (94-95%, $p < 0.05$) and body weight gain (53-65%, $p < 0.01$) of control values; an increased incidence of punctate foci on the cornea; slight reductions in cholesterol levels in females ($p < 0.05$); decreased urine volume in males, slightly raised specific gravity of the urine in both sexes and reductions in urinary protein levels in males. At 16.7 micrograms/L, the following was observed: salivation, lachrymation, auditory hypoaesthesia, paw flicking, tail erection, splayed gait, decreased activity, reduced foot withdrawal (males only), head flicking, reduced righting reflex, shaking (males only), sides pinched in, reduced splay reflex, decreased visual placing response, absent pinna reflex (females only), ungroomed appearance (females only), tiptoe gait (males only), respiratory noise; decreased body weight (85-88%, $p < 0.01$) and body weight gain (< 3-14%, $p < 0.01$) of control values); decreased food consumption (46-91% (males), 56-87% (females) of controls); changes in selected clinical chemistry values, particularly in females; decreased urine volume, increased urine specific gravity, and decreased urinary protein. There was also a slight increase in the incidence of alveolitis in high dose females.

The NOAEL is 0.3 micrograms/L (0.08 mg/kg/day) and the LOAEL is 3.3 micrograms/L (0.90 mg/kg/day) based on clinical signs of neurotoxicity, decreased body weight gains, increased incidence of punctate foci in the cornea, slight reductions in cholesterol in females and slight changes in selected urinalysis parameters.

This inhalation toxicity study is classified as **acceptable nonguideline** and does not satisfy any particular guideline requirement. The study is too short for a guideline study and individual animal data were not provided.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, Quality Assurance, and Flagging statements were provided.

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: [1 alpha (S*), 3 alpha (Z)]-(+/-)-cyano(3-phenoxyphenyl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate

Description: Brown/black viscous liquid
Batch #(s), Other #(s): ADH 553 225, Batch 367
Purity: Total pyrethroid content 91.6%, cis B content 81.5%
Source: ICI Agrochemicals, Fernhurst, Surrey, UK
Vehicle (if applicable): None
Positive Control(s) (if applicable): None

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): Male and female SPF Alpk:APfSD Wistar-derived) albino rats

Age: 8 weeks
Weight(s): 238-297 g (males), 195-241 g (females)
Source(s): Alderley Park, Cheshire, UK

3. Procedure:

a. Atmosphere Generation: The test material was warmed to 70°C. The report stated that the "atmospheres were generated into a reservoir chamber using a glass concentric jet atomiser with a size-selective cyclone. The test compound was delivered to the atomiser using a peristaltic pump. A glass concentric jet atomiser was used above each exposure chamber to create a venturi, which pulled test atmosphere from the reservoir chamber, along a delivery tube and into the exposure chamber. Variation of flow rate through the atomiser was used to control the exposure chamber concentrations. Clean, dry air...was supplied to the exposure chamber via the atomiser and also directly as diluting air. Air flow rates were measured using variable area flowmeters".

Measurement of Particulate Concentrations: Particulate concentrations of the test atmospheres were measured gravimetrically (close to the animals breathing zone) at least 3 times during each exposure. The test atmosphere was drawn through a VM-1 filter at a flow rate of 2 liters/minute for a known time and the filter was weighed before and after sampling.

Measurement of Aerodynamic Particle Size Distributions: The particle size of the test atmosphere was measured daily for the first 3 days and once a week thereafter by means of a Marple Cascade Impactor. The mean amount of aerosol, by weight, in each size range, was then used to calculate the aerodynamic particle size distribution of the aerosol. The mass median aerodynamic diameter (D_{50}) and the geometric standard deviation (GSD) were calculated.

Determination of Atmospheric Concentrations: The atmospheric concentration of lambda-cyhalothrin was determined by dissolving the formulation deposited on the VM-1 filters and the stages of the cascade Impactor in ethyl acetate and then diluting further with ethyl acetate where necessary. The resultant solutions were then analysed by gas chromatography.

Exposure System: The animals were exposed nose-only for 6 hours/day for 5 days/week, giving a total of 15 days out of a 21-day period. Temperature and relative humidity were measured within each chamber during exposure.

b. Basis for Selection of Dose Levels: Dose levels were selected on the basis of the results from a 3-day preliminary inhalation study.

c. Animal Assignment and Dose Levels:

Table 1: Target Concentrations

Test Group	Target Exposure Level	Study Length 15/21 days	
	µg/L	Male	Female
Control	0	10	10
1	0.25	10	10
2	2.5	10	10
3	15.0	10	10

d. Clinical Observations and Mortality: Animals were examined daily every 30 minutes during exposure and following each exposure, and also daily on non-exposure days. Detailed clinical examinations were given following exposure days 1, 2, and 3 (males) and days 1, 2, and 5 (females), and on days 7, 11, 15, 18 and 22 (prior to post mortem).

e. Body Weight Determinations: Bodyweights were recorded prior to exposure on the same days as the detailed clinical examinations.

f. Food and/or Water Consumption: Weekly food consumption was calculated for each cage of rats from measurements made at the same time as bodyweights.

g. Ophthalmological Examinations (if applicable): The eyes of all animals were examined prior to exposure using a Fisons indirect ophthalmoscope after instillation of 0.5% tropicamide. Following exposure on day 21, the eyes of all animals were again examined.

h. Clinical Pathology: (*) recommended by Guidelines

1) Hematology:

Collection times for blood (including # of animals): Cardiac blood samples were taken at post mortem examination from all animals.

