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TOXIC SUBSTANCES

NOTE: This document contains an expanded explanation of why a database uncertainty factor is not needed in the absence of the required developmental neurotoxicity study.

TXR NO. 0051125

DATE: September 12, 2002

MEMORANDUM

SUBJECT: **CYHALOTHRIN AND LAMBDA-CYHALOTHRIN**- 4th Report of the Hazard Identification Assessment Review Committee.

FROM: Pamela Hurley Pamela M Hurley
Registration Action Branch 2
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair 9/12/02
and
Elizabeth Doyle, Co-Chair for RD
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Pamela Hurley, Risk Assessor
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PC Codes: 128867 and 128897

On April 9, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for cyhalothrin and lambda-cyhalothrin with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to cyhalothrin and lambda-cyhalothrin was also evaluated as required by the Food Quality Protection Act (FQPA) under the February 2002, OPP 10X guidance document. On May 21, 2002, the HIARC reevaluated the need for a database uncertainty factor in the absence of the required developmental neurotoxicity study. The conclusions drawn at both of these meetings are presented in this report.

Committee Members in Attendance

Members present were: Ayaad Assaad, William Burnam, Paula Deschamp, Elizabeth Doyle, Pamela Hurley, John Liccione, Elizabeth Mendez, David Nixon, Jess Rowland, Brenda Tarplee

Member(s) in absentia: Jonathan Chen

Data evaluation prepared by: Pamela M. Hurley, Registration Action Branch 2

Also in attendance were: Susan Makris (Toxicology Branch)

Data Evaluation / Report Presentation

Pamela M Hurley
Pamela Hurley
Toxicologist

INTRODUCTION

On April 9, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for cyhalothrin and lambda-cyhalothrin with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to cyhalothrin and lambda-cyhalothrin was also evaluated as required by the Food Quality Protection Act (FQPA) under the February 2002, OPP 10X guidance document. On May 21, 2002, the HIARC reevaluated the need for a database uncertainty factor in the absence of the required developmental neurotoxicity study.

I. FQPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base

The HIARC concluded that the combined database for cyhalothrin and lambda-cyhalothrin is adequate for FQPA considerations. The following studies are available.

-- Acute delayed neurotoxicity study in hen (cyhalothrin)
-- Acute neurotoxicity study (lambda-cyhalothrin)
-- Developmental toxicity studies in the rat & rabbit (cyhalothrin)
-- Three-generation reproduction study (cyhalothrin)

2. Evidence of Neurotoxicity

The HIARC concluded that there is a concern for neurotoxicity resulting from exposure to cyhalothrin and lambda-cyhalothrin.

a. Technical cyhalothrin (91.3% pyrethroid of which 97.7% is cyhalothrin) was tested in an acute delayed neurotoxicity study in which 6 groups of 10 domestic hens/dose were dosed once by gavage a 70% (w/v) suspension in corn oil at 0, 2500, 5000 or 10000 (two groups) mg/kg. The positive control group received a single dose of tri-ortho-cresyl phosphate (TOCP) in corn oil at 500 mg/kg (5.2 ml/bird). The vehicle control hens received corn oil at 30.7 ml/bird. No clinical signs of neurotoxicity were observed in any of the cyhalothrin treated groups. Nine of 10 hens in the TOCP group showed signs of ataxia beginning at day 10 after dosing; one was sacrificed at day 16 after showing severe (grade 8) ataxia. Statistically significant decreases in body weight gain ($p<0.05$) were observed in the 5000 and 10000 mg/kg groups when compared to the vehicle control group. Food consumption was comparable to or exceeded the negative control group. Microscopic examinations indicated no treatment-related effects for cyhalothrin at any dose level. The positive control TOCP group showed "morphological evidence of neurotoxicity, maximal in the cervical cord." **The NOAEL is 2500 mg/kg and the LOAEL is 5000 mg/kg based on significant decreases in body weight gain.**

b. In an acute oral neurotoxicity study (MRID 44861510), lambda-cyhalothrin in corn oil was administered in a single dose by gavage to 10 Alpk:AP_fSD 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 deeply anesthetized with intraperitoneal sodium pentobarbitone and then 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 ($\downarrow$21%, $p \leq 0.05$), and decreased ($p \leq 0.05$ or 0.01) hindlimb grip strength was observed on days 1, 8, and 15 ($\downarrow$19%, $\downarrow$31%, $\downarrow$32%) in males. Females displayed increased time to tail-flick on day 1 ($\uparrow$71%, $p \leq 0.05$). 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.

c. Evidence of neurotoxicity from other toxicity studies: clinical signs of neurotoxicity were

observed in the chronic and subchronic dog (gait abnormalities, muscle tremors and convulsions, subdued behavior, head shaking, excessive salivation); developmental rat (gait abnormalities); subchronic mouse (gait abnormalities, hunched posture); 21-day dermal rat (reduced splay reflex, gait abnormalities, reduced stability); 21-day inhalation rat (gait abnormalities, salivation, paw flicking, tail erections, lachrymation, reduced foot withdrawal, reduced righting reflex, shaking, head flicking, reduced splay reflex, decreased visual placing response); and 28 day feeding rat (gait abnormalities, hunched posture, tail erect, salivation) studies.

3. Developmental Toxicity Study Conclusions

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). 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.

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). 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.

4. Reproductive Toxicity Study Conclusions

In the three-generation reproduction study, groups of 15male 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). 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.

5. Additional Information from Literature Sources

A literature search was not conducted for this revisit.

6. Pre-and/or Postnatal Toxicity

The HIARC concluded that there is no concern for pre- and/or postnatal toxicity resulting from exposure to cyhalothrin and lambda-cyhalothrin.

A. Determination of Susceptibility

No quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses to *in utero* exposure in the developmental studies was observed. No developmental toxicity was observed in either of these studies. In the developmental toxicity study in rats, technical cyhalothrin was tested up to a dose level of 15 mg/kg/day. Maternal toxicity was observed at 15 mg/kg/day (uncoordinated movements in the limbs and a decrease in body weight gain and food consumption. No treatment-related developmental effects were observed at any dose level. In the developmental toxicity study in rabbits, technical cyhalothrin was tested up to a dose level of 30 mg/kg/day. Maternal toxicity was observed at 30 mg/kg/day (decrease in body weight gain and food consumption. No treatment-related developmental effects were observed at any dose

level.

No quantitative or qualitative evidence of increased susceptibility was observed in the 3-generation reproduction study in rats. In that study, technical cyhalothrin was fed in the diet at dose levels up to 100 ppm (approximately 5.0 mg/kg/day). Parental and offspring toxicity were observed at 5.0 mg/kg/day (decreased body weight and body weight gain during the premating and gestation periods and reduced pup weight and pup weight gains during lactation. No other effects were observed.

B. Degree of Concern Analysis and Residual Uncertainties

Since no developmental toxicity was observed in the developmental studies, there are no concerns or residual uncertainties for pre-natal toxicity. Offspring toxicity (decreased pup weight and pup weight gain) was observed in the reproduction study at the same dose level as parental toxicity (decreased body weight and body weight gain). These effects are not considered to be more severe than the effects in the parents.

7. Recommendation for a Developmental Neurotoxicity Study

The requirement for a developmental neurotoxicity study is triggered due to clinical signs of neurotoxicity in the acute mammalian neurotoxicity study as well as in the other toxicity studies. The cyhalothrins induce clinical signs of neurotoxicity in at least three species (rats, mice and dogs). In addition, the cyhalothrins are pyrethroids. SAR indicates that members of this class of compounds are uniformly neurotoxic. Lambda-cyhalothrin is the preferred test compound since neurotoxic effects are observed with this compound at slightly lower dose levels in dogs than with cyhalothrin. Using lambda-cyhalothrin will most likely result in a NOAEL/LOAEL that is protective of any effects noted in a study with cyhalothrin, thus negating the need for studies for each chemical.

A. Evidence That **Support Requiring** a Developmental Neurotoxicity Study:

- The cyhalothrins induce clinical signs of neurotoxicity in at least three species (rats, mice and dogs) and across routes of administration (oral, dermal and inhalation).
- In the acute neurotoxicity study conducted with lambda-cyhalothrin, ataxia and related conditions and increased salivation were observed.
- The cyhalothrins are members of the synthetic pyrethroid class of insecticides, which are known to induce transient clinical signs of neurotoxicity in mammals.