The following CHECKED (X) parameters were examined:

X		X	
x	Hematocrit (HCT)*	x	Mean corpuscular HGB (MCH)
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB conc. (MCHC)
x	Leukocyte count (WBC)*	x	Mean corpuscular volume (MCV)
x	Erythrocyte count (RBC)*		Reticulocytes
x	Platelet count*		
	Total plasma protein (TP)		
	Leukocyte differential count*		

2) Clinical Chemistry:

The following CHECKED (X) parameters were examined:

X		X	
	Electrolytes:		Other:
x	Calcium*	x	Albumin*
	Chloride*	x	Blood creatinine*
	Magnesium*		Blood urea nitrogen*
x	Phosphorus*	x	Cholesterol*
x	Potassium*		Globulins
x	Sodium*	x	Glucose*
	Enzymes:	x	Total bilirubin*
x	Alkaline phosphatase	x	Total protein*
	Cholinesterase	x	Triglycerides
x	Creatine phosphokinase*		A/G Ratio
	Lactic acid dehydrogenase	x	Plasma Urea
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		
	Gamma-glutamyl transpeptidase (GGTP)		

3) Urinalysis:

Collection times for urine (including # of animals): Urine samples were collected from five males and five females in each group after exposure day 20. The animals were deprived of food and water for 14 hours while the urine samples were being collected.

The following CHECKED (X) parameters were examined:

X		X	
| |	Appearance*	|x|	Glucose*
|x|	Volume*	|x|	Ketones*
|x|	Specific gravity*	| |	Bilirubin*
|x|	pH	|x|	Blood*
|x|	Sediment (microscopic)*	| |	Nitrate
|x|	Protein*	|x|	Urobilinogen

i. Gross Necropsy:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to end of exposure period and were subjected to complete gross pathological examinations: None.

Animals (groups) sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations: All animals.

j. Histopathology:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to the end of the exposure period and were subjected to microscopic examination: None.

Animals (groups) which were sacrificed at the end of the treatment/observation period and were subjected to microscopic examination: Tissues were removed from all animals and preserved. Tissues from the control and high dose group were prepared and examined microscopically, except the eye, Harderian gland, mammary gland, skin, spinal cord and voluntary muscle. Lung and abnormal tissues were prepared and examined in the low and mid-dose groups as well.

CHECKED (X) tissues were preserved for histopathological examination and (XX) tissues were weighed upon removal from the animal. The (*) tissues were recommended by the Guidelines. Paired organs were weighed together.

X		X		X	
	Digestive system		Cardiovasc./Hemat		Neurologic
	Tongue	x	Aorta*	xx	Brain*
x	Salivary glands*	xx	Heart*	x	Periph. nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord
					(3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	x	Spleen*		Eyes (optic n.)*
x	Jejunum*	x	Thymus*		Glandular
x	Ileum*		Urogenital	xx	Adrenals*
x	Cecum*	xx	Kidneys*		Lacrimal gland
x	Colon*	xx	Urinary bladder		Mammary gland*
x	Rectum*	x	Testes*	x	Parathyroids*
xx	Liver		Epididymides	x	Thyroids*
	Gall bladder*	x	Prostate		Other
x	Pancreas*	x	Seminal vesicle	x	Bone* (femur, sternum)
	Respiratory	x	Ovaries	x	Skeletal muscle*
xx	Trachea*	x	Uterus*		Skin
xx	Lung*	x	Cervix	x	All gross lesions and masses
x	Larynx				
x	Nasal cavity				

k. Statistical Analyses: The following types of statistically analyses were conducted: analysis of variance, analysis of covariance and two-sided Student's t-test.

B. RESULTS:

1. Atmospheric Generation and Measurements: The following table summarizes the study mean (mean of daily means) concentrations of the test chemical determined both gravimetrically and analytically.

Table 2: Concentrations of Test Chemical

Group	Target Concentration (Lambda-Cyhalothrin) (µg/l)	Mean Particulate Concentration +/- SD (µg/l)	Mean Analysed Lambda-Cyhalothrin Concentration +/- SD (µg/l)
1	0	-	None detected
2	0.25	0.3 +/- 0.06	0.21 +/- 0.05
3	2.5	3.3 +/- 0.7	2.64 +/- 0.58
4	15.0	16.7 +/- 2.9	12.80 +/- 2.65

The report stated that "the analyzed lambda-cyhalothrin content of the total particulate represented an average of approximately 76% and was close to the

analysed purity of the production material. The particulate was therefore considered to represent lambda-cyhalothrin production material."

The following table summarizes the mean aerodynamic particle size distribution of the total particulate.

Table 3: Mean Particle Size Distribution

Group	Particulate Concentration Lambda-Cyhalothrin Production Material (µg/l)	MMAD (+/- SD) micrometers	GSD (+/- SD)
2	0.3	1.91 +/- 0.47	2.24 +/- 0.41
3	3.3	1.48 +/- 0.21	1.82 +/- 0.14
4	16.7	1.47 +/- 0.10	1.68 +/- 0.10

MMAD = Mass median aerodynamic diameter
GSD = Geometric standard deviation

The report stated that "the percentages on the stages of the cascade impactor were similar when calculated using the particulate data and the analysed concentrations".

2. Clinical Observations and Mortality: Observation results were divided into three categories: during exposure, immediately following exposure and observation on non-exposure days.

Observations During Exposure: These included clinical signs generally associated with restraint (stains around the snout, wet fur and chromodacryorrhea). These signs were seen in both test and control animals. Salivation and lachrymation were observed in some animals exposed to 3.3 and 16.7 µg/l of the test material, and auditory hypoaesthesia was present in most animals exposed to 16.7 µg/l.

Observations Immediately Following Exposure: Again, clinical signs generally associated with restraint were observed in all groups, including controls (hunched posture, piloerection, stains around the nose, chromodacryorrhea and wet fur). No toxicologically significant effects were seen at the 0.3µg/l dose level. Treatment-related effects were seen at both the mid- and high dose levels. These effects were either neurological in nature (i.e. paw flicking or tail erections) or indicative of irritancy (i.e. lachrymation or salivation). The effects were more severe and were of a greater range in the high dose animals (See Table 4).

Table 4: 21-Day Inhalation Study with Lambda-Cyhalothrin: Incidences of Clinical Signs Following Exposure								
Clinical Sign	Males (10/dose)				Females (10/dose)			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
Paw flicking			2 (3)	9 (1)				10 (1)
Tail Erection			3 (3)	8 (1)	1 (15)		5 (5)	10 (1)
Lachrymation			2 (3)	8 (1)	1 (7)		5 (1)	10 (1)
Salivation			8 (1)	10 (1)			3 (2)	10 (1)
Splayed gait			2 (3)	10 (1)				10 (1)
Activity decreased				7 (1)				9 (2)
Reduced foot withdrawal				1 (1)				
Head flicking				2 (1)				1 (7)
Reduced righting reflex				3 (1)				1 (2)
Shaking				3 (1)				
Sides pinched in				1 (11)				3 (7)
Reduced splay reflex				3 (1)				2 (5)
Tip toe gait				8 (1)			3 (7)	10 (1)
Dec/SD Visual Plac. Resp.				2 (1)				
Incr./SD response to touch					2 (7)		1 (15)	1 (7)
Pinna reflex absent								1 (15)
Ungroomed								2 (11)

* Highest number of animals affected on any one day (day sign first observed)

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Observations on Non-Exposure Days: The authors stated that "the only significant effects were tail erections and tiptoe gait in some animals exposed to " the 16.7 µg/l dose level.

The authors also stated that respiratory noise was present in a few animals from all test groups throughout the study and was possibly due to irritancy caused by deposition of the test compound in the upper respiratory tract. There were no histological findings in these regions. Therefore, these effects were not considered to be of toxicological significance.

3. Body Weight Determinations: At the highest dose level, body weight and body weight gain were reduced in both sexes when compared to controls. By the end of the study, mean body weights were 15% and 12% and mean body weight gains were 14% and less than 3% of the mean control values for males and females, respectively. The authors stated that the effects on bodyweight gain in females appeared to be dependent on whether or not the bodyweights were recorded on an exposure day or on a non-exposure day since there appeared to be some recovery in bodyweight gain in females on non-exposure days. Males appeared to have a steady but reduced bodyweight gain over the duration of the study, but in females, the overall pattern was an approximate maintenance of the starting weight. The effects at the mid-dose level were similar but at a reduced level. At this dose level, the final mean body weights were 5% and 6% and the final mean body weight gains were 65% and 53% of the mean control levels for males and females, respectively. There were no effects in either bodyweight or bodyweight gain at the low dose level. The following table summarizes the results.

Table 5. Bodyweight Gain (g) in a 21-Day Inhalation Study

Exposure Level (µg/l)

Males

Day	0 (Contr.)	0.3	3.3	16.7
1 Initial Weight	258.0	261.6 (101%)	266.1 (103%)	266.1 (103%)
7	24.7	23.1	5.8**	-8.4**
15	55.1	54.1	26.9**	1.2**
22	64.8	67.6	42.1**	9.3**
Final Weight	322.8	329.2 (102%)	308.2 (95%)	275.4** (85%)

Females

1 Initial Weight	216.8	218.0 (101%)	216.4 (100%)	219.7 (101%)
7	8.4	9.4	0.2**	-6.8**
15	23.1	22.7	11.5**	-6.5**
22	29.7	30.4	15.8**	-3.2**
Final Weight	246.5	248.4 (101%)	232.2* (94%)	216.5** (88%)

** Statistically significant $p<0.01$.
* Statistically significant $p<0.05$.

4. Food and/or Water Consumption: A statistically significant reduction in food consumption over control values was observed in both sexes at the high dose up to day 18 and a slight reduction between days 18 to 22. At the mid-dose level reduced food consumption was observed in males during the first week of the study, statistically significant on days 1-2, 3-7, and 7-11. In females, significant reductions in food consumption were observed on days 2-5 and 11-15.

Table 6: 21-Day Inhalation Study with Lambda-Cyhalothrin: Food Consumption (g/rat/day)								
Period (Days)	Males				Females			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
-1 to 1	24.0	21.5*	24.0	24.5	19.0	18.0	19.0	20.5
1-2	26.0	24.5	20.0**	12.0**	21.5	18.5	18.0	12.0**
2-3	27.0	24.5	23.5	17.5**	23.5	23.0	21.5*	20.5**
3-7	29.5	28.0	25.0*	23.5*	22.0	22.5	20.0	13.5**
7-11	29.5	29.0	25.5*	20.5**	23.0	23.5	21.0	19.5*
11-15	32.0	30.5	28.5	27.0*	25.0	24.0	23.5*	18.5*
15-18	30.0	29.5	26.0	22.5*	24.0	25.0	23.5	21.0*
18-22	28.5	28.5	28.5	26.0	23.5	23.0	20.0	18.5*

* $p < 0.05$
** $p < 0.01$

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5. Ophthalmological Examinations: The authors stated that there was a dose-related increase in the incidence of punctate foci on the cornea in both sexes exposed to the mid- and high dose levels. No effects were observed at the low dose level or on histological examination of the eyes. The incidences were as follows: 0, 0, 3 and 5 out of 10/dose in males and 1, 1, 3 and 7 out of 10/dose in females.

6. Hematology: The report stated that "the platelet count was reduced in all female treated groups and the prothrombin time was slightly raised in top dose females. There were changes in other hematological parameters although these, together with the changes in the platelet count of females, are considered to be of no toxicological significance."

7. Clinical Chemistry: At the high dose level, reductions in plasma urea, albumin, cholesterol and total protein were observed as well as increases in aspartate transaminase and alkaline phosphatase activities in females. In males, small reductions were seen in triglyceride levels at this dose level. At the mid-dose level, slight reductions in plasma albumin, total protein and cholesterol levels were observed in females as well as minimal reductions in albumin and total protein levels in males. All of these values were statistically significant over control values. No other biologically significant changes were seen.