B. Evidence That **Support Not Requiring** a Developmental Neurotoxicity Study:

- There was no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to cyhalothrin.
- There is no indication of light microscopy neuropathology with any of the other

pyrethroids that have been tested thus far in standard toxicity studies. Mammalian neurotoxicity testing with this group of chemicals has only recently been initiated.

- No neuropathology has been observed in the acute mammalian neurotoxicity study.

- No malformations of the central nervous system were observed in the developmental and reproduction studies.

- The hypothetical mechanism of action for pyrethroids proposed by the Pyrethroid Working Group does not lend itself to developmental neuropathology.

On May 21, 2002, the HIARC reevaluated the need for a database uncertainty factor in the absence of the required developmental neurotoxicity study. In accordance with *the February, 2002, OPP 10X Guidance Document on Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment*, this data requirement is considered to be "confirmatory" and therefore, the HIARC concluded that a Database Uncertainty Factor is NOT required.

EPA has required that a DNT be conducted for lambda-cyhalothrin based upon structure activity relationship (SAR), mode of action, and toxicity information that identifies cyhalothrin and lambda-cyhalothrin as neurotoxic pesticides. Developmental neurotoxicity testing with cyhalothrin is required to further characterize the potential hazard to the developing animal, in accordance with standard OPP guidance. This determination was based upon a weight-of-evidence evaluation of the database, conducted in accordance with principles first developed at a 1989 Agency workshop on quantitative and qualitative comparability of human and animal developmental neurotoxicity (Levine and Butcher, 1990), and which have been subsequently reviewed by the FIFRA Scientific Advisory Panel in connection with DNT guideline development (1989), the retrospective analysis of DNT studies submitted to OPPTS (December, 1998), and FQPA 10X guidance (May, 1999).

Although a DNT has been required, EPA evaluated whether the existing reliable toxicity data for lambda-cyhalothrin provided EPA with the confidence to make a safety finding for infants and children using a different safety factor than the default additional safety factor of 10X. For the reasons set forth, EPA has concluded that existing, reliable toxicity data provide reasonable certainty that a risk assessment conducted using no additional factor (1X) will protect the safety of infants and children. First, it is noted that there was no indication, in the developmental or reproductive toxicity studies or in any published literature studies, of increased sensitivity in the offspring of rats or rabbits to *in utero* and/or postnatal exposure to cyhalothrin. Since there is no evidence that immature animals respond more severely than adults to cyhalothrin exposure in these studies, there is less concern regarding the potential for increased sensitivity in a developmental neurotoxicity study.

Second, an extensive evaluation of the data base for the cyhalothrins revealed that no damage to the neurological system (i.e., microscopic lesions, commonly referred to as "neuropathology") was observed in the brain of rats or dogs following subchronic or chronic exposure and with

formalin fixation of tissues. Even more importantly, in the acute neurotoxicity study with lambda-cyhalothrin, both central and peripheral nervous system tissues were examined following *in situ* perfusion fixation of tissues (which reduces microscopic artifacts that can result during processing). As per guideline recommendations, this included more extensive sampling and microscopic evaluation of these tissues than is required in standard subchronic or chronic studies. Even with this expanded examination, no treatment-related lesions were observed in the central and peripheral nervous system. (The subchronic neurotoxicity study with lambda-cyhalothrin is currently under review by EPA and was not available at the time of the prior EPA review; however, preliminary evaluation of the neuropathology data by EPA scientists did not reveal the presence of treatment-related lesions.) These findings demonstrate that lambda-cyhalothrin does not alter nervous system structure in adult rats, even at the microscopic level. Additionally, there was no evidence from the prenatal developmental toxicity studies (in rats and rabbits) and the two-generation reproduction study in rats, of malformations or variations of the central nervous system in offspring following *in utero* and/or postnatal exposures. Further, the generally accepted mechanism of action for pyrethroids, sodium channel disruption, has not been traditionally associated with developmental neuropathology. Together with the apparent lack of structural alterations in the nervous system of either adult or developing animals, this line of evidence leads to reduced concern regarding the potential that such effects would be observed in guideline developmental neurotoxicity testing.

Another critical factor in the database that supports EPA's determination that a safety finding can be made without use of an additional safety factor are the data bearing on the level at which neurotoxic effects and non-neurotoxic effects are observed in the rat (the animal used in performing DNTs) and the data pertaining to the level at which neurotoxic effects occur in dogs. While the precise outcome of a DNT study with lambda-cyhalothrin can not be known prior to completion of the study, the existing toxicity data provide important information on whether any information is likely to emerge from the lambda-cyhalothrin DNT that would change the dose level used in estimating safe exposure levels to lambda-cyhalothrin in the risk assessment using common principles of dose-setting, which utilize data from less complicated studies to inform the design of more complicated studies, it is highly probable that dietary dose levels for the DNT study will be based upon toxicity observed in the reproduction study in rats, considered in context of the complete toxicology database. In the reproduction study, parental and offspring effects consisted solely of body weight and body weight gain reductions at a dietary level of 100 ppm (approximately 5.0 mg/kg/day), and a NOAEL was established at 30 ppm (approximately 1.5 mg/kg/day) which was the mid-dose level on that study. Neurotoxicity effects have only been seen in the rat at significantly higher doses (acute oral neurotoxicity study having a NOAEL of 10 mg/kg/day and a LOAEL of 35 mg/kg/day). In the dog, neurotoxic effects have been found at lower levels (NOAEL of 0.5 mg/kg/day) than the non-neurotoxic effects seen in the rat reproductive study. What this indicates is that the DNT will likely be conducted at dose levels significantly lower than at which any neurotoxic effects have previously been seen in the rat but still significantly greater than the levels used for assessing acute and chronic risk. Thus, the results from the DNT, even if they show sensitivity in the rat young (which would not be expected), are unlikely to change the levels used for assessing chronic and acute risk.

Reference: Levine, T.E and R.E. Butcher (1990) Triggers for developmental neurotoxicity testing. *Neurotoxicology and Teratology* 12:281-284.

8. Hazard Based Special FQPA Safety Factor

The HIARC concluded that there are no concerns or residual uncertainties for pre- and/or postnatal toxicity with cyhalothrin. There was no developmental toxicity and the offspring toxicity (decreased pup weight and pup weight gain) observed in the reproduction study was found at the same dose level as parental toxicity (decreased body weight and body weight gain). These effects are not considered to be more severe than the effects in the parents. Therefore, the hazard-based default special FQPA safety factor can be removed (1X) when assessing dietary and residential (non-dietary) risks resulting from the use of cyhalothrin or lambda-cyhalothrin.

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - General Population Including Infants and Children

Study Selected: Chronic oral study in the dog (lambda-cyhalothrin) § 870.4100

MRID No.: 40027902

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.**

Dose and Endpoint for Establishing aRfD: 0.5 mg/kg/day based on clinical signs of neurotoxicity (ataxia) observed from day 2, three to seven hours post-dosing at 3.5 mg/kg/day.

Uncertainty Factor (UF): 100 (10x for interspecies extrapolation; 10x for intraspecies variation)

Comments about Study/Endpoint/Uncertainty Factor: The dose (0.5 mg/kg/day) selected is applicable only for this risk assessment and differs form the study NOAEL/LOAEL. Although an acute mammalian neurotoxicity study is available, an endpoint from the chronic dog study was selected because dogs appear to be the most sensitive species and ataxia was observed in two dogs, starting on day 2. There is no indication of either quantitative or qualitative susceptibility in any of the prenatal or postnatal studies conducted with cyhalothrin. No potential acute dietary endpoints for females 13-50 were found in the available database.

Acute RfD (General Population) = $\frac{0.5 \text{ mg/kg}}{100} = 0.005 \text{ mg/kg}$

2. Chronic Reference Dose (cRfD)

Study Selected: Chronic oral study in the dog (lambda-cyhalothrin) § 870.4100

MRID No.: 40027902

Executive Summary: See acute dietary endpoint.

Dose and Endpoint for Establishing cRfD: NOAEL of 0.1 mg/kg/day based on gait abnormalities observed in 2 dogs at 0.5 mg/kg/day, the LOAEL.

Uncertainty Factor(s): 100 (10x for interspecies extrapolation; 10x for intraspecies variation)

Comments about Study/Endpoint/Uncertainty Factor: This study is the most appropriate route of administration (oral) in the most sensitive species (dog). It is applicable to both short and long-term exposure because the first effect was observed during week 2. In addition, this study will be protective of exposure to both cyhalothrin and lambda-cyhalothrin because it is conducted

with lambda-cyhalothrin, which is likely to be the more toxic of the two isomer mixtures. For further discussion of this endpoint, see the acute dietary section.