Table 7: 21-Day Inhalation Study with Lambda-Cyhalothrin: Selected Clinical Chemistry Values								
Clinical Chemistry Parameter	Males (4/dose)				Females (4/dose)			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
Urea (mg/100 ml)	47.9	47.1	50.8	45.7	54.7	51.5	50.5	42.8**
Albumin (g/100 ml)	4.43	4.40	4.17**	4.39	4.44	4.32	4.20**	4.05**
Cholesterol (mg/100 ml)	72.2	70.1	68.7	72.0	74.5	78.9	62.5*	59.5*
Total Protein (g/100 ml)	6.42	6.40	6.16*	6.21	6.48	6.44	6.11**	5.95**
Aspartate transaminase (mU/ml)	64.7	59.1	63.4	70.6	69.4	73.2	78.6	82.6*
Alkaline phosphatase (mU/ml)	258	242	239	245	151	169	165	184*
Triglycerides (mg/100 ml)	129	133	129	105*	101	99	102	107

* $p < 0.05$, ** $p < 0.01$

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8. Urinalysis (Table 8): The urine volume was reduced in all treated groups in males and in high dose females. The apparent reduction in volume in low dose males was considered to reflect a few extreme control values giving rise to a high control mean and was not considered to be of any toxicological significance. The specific gravity was slightly raised in both sexes at the mid- and high dose levels and there were reductions in protein levels in mid- and high dose males and in high dose females (not statistically significant). All values were statistically significant over control values unless otherwise noted.

Table 8: 21-Day Inhalation Study with Lambda-Cyhalothrin: Selected Urinalysis Values								
Uninalysis Parameter	Males (5/dose)				Females (5/dose)			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
Urine volume (ml)	7.50	5.08*	3.02**	2.72**	5.34	4.48	3.32	2.28**
Specific gravity	1.041	1.048	1.061**	1.064**	1.045	1.047	1.053*	1.060**
Protein (mg/TPV)	13.78	10.36	7.80**	6.01**	1.18	0.92	1.06	0.56

* $p < 0.05$, ** $p < 0.01$

Table 9: 21-Day Inhalation Study with Lambda-Cyhalothrin: Mean Liver Weights (Absolute and Adjusted for Body Weight; g)								
	Males (10/dose)				Females (10/dose)			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
Absolute Liver Weight	13.9	13.8	13.9	12.4*	10.8	10.8	9.6**	9.4**
Adjusted for Body Weight	13.0	12.4	13.9*	14.6**	10.3	10.1	9.8	10.4

* $p < 0.05$, ** $p < 0.01$

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Table 10: 21-Day Inhalation Study with Lambda-Cyhalothrin: Microscopic Examination: Selected Tissues								
	Males (10/dose)				Females (10/dose)			
Concentration µg/L	0	0.3	3.3	16.7	0	0.3	3.3	16.7
Kidney (# examined) Unilateral hydronephrosis Intratubular microlithiasis	10 4 0	0 - -	0 - -	10 6 0	10 2 7	0 - -	0 - -	10 0 10
Adrenal Gland (# examined) Enlarged Pale	Did not find anything				10 0 1	10 0 0	10 0 1	10 2 4
Brain (# examined) Meningioma	10 0	0 -	0 -	10 1	Did not find anything			
Heart (# examined) Degenerative myocarditis	10 0	0 -	0 -	10 1	Did not find anything			
Lung (# examined) Alveolitis	10 1	10 4	10 3	10 1	10 1	10 1	10 2	10 7

* $p < 0.05$, ** $p < 0.01$

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9. Gross Pathology: No treatment-related macroscopic findings were observed.

10. Organ Weights (Table 9): Statistically significant decreases in absolute liver weights over controls were observed in high dose males and in mid- and high dose females. Statistically significant increases in relative liver weights over controls were observed for mid- and high dose males. Since these do not correlate with each other, the changes are not considered to be biologically significant.

11. Histopathology (Table 10): There was a slight increase in the incidence of alveolitis in high dose females. The report stated that one high dose male had a benign meningioma in the brain. They also stated that "this is a rare tumor, especially in a young rat, but it is considered highly unlikely that this tumor was caused by exposure to lambda-cyhalothrin production material."

C. DISCUSSION: The mean particulate concentrations were 0.3, 3.3 and 16.7 µg/l for the low, lid- and high dose groups, respectively. The target concentrations were 0.25, 2.5 and 15.0 µg/l for the low, mid- and high dose groups, respectively. Therefore, the measured concentration values were fairly close to the target values. The mass median aerodynamic diameters (MMAD) were 1.91, 1.48 and 1.47 µm for the low, mid- and high dose groups, respectively. These are close to 1 µm which is the respirable value accepted by the Agency at present. The NOAEL for systemic effects is 0.3 µg/l and the LOAEL was 3.3 µg/l based on decreased bodyweight gains; clinical signs of neurotoxicity; punctate foci on the cornea and changes in clinical chemistry and urinalysis. The authors provided the following statements about the observed effects:

"The major clinical effects seen...were either neurological in nature or indicated irritancy. This is consistent with the known effects of synthetic pyrethroids. On non-exposure days throughout the study, the majority of the abnormalities had disappeared, again consistent with the effects of synthetic pyrethroids....The small increases in [the relative] liver weight[s]...in male rats...in the absence of any histopathological findings, are considered to be an adaptive response to exposure to the test material and of no toxicological significance...The changes seen in some clinical chemistry and haematological parameters in both sexes suggest a minimal effect on liver metabolism and together with the other changes in the urine profile and plasma urea, probably reflect the general toxicity of lambda-cyhalothrin...The presence of an increased incidence of punctate foci on the cornea in ...[both sexes]...indicates a dose response to treatment. In view of the clinical observation of excess lachrymation during exposure, the absence of histopathological change and the nature of the ophthalmoscopic effect, it is considered likely that this treatment-related increase represented an abnormal pre-corneal film due to excessive lachrymation. As such, it is of no toxicological significance...The slight increase in the incidence of alveolitis in top dose females was possibly due to an irritant effect of the test material depositing in the lung." The Agency notes that these explanations are all plausible. With the exception of length of exposure (days) and the exclusion of individual animal data, this study appears to be within guideline requirements for a repeated dose inhalation study. The study is classified as acceptable nonguideline.

EPA Reviewer: Pamela M. Hurley
Registration Action Branch 2 (7509C)
TXR No. 0050580

Pamela M Hurley . Date 3/26/2004

DATA EVALUATION RECORD
Supplement to DER for MRID No.: 00154806 Cyhalothrin: 28-Day Feeding Study in the rat. TXR No. 005100

STUDY TYPE: 28-Day Feeding Study - Rat
OPPTS Number: N/A OPP Guideline Number: § N/A

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (89.2% a.i.)