Chronic RfD =	0.1 mg/kg/day (NOAEL) / 100 (UF) =	**0.001 mg/kg/day**

3. Incidental Oral Exposure: Short- and Intermediate Term (1-30 days and 1-6 Months)

Study Selected: Chronic oral study in the dog (lambda-cyhalothrin) § 870.4100

MRID No.: 40027902

Executive Summary: See acute dietary endpoint.

Dose and Endpoint for Risk Assessment: NOAEL of 0.1 mg/kg/day based on gait abnormalities observed in 2 dogs at 0.5 mg/kg/day, the LOAEL.

Comments about Study/Endpoint: This study is the most appropriate route of administration (oral) in the most sensitive species (dog). It is applicable to both short- and intermediate-term exposure because the first effect was observed during week 2. In addition, this study will be protective of exposure to both cyhalothrin and lambda-cyhalothrin because it is conducted with lambda-cyhalothrin, which is likely to be the more toxic of the two isomer mixtures. For a more complete discussion, see the acute dietary section.

4. Dermal Absorption

Dermal Absorption Factor: 1% based on a human study. In that study, lambda-cyhalothrin was administered to adult male volunteers. The study was conducted in 3 phases. In phase I, lambda-cyhalothrin was administered dermally at a dose of 1.25 mg/50 cm^2 to 6 individuals to determine direct dermal effects. No irritant effects were observed. In phase II, each individual received a single oral dose of 5 mg lambda-cyhalothrin. In phase III, each individual received a dermal dose of 20 mg lambda-cyhalothrin/800 cm^2 on the back. The application site was washed quantitatively after 8 hours. Each subject wore a clean cotton t-shirt for 24 hours after dosing and a second t-shirt 24-48 hours after dosing. The t-shirts were extracted and analyzed for lambda-cyhalothrin. In phases II and III, venous blood samples were collected at pre-dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 31 and 48 hours post-dosing. Urine was collected from 0-2, 2-4, 4-6, 6-8, 8-10, 10-12, 12-14 and 14-24 hours and then for 12- hour intervals up to 120 hours. Fecal samples were also collected for the periods of 0-1, 1-2, and 2-3 days after oral dosing (phase II). Samples were analyzed for 3 metabolites: TFMCVA, 3-PBA and 4-OH3PBA. The dose of lambda-cyhalothrin was followed by quantitatively analyzing for either TFMCVA or 3-PBA plus 4-OH3PBA. Minimal oral absorption was estimated to be from 50.35 to 56.71%. The minimal dermal absorption was estimated to be from 0.115 to 0.122%. The estimated dermal absorption of 1% was determined by rounding these values up to the nearest whole number.

5. Dermal Exposure (All Durations)

Study Selected: 21-Day dermal toxicity study in the rat (lambda-cyhalothrin) § 870.3200

MRID No.: 44333802

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.**

Dose and Endpoint for Risk Assessment: NOAEL of 10 mg/kg/day based on clinical signs of neurotoxicity (observed from day 2) and decreased body weight and body weight gain at 50 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This study is the most appropriate route of administration (dermal) and the study indicates the effects of concern (clinical signs of neurotoxicity). Since the clinical signs were observed from day 2, this study is appropriate for short-term exposure. Although the duration of this study is only 21-days, it is anticipated that this study will be protective of longer-term exposure because a comparison of the 90-day oral study in rats with the chronic feeding study in rats indicates that toxicity is not induced at lower dose levels when rats are exposed over a longer period of time. The NOAEL/LOAEL for the 90-day oral study are 2.5/12.5 mg/kg/day based on decreased body weight gain and the NOAEL/LOAEL for the chronic feeding study in rats are 2.5/12.5 mg/kg/day based on decreases in mean body weight. This study will be protective of exposure to both cyhalothrin and lambda-cyhalothrin because it is conducted with lambda-cyhalothrin, which is likely to be the more toxic of the two isomer

mixtures. No developmental effects were observed in any of the developmental studies. In addition, application of the 1% dermal absorption factor to the oral NOAEL of 0.1 mg/kg/day established in the chronic dog study yields a dermal equivalent dose of 10 mg/kg/day (0.1 ÷ 0.01 = 10.0) which is the same dermal NOAEL used for the dermal risk assessment. Thus, the comparable NOAELs in rats and dogs is protective of dogs being the more sensitive species. Therefore, since the design of the 21-day dermal study is similar to most of the oral studies, it is expected that the dermal study will pick up any other effects that may be observed in any of the oral studies. There is no indication of either quantitative or qualitative susceptibility in any of the prenatal or postnatal studies conducted with cyhalothrin.

7. **Inhalation Exposure: (All Durations)**

Study Selected: 21-Day Inhalation Study in Rats (lambda-cyhalothrin) § N/A

MRID No.: 41387702

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 µg/L (estimated to be approximately 0, 0.08, 0.90 or 4.5 mg/kg/day). The MMAD ranged from 1.47 to 1.91µm and the GSD ranged from 1.02 to 2.24 µm.

No treatment-related effects were observed at 0.3 µg/L. At 3.3 µg/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 µg/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% (♂), 56-87% (♀) 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 µg/L (0.08 mg/kg/day) and the LOAEL is 3.3 µg/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.

Dose/Endpoint for Risk Assessment: NOAEL of 0.08 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 at 0.90 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This study is the most appropriate route of administration (inhalation) and the study indicates the effects of concern (clinical signs of neurotoxicity). This study will be protective of exposure to both cyhalothrin and lambda-cyhalothrin because it is conducted with lambda-cyhalothrin, which is likely to be the more toxic of the two isomer mixtures. No developmental effects were observed in any of the developmental studies. Therefore, since the design of the 21-day inhalation study is similar to most of the oral studies, it is expected that the inhalation study will pick up any other effects that may be observed in any of the oral studies. Although the duration of this study is only 21-days, it is anticipated that this study will be protective of longer-term exposure because a comparison of the 90-day oral study in rats with the chronic feeding study in rats indicates that toxicity is not induced at lower dose levels when rats are exposed over a longer period of time. The NOAEL/LOAEL for the 90-day oral study are 2.5/12.5 mg/kg/day based on decreased body weight gain and the NOAEL/LOAEL for the chronic feeding study in rats are 2.5/12.5 mg/kg/day based on decreases in mean body weight. There is no indication of either quantitative or qualitative susceptibility in any of the prenatal or postnatal studies conducted with cyhalothrin. There is a low degree of concern. The inhalation endpoint (all durations) is protective of any potential developmental or postnatal offspring effects. No developmental effects were observed in either of the developmental studies; the lowest NOAEL for developmental effects is 15 mg/kg/day, the highest dose tested in the rat developmental study. The NOAEL for offspring effects in the 2-generation reproduction study is 1.5 mg/kg/day. The NOAEL selected for the inhalation endpoint (all durations) is 0.08 mg/kg/day.

9. Margins of Exposure

The target Margins of Exposure (MOEs) for **occupational** exposure risk assessments are as follows:

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Dermal	100	100	100
Inhalation	100	100	100

The MOEs for dermal and inhalation exposures may be combined for occupational exposure risk assessment because the toxicity endpoints for these routes of exposure are the same (clinical signs of neurotoxicity).

10. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The toxicity endpoints selected for these routes of exposure may be aggregated as follows: for short-, intermediate- and long-term aggregate exposure risk assessments, the oral, dermal and inhalation routes can be combined because of the common toxicity endpoints (clinical signs of neurotoxicity) via these routes.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 00154803

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. 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.

Discussion of Tumor Data: No increase in any tumors were observed under the conditions of the study.

Adequacy of the Dose Levels Tested: 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.

2. Carcinogenicity Study in Mice

MRID No. 00150842

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.

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.

Discussion of Tumor Data: There were increased incidences of mammary tumors in females (1/52, 0/52, 7/52, 6/52) when compared to the concurrent control group. No increases in any other tumor types were observed.

Adequacy of the Dose Levels Tested: 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.
Classification of Carcinogenic Potential: Although the 2/12/93 RfD/Peer Review Committee had

concern over the increased incidences of mammary tumors in female mice, on 6/16/94, the 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.