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

CITATION: Moyes, A.; Godley, M.; Hall, M., et al. (1984) Cyhalothrin: 28-Day Feeding Study in the Rat (Second Study): Summary Report: Report No: CTL/P/1013. Unpublished study prepared by Imperial Chemical Industries PLC. 33 p. MRID 00154806

SPONSOR: Imperial Chemical Industries, PLC, Macclesfield, Cheshire, U.K.

EXECUTIVE SUMMARY:

In an oral toxicity study SPF Wistar (Alderly Park strain) rats (8/sex/dose) were dosed with cyhalothrin (89.2% a.i.) in the diet at 0, 1, 5, 10, 20 or 250 ppm (approximately 0, 0.1, 0.5, 1.0, 2.0 or 25.0 mg/kg/day using a factor of 10 for young animals) for 28 days (MRID 00154806). Animals were examined for clinical signs of toxicity and the following parameters were measured: body weights, liver weights and hepatic aminopyrene-N-demethylase (APDM) activity. In addition, the livers were subjected to electron microscopic examinations.

No effects were observed at 1, 5 and 10 ppm. At 20 ppm and above, a reduction in mean body weight gain was observed in females (p less than or equal to 0.05; 22% less than the control value for weeks 0-4); however, body weight was not affected. At 250 ppm, a reduction in mean body weight gain was observed in males (13% less than the control value for weeks 0-4). In addition, increases and/or proliferation in APDM (14-40%) and smooth endoplasmic reticulum (SER) was observed in both sexes. Relative liver weights were increased in males (7%); however, absolute liver weights were not affected. **The NOAEL is 10 ppm (1.0 mg/kg/day in females) and 20 ppm (2.0 mg/kg/day in males) and the LOAEL is 20 ppm (2.0 mg/kg/day in females) and 250 ppm (25.0 mg/kg/day in males) based on decreases in mean body weight gain in females at 20 ppm and above and in males at 250 ppm, and increases and/ or**

proliferation in APDM and SER in in both sexes at 250 ppm.

This study is classified as **acceptable nonguideline** and does not satisfy any particular guideline requirement.

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:

Robert J. Weir, Ph.D.
Principal Author
Dynamac Corporation

Signature: Robert J. Weir
Date: 9/3/85

Finis L. Cavender, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Finis L. Cavender
Date: 9/3/85

6. APPROVED BY:

William McLellan, Ph.D.
Chronic Toxicity
Technical Quality Control
Dynamac Corporation

Signature: William L. McLellan
Date: Sept 3, 1985

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

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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.

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

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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).

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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.

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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 ($p \leq 0.01$).

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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 concommitant 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.

005100

Item 15 - see footnote 1.

16. CBI APPENDIX:

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

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

APPENDIX A

Materials and Methods

(CBI pp. 2-7)

US EPA ARCHIVE DOCUMENT

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7

EPA Reviewer: Pamela M. Hurley
Registration Action Branch 2 (7509C)
TXR No. 0050580

Pamela M Hurley Date 3/26/2004

DATA EVALUATION RECORD
Supplement to DER for MRID Nos.: 00154869, 41062701
Cyhalothrin: Repeated Dose Dermal Study in the Rabbit. TXR Nos. 005100, 006618, 007455

STUDY TYPE: Repeated Dose Dermal Toxicity Study - Rabbit
OPPTS Number: 870.3200 OPP Guideline Number: §82-2

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Cyhalothrin Technical (90.2% a.i.)

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

CITATION: Henderson, C.; Jackson, S. (1982) Cyhalothrin: Subacute Dermal Toxicity Study in Rabbits: Report No. CTL/P/680. Unpublished study prepared by Imperial Chemical Industries PLC. 64 p. MRID 00154869

Ierley, D. (1989) Addendum to MRID #40387701, Cyhalothrin: Subacute Dermal Toxicity in Rabbits: Proj. ID CTL/P/680. Unpublished study prepared by ICI Central Toxicology Laboratory. 5 p. MRID 41062701

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: In a repeated dose dermal toxicity study (MRIDs 00154869, 41062701), cyhalothrin (90.2% a.i.) was applied to the clipped skin of 10 New Zealand White rabbits/sex/dose at dose levels of 10, 100 or 1000 mg/kg/day for 6 hours/day, 5 days/week for a total of 15 applications. One half the animals had abraded skin and the other half had non-abraded skin. The control group consisted of 14/sex treated with 2 ml/kg/day of polyethylene glycol 300 (PEG 300). The rabbits were observed daily for clinical signs of toxicity, skin irritation and individual body weights. Food consumption, hematology, clinical chemistry measurements were also taken. Gross necropsy and microscopic examinations were conducted.

There was no difference in clinical signs of toxicity between the abraded and non-abraded animals. No treatment-related clinical signs of toxicity were observed at any dose level. Some of the clinical signs which are similar to those normally observed with pyrethroids were due to physical injury. In nonabraded animals, with the exception of low dose males, all rabbits lost weight, including the controls. Statistical significance in weight loss was achieved at 1000 mg/kg/day in males. This dose group lost 10% of their body weight. The controls lost <1% of

their body weight. In females, the controls lost 5% of their body weight and the 1000 mg/kg/day group lost 11% of their body weight. Food consumption in the high dose group varied. At times it was less and at times it was more. There was no consistent pattern. Slight to severe irritation was observed in all test groups, including controls. In nonabraded animals, there appeared to be an increase in the number of animals affected by irritation starting at 100 mg/kg/day. **The NOAEL for dermal irritation is 10 mg/kg/day and the LOAEL for dermal irritation is 100 mg/kg/day. The systemic NOAEL is 100 mg/kg/day for both sexes. The systemic LOAEL is 1000 mg/kg/day for both sexes, based on significant weight loss when compared to the control groups..**

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a repeated dose dermal study (**§82-2**) in the rabbit.

Notations on the study: There was considerable correspondence concerning this study over the health of the rabbits. Slides from the heart and liver were submitted by the Registrant for review by HED's pathologist. HED had concern over the incidences of myocardial fibrosis and portal tract inflammation because HED was unable to determine whether these lesions were treatment-related or they were due to infection with Eimeria stiedae. After reviewing the submitted slides, the HED pathologist determined that the liver lesions were representative of hepatic coccidiosis and are not compound-related and the cardiac lesion was spontaneous in nature and extent and was consistent with the historical control data (memorandum from P. Hurley to G. LaRocca, dated April 27, 1988). In addition, after further analysis, discussion and submissions from the Registrant, the HED pathologist also concluded that most of the rabbits, including controls had severe hypogammaglobulinemia and that the animals were immune-incompetent (memorandum from P. Hurley to G. LaRocca, dated 8/25/89). Unfortunately, actual measurements of the globulins were not conducted. HED did not require a repeat of the study at that time for the following reasons: there were no significant toxicological effects, effects on the immune system are not an endpoint that is normally examined in a repeated-dose dermal study, and weight of the evidence on this chemical indicate that any effects on the immune system would not likely affect any toxicological endpoints that would have been expected in this study (i.e. clinical signs of neurotoxicity).

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

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.

APPROVED BY:

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

Signature: I Cecil Felkner
Date: 9-13-85

4

1. CHEMICAL: Cyhalothrin; PP563, ICI 146, B14; (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:

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

Signature: Ira Cecil Felton for
Date: 9-12-85

William Butler, Jr., M.S.
Independent Reviewer
Dynamac Corporation

Signature: William Butler Jr.
Date: 9-12-85

6. APPROVED BY:

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

Signature: Finis Cavender
Date: 9/12/85

Pamela Hurley, Ph.D.
EPA Reviewer

Signature: Pamela Hurley
Date: 4/23/86

Edwin Budd
EPA Section Head

Signature: John Schoff
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.

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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.

7

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.

8

APPENDIX A

Results

US EPA ARCHIVE DOCUMENT

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The material not included contains the following type of information:

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S

EPA Reviewer: Pamela M. Hurley
Registration Action Branch 2 (7509C)
TXR No. 0050580

Pamela M Hurley Date 3/26/2004

DATA EVALUATION RECORD
Supplement to DER for MRID No.: 00153028 Lambda-cyhalothrin: 90-Day Feeding Study in Rats. TXR No. 005316

STUDY TYPE: 90-Day Feeding Study in the Rat
OPPTS Number: 870.3100 OPP Guideline Number: §82-1

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128867, 128897 TOX. CHEM. NO.: 271F, 725C

TEST MATERIAL (PURITY): Lambda-cyhalothrin technical (96.5% a.i.)

SYNONYMS: α-Cyano-3-phenoxybenzyl 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate; PP321

CITATION: Hart, D.; Banham, P.; Chart, I.; et al. (1985) PP321: 90 Day Feeding Study in Rats: CTL Study No. PR0584: Report No. CTL/P/1045. Unpublished study prepared by Imperial Chemical Industries, PLC. 76 p. MRID 00153028

SPONSOR: Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK

EXECUTIVE SUMMARY: In a 90-day feeding study in male and female SPF Alk/AP Wistar-derived rats (20/sex/dose), lambda-cyhalothrin (96.5%) was fed in the diet at levels of 0, 10, 50 or 250 ppm (0, 0.5, 2.5, 12.5 mg/kg/day; MRID 00153028). The animals were examined once daily for clinical signs of toxicity. Bodyweights, food consumption, hematological and clinical chemistry parameters, urinalysis parameters, organ weights, and macroscopic and microscopic observations were recorded.

No treatment-related effects were observed at 0.5 mg/kg/day. At 2.5 mg/kg/day, increased mean liver weight and increased activity of hepatic aminopyrine-N-demethylase (APDM) were observed in males. This is considered to be an adaptive response. At 12.5 mg/kg/day significantly reduced body weight gain and food consumption were observed in both sexes as well as increased mean liver weight and increased APDM activity in both sexes. There was also a slight but statistically significant reduction in food efficiency in females at this dose level.

The NOAEL is 2.5 mg/kg/day and the LOAEL is 12.5 mg/kg/day based on reduction in bodyweight gain and food consumption in both sexes and food efficiency in females.

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a subchronic feeding study (**§82-1**) in the rat.

Table 1: Lambda-Cyhalothrin 90-Day Feeding Study: Body Weight Gains (g)								
Weeks	Males				Females			
mg/kg/day	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Initial Wt.	132.5	129.9	126.3	127.0	117.2	114.3	114.3	118.3
1	52.0	48.1**	48.3**	22.7**	35.3	33.1	33.9	16.1**
4	189.2	187.0	190.5	158.0**	94.9	90.1	97.4	75.7**
8	290.2	283.1	291.8	246.6**	134.7	126.7	137.1	114.3**
13	357.3	352.1	359.0	308.3** (86)	154.7	148.1	155.1	133.7** (86)
Final Weight	489.8	482.0	485.3	435.3[a] (89)	271.9	262.4*	269.4	251.9** (93)

* $p < 0.05$, ** $p < 0.01$

[a]Line missing. Statistical analysis not available for males.