IV. MUTAGENICITY

Lambda-cyhalothrin tested negatively in a reverse mutation assay in Salmonella typhimurium, a forward mutation assay in L5178Y mouse lymphoma cells at concentrations that did not exceed the solubility limit, a mouse micronucleus test in C57Bl/6J mice, and an in vitro cytogenetics study in human lymphocytes. Cyhalothrin tested negatively in a reverse mutation assay in Salmonella typhimurium. An in vivo cytogenetics study in male Wistar rats, an oral gavage dominant lethal assay in male CD-1 mice and a cell culture transformation assay in BHK21 C13 cells were considered to be inconclusive.

a. Technical lambda-cyhalothrin (96.5%) was tested in a gene mutation study in 5 Salmonella typhimurium strains at the following concentrations: 0, 1.6, 8.0, 40, 200, 1000, or 5000 µg/plate, both with and without metabolic activation (MRID 00153031). The positive control substances included 2-aminoanthracene (with S-9 mix for all strains), N-methyl-N'-nitro-N-nitrosoguanidine (without S-9 mix for TA 1535 and TA 100), 2-methoxy-6-chloro-9-(3(2-chloroethyl)aminopropylamino)acridine (without S-9 mix for TA 1537), 4-nitro-o-phenylenediamine (without S-9 mix for TA 1538) and Daunorubicin (without S-9 mix for TA 98). Both solvent and "absolute" negative controls were included in the test. Under the conditions of the assay, lambda-cyhalothrin was not considered to be mutagenic. It precipitated at the two highest dose levels, indicating a limit of solubility of the test compound in the assay system.

b. Technical lambda-cyhalothrin (96.5%) was tested for potential to induce gene mutation in L5178Y mouse lymphoma cells, either with or without metabolic activation at concentrations ranging from 125 µg/ml to 4000 µg/ml (MRID 00153033). The positive controls included benzo(a)pyrene and ethylmethanesulphonate. The vehicle control was DMSO. There was little difference in survival rate with or without metabolic activation. The chemical precipitated at all concentrations, particularly at 1000 µg/ml and above. There was an apparent increase in mutagenic activity both with and without metabolic activation at concentrations where the test chemical exceeded the solubility limit (at 1000 µg/ml and above. At concentrations that did not exceed the solubility limit, lambda-cyhalothrin did not induce a significant increase in gene mutation under the conditions of the study.

c. Technical lambda-cyhalothrin (96.5%) was tested in a mouse micronucleus test in male and female C57Bl/6J mice at doses equivalent to 50% or 80% of the 7-day median lethal dose (MLD/7) or 22 or 35 mg/kg, respectively (MRID 00153032). The negative controls received corn oil and the positive controls received cyclophosphamide. A cytotoxic effect was observed at both dose levels. There was a statistically significant reduction in the ratios of polychromatic erythrocytes to mature erythrocytes in the treated animals at both dose levels at 48 hours (but not at any other time point) when compared to the control groups. **No statistically significant increases in the frequency of micronuclei were observed at any dose level at any of the 3**

sampling times. The positive control exhibited significant increases in micronuclei at 24 and 48 hours, but by 72 hours the incidence of micronuclei had dropped back to control levels.

d. Technical lambda-cyhalothrin (96.6%) was tested in an in vitro cytogenetics study in human lymphocytes (MRID 00153034). The lymphocytes were obtained from blood samples from 2 healthy donors, one male and one female. A solvent control, DMSO and two positive controls, mitomycin C and cyclophosphamide were also included. Lambda-cyhalothrin was tested for clastogenic activity at the following concentrations: 0, 100, 500 and 1000 µg/ml. The dose concentrations were based on the limit of solubility of the test sample in DMSO at room temperature. No significant increases in aberrations over solvent controls were observed at any dose concentration, either with or without metabolic activation. The main difficulty with this study is that only one exposure time and only one harvesting time were done. As a result, some possible aberrations may have been missed. It would have been better if multiple harvest times had been conducted, so that the first daughter cells after treatment were certain to be sampled.