( ) = % of control group

Table 2: Lambda-Cyhalothrin 90-Day Feeding Study: Food Consumption (g/rat/day)								
Weeks	Males				Females			
mg/kg/day	0	0.5	2.5	12.5	0	0.5	2.5	12.5
1	22.6	22.1	21.2**	14.1**	19.5	18.7	18.7	13.6**
4	28.2	28.0	27.9	25.8**	19.0	18.1	19.5	17.3**
8	27.9	27.5	28.3	25.3*	19.7	19.0	19.9	18.2**

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Table 2: Lambda-Cyhalothrin 90-Day Feeding Study: Food Consumption (g/rat/day)								
Weeks	Males				Females			
mg/kg/day	0	0.5	2.5	12.5	0	0.5	2.5	12.5
13	28.0	28.4	28.2	25.4**	19.1	18.2	18.5	17.5**
Total (g)	2533.6	2526.9	2524.1	2248.3** (89)	1808.8	1732.1*	1800.8	1641.3** (91)

* $p < 0.05$, ** $p < 0.01$
( ) = % of control group

Table 3: Lambda-Cyhalothrin 90-Day Feeding Study: Food Utilization (g Food/g Growth)								
Weeks	Males				Females			
mg/kg/day	0	0.5	2.5	12.5	0	0.5	2.5	12.5
1-4	3.90	3.91	3.79	3.87	5.82	5.87	5.69	6.39**
5-8	7.83	8.15	7.86	8.13	14.24	14.73	14.38	13.22
9-13	15.05	15.16	15.13	15.13	37.32	32.77	38.60	33.81
Overall (1-13)	7.09	7.20	7.05	7.31	11.74	11.71	11.68	12.20*

* $p < 0.05$, ** $p < 0.01$
( ) = % of control group

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Table 4: Lambda-Cyhalothrin 90-Day Feeding Study: Organ Weights (g)								
Weeks	Males				Females			
mg/kg/day	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Brain Absolute Adjusted for Body weight	2.133 2.118	2.095 2.087	2.094 2.083	2.068** (97) 2.102	1.965 1.959	1.933* 1.934	1.953 1.949	1.952 1.961
Heart Absolute Adjusted for Body weight	1.345 1.307	1.319 1.299	1.329 1.302	1.217** (90) 1.302	0.896 0.878	0.869 0.872	0.891 0.879	0.871 0.898
Kidney Absolute Adjusted for Body weight	3.13 3.05	3.12 3.08	3.06 3.00	2.82** (90) 3.01	1.87 1.83	1.87 1.88	1.86 1.84	1.80 1.85
Lung Absolute Adjusted for Body weight	1.71 1.66	1.67 1.65	1.71 1.68	1.51** (88) 1.62	1.22 1.19	1.18 1.18	1.20 1.18	1.17 1.21
Spleen Absolute Adjusted for Body weight	0.914 0.897	0.911 0.900	0.907 0.894	0.821** (90) 0.858	0.644 0.626	0.621 0.624	0.623 0.611	0.576** (89) 0.603

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Table 4: Lambda-Cyhalothrin 90-Day Feeding Study: Organ Weights (g)								
Weeks	Males				Females			
mg/kg/day	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Ovary Absolute Adjusted for Body weight	-	-	-	-	0.095 0.093	0.105 0.105	0.103 0.101	0.105 0.108* (116)
Testes Absolute Adjusted for Body weight	3.47 3.45	3.42 3.42	3.48 3.46	3.28** (95) 3.32	-	-	-	-
Liver Absolute Adjusted for Body weight	18.7 17.9	18.9 18.4	19.5 18.9**	17.7 19.4** (108)	10.2 9.8	10.0 10.1	10.2 9.9	10.0 10.6** (108)

* $p < 0.05$, ** $p < 0.01$
( ) = % Control group

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Table 5: Lambda-Cyhalothrin 90-Day Feeding Study: Hepatic Aminopyrine-N-Demethylase Activity (µmol Formaldehyde/h/g liver)								
Weeks	Males				Females			
mg/kg/day	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Mean	17.1	17.8	20.9	27.8	5.2	5.4	4.7	8.0
Mean Transformed Value	2.77	2.84	2.96* (106)	3.24** (117)	1.62	1.67	1.47	2.06* (127)

* $p < 0.05$, ** $p < 0.01$
( ) = % Control group

Table 6: Lambda-Cyhalothrin 90-Day Feeding Study: Microscopic Findings								
Weeks	Males				Females			
mg/kg/day	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Liver								
# Examined	20	20	20	20	20	20	20	20
Extramedullary hematopoiesis - minimal	4	0	0	1	0	0	0	0
Inflammatory cell infiltration, portal/focal -minimal	4	1	0	3	2	1	0	2
Brain								
# Examined	20	0	0	20	20	0	0	20
Vacuolation of white matter, diffuse/multifocal - slight/moderate	2	0	0	1	0	0	0	0

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Table 6: Lambda-Cyhalothrin 90-Day Feeding Study: Microscopic Findings								
Weeks	Males				Females			
mg/kg/day	0	0.5	2.5	12.5	0	0.5	2.5	12.5
Sciatic Nerve								
# Examined	20	0	0	20	20	0	0	20
Wallerian degeneration, focal - minimal	8	0	0	5	2	0	0	1
Kidney								
# Examined	20	20	20	20	20	20	20	20
Intratubular microlithiasis - minimal/slight	2	1	0	1	10	15	15	17
- moderate	0	0	0	0	10	5	5	1
Heart								
# Examined	20	0	0	20	20	0	0	20
Myocardial fibrosis, focal - minimal/slight	2	0	0	0	1	0	0	0
Myocarditis, focal - minimal	1	0	0	2	0	0	0	0

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

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DATA EVALUATION REPORT

STUDY TYPE: Subchronic feeding 82-1 (rat) TOX. CHEM. NO.: 725C

ACCESSION NUMBER: 073980

TEST MATERIAL: (RS)-alpha-cyano-3-phenoxybenzyl, (1RS), cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethyl cyclopropane carboxylate

SYNONYMS: PP321, Karate (substituent of Cyhalothrin, Grenade)

STUDY NUMBER(S): PRO584

REPORT NUMBER: CTL/P/1045

SPONSOR: ICI PLC, Plant Protection Division, Jealott's Hill, Bracknell, UK

TESTING FACILITY: ICI PLC Cntrl. Tox. Lab, Alderly Park, Macclefield, UK

TITLE OF REPORT: PP321: 90 Day Feeding Study in Rats

AUTHOR(S): Hart D, Banham PB, Chart IS, Evans DP, Gore CW, Stonard MD, Moreland S, Godley MJ, Robinson M.

REPORT ISSUED: 2/14/85

IDENTIFYING VOLUME: Volume II, Book 1, Section C, Tab 8C

CONCLUSION: The NOEL is 50 ppm and the LOEL is 250 ppm based on reduction in in body weight gain.

Classification: Core Guideline

MATERIALS AND METHODS:

Chemical:

PP321 was supplied by ICI PLC, Plant Protection Division, Bracknell, Berkshire, UK. The purity was 96.5% w/w and the reference #'s were: CTL ref. # YO2537/001/005 and batch P13. The chemical was supplied as a buff solid.

Animals:

One hundred male and female SPF Alk/AP Wistar-derived rats were obtained from the Animal Breeding Unit at ICI PLC, Alderly Park. All rats were approximately 21 days old when transported. Twenty rats per sex were assigned to each dose level: 0, 10, 50 and 250 ppm.

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Protocol:

All animals were maintained on the appropriate experimental diet for 90 days. Animals were examined pre-experimentally and once daily for abnormalities in clinical condition and/or behavior. Detailed clinical observations were conducted when the animals were weighed. Bodyweights were recorded immediately before the start of the experiment and once weekly thereafter. Food consumption was also recorded once weekly. Ten animals of each sex per group were selected for blood sampling. Samples were taken from the tail vein prior to the start of the experiment and at 4 weeks into the experiment. Blood was removed from these same animals at termination via cardiac puncture. The following hematological measurements were taken:

hemoglobin, hematocrit, red cell count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, total white cell count, platelet count, differential white cell count and kaolin-cephalin and prothrombin times (at termination only).

Clinical chemistry measurements were taken on ten other male and female animals per group at the same predesignated times as the hematological measurements. The following measurements were taken:

plasma alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), triglycerides, plasma cholesterol, urea, glucose, albumin and total protein.

Urine samples were taken from the same animals from which the clinical chemistry measurements were taken, at the same predesignated times. The samples were collected over an 18 hour period. The following measurements were taken: volume, pH, specific gravity, protein, glucose, ketones and urobilinogen. During the week prior to termination, the eyes of the animals from the control and 250 ppm groups were examined using a Fison's binocular indirect ophthalmoscope.

At termination, all animals were given a full post mortem examination. The following organs were weighed: gonads (combined), spleen, adrenals (combined), kidneys (combined), liver, heart, lungs (combined with trachea attached) and brain. Tissues from the following list were removed from the high dose animals and controls and examined histopathologically together with liver, kidneys, lungs and any abnormal tissues from the lower dose groups:

adrenal glands, aorta, bladder, bone (left femur) including knee joint, brain, cecum, cervical lymph node, cervix, colon, duodenum, epididymis (L+R), eyes (+ Harderian gland), heart, jejunum, ileum, kidneys, lung, liver, mammary gland (female only (x2 inguinal)), mesenteric lymph nodes, esophagus, ovaries, pancreas, pituitary gland, prostate, rectum, salivary glands, sciatic nerves (L+R), seminal vesicles, skin (r. flank), spinal cord, spleen, sternum with bone marrow, stomach, testis (L+R), thymus, thyroid, parathyroid, trachea, uterus, voluntary muscle and abnormal tissue.

All other tissues were fixed and kept for future reference.

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Hepatic aminopyrine-N-demethylase activity (APDM) was determined from the livers of 6 male and 6 female predesignated animals. Statistical analyses were conducted on cumulative bodyweight gains, weekly and total food consumption, food utilization, biochemical and hematological data, organ weights, APDM activity and other appropriate measurements.

RESULTS:

All rats survived the study and no treatment related clinical observations were noted during the study. Body weight gain was significantly reduced for both sexes at the highest dose level. It was also reduced for the 10 and 50 ppm males for week 1. In females, bodyweight gain was slightly reduced for the lowest dose group but not for the mid-dose group. Food consumption was reduced in both sexes at the highest dose level throughout the study and in males at 50 ppm during week 1. In females, there was a slight reduction in food consumption for the 10 ppm group. There was also a small statistically significant reduction in the efficiency of food utilization for females at the 250 ppm level for weeks 1 to 4 and for overall.

Sporadic significant differences in hematologic values of treated versus control groups were noted, but were not considered to be of biological significance. ALT activity was significantly reduced for the 250 ppm males after 4 weeks. ALP activity was also significantly reduced for the 250 ppm females after 13 weeks. Plasma triglycerides were reduced for the 50 and 250 ppm males after 4 and 13 weeks, but was statistically significant only for the 250 ppm males. A small, but significant decrease in urine volume was observed at 4 weeks in the 250 ppm males.

No treatment related changes were noted in the ophthalmologic examinations. A significant increase in liver weights was observed for both sexes fed 250 ppm and for males fed 50 ppm. Ovary weights were higher for all treated groups, but significant only at the 250 ppm level. However, all values were within the historical control range.

The activity of hepatic APDM was significantly increased in both sexes fed 250 ppm and in males fed 50 ppm. No treatment related macroscopic or microscopic changes were noted at termination of the study.

DISCUSSION:

This was a well conducted study. There was a significant reduction in body weight gain and in food consumption at the highest dose level (250 ppm). The authors suggested that since in males the bodyweight gain continued to diverge from that of the controls, this was a continuing toxic effect rather than a palatability problem. In actuality, the data are borderline. The reduction in food consumption and bodyweight gain at the highest dose level could be due to lack of palatability of the diet. The reduction in ALT and ALP activities and triglyceride levels support the possibility of slight starvation of the animals. The authors also stated that the increase in liver weights and in APDM activities were indicative of an adaptive response. This is likely to be the case. Other similar insecticides have been known to induce liver

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enlargement as an adaptive response (e.g. pyrethrum (85 mg/kg/day in the rat)). These results were supported by the results of the subchronic study conducted on rats with cyhalothrin, of which PP321 is the resolved enantiomer pair. In that study, the increase in APDM was also considered to be adaptive. The NOEL for this study is considered to be 50 ppm, which is also the NOEL for the cyhalothrin subchronic study in rats.

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Chemical:	**lambda-Cyhalothrin**
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