e. Technical cyhalothrin (90.2%) was tested in a gene mutation study in 5 Salmonella typhimurium strains at the following concentrations: 0, 4.0, 20, 100, 500, or 2500 µg/plate, both with and without metabolic activation (MRID 00154796). The positive control substances included 2-aminoanthracene, –methyl-N'-nitro-N-nitrosoguanidine, 4-nitroquinoline –oxide, and 9-aminoacridine. Both solvent (DMSO) and "absolute" negative controls were included in the test. Cyhalothrin did not significantly alter the rate of reversion to histidine independence under the conditions of the assay. Cyhalothrin precipitated at the highest dose level, 2500 µg/plate. There is some question concerning the activity of the S-9 mix. It did not allow for a positive response to be induced by all of the positive controls in all of the tester strains. All of the positive controls did induce positive responses without metabolic activation, thus validating the activity of the tester strains. Although there were questions, the study was classified as acceptable.

f. Technical cyhalothrin (89.2%) was tested in an in vivo cytogenetics study in male Wistar rats (MRID 00154798). Five groups of 8 rats/dose group were dosed with 0, 1.5, 7.5 or 15 mg/kg by gavage (1 ml/100g bw). The vehicle was corn oil and the positive control was ethyl methane sulphonate (EMS). The positive and vehicle control groups had 12 rats/group. Single dose and multiple dose studies were conducted. Groups at each dose level were sacrificed at 6 and 24 hours after a single dose of the chemical and 6 hours after the last of five consecutive daily doses. Bone marrow samples were collected and prepared. Cyhalothrin was not found to induce chromosomal damage in rat bone marrow under the conditions of the study. EMS produced a statistically significant increase in the proportion of cells with abnormalities with the single dose 24-hour sacrifice (including gaps) and with the multiple dose 6-hour sacrifice (both including and excluding gaps). It also produced a statistically significant increase in the proportion of animals with abnormalities other than gaps with the multiple dose 6-hour sacrifice.

This study was classified as inconclusive because there are insufficient data to determine whether or not the dose levels were adequately high enough to provide a credible negative response or if the chemical reached the target tissue. In addition, the data should have been presented as numerical counts of chromosomal aberrations/cell as opposed to percentage of aberrant cells. In addition, if one excludes gaps, it does not appear that the EMS positive control induced much of a response at either the 6 or 24 hour kill.

g. Technical cyhalothrin (89.2%) was tested in an oral gavage dominant lethal assay in groups of 20 male CD-1 mice at the following dose levels: 0, 1, 5 or 10 mg/kg/day in 10 ml/kg maize oil for 5 consecutive days (MRID 00154799). Cyclophosphamide was the positive control. This chemical was administered intraperitoneally, one time on the fifth day. Cyhalothrin was not found to increase the frequency of dominant lethal mutations under the conditions of this study. There was no effect of treatment with cyhalothrin on pregnancy index in any mating week. This study was classified as inconclusive. There were insufficient data submitted to determine whether or not the maximum tolerated dose was correctly calculated. It appears that the highest dose may not have been sufficiently high for a negative study or if the chemical reached the target tissue. In addition, the positive control was for intraperitoneal injection studies. There should have been a positive control for an oral study. **Note:** The registrant responded to this conclusion and HED postponed a final classification on this study until the report on the preliminary dose range-finding study was received and reviewed. That data has not been submitted as yet.

h. Technical cyhalothrin (89.2%) was tested in a cell culture transformation assay in BHK21 C13 cells (baby hamster kidney cells clone 13) with and without metabolic activation at the following concentrations: without S-9: 0, 50, 250, 500, 750 or 1000 µg/ml and with S-9: 0, 1000, 2000, 3000, 4000 or 5000 µg/ml (MRID 00154797). DMSO was the solvent and the positive controls were 4-nitroquinoline-N-oxide and p-dimethylaminoazobenzene. Cyhalothrin induced an inconclusive response when tested in the absence of metabolic activation and did not induce a significant response when tested with metabolic activation. Although the contracting laboratory stated that the results of the cell transformation assay on cyhalothrin without metabolic activation was positive, the results were actually inconclusive because of an erratic increase in the numbers of transformed colonies (0, 0, 2, 14, 3) with increasing dose and because of an inconsistent dose-response in transformation frequency. This also occurred in the studies using the S-9 mix although the results were not statistically significant. HED is not requiring a repeat of this particular study; however, based on the suggestive activity, a second cell transformation assay using more established techniques and cells would be appropriate.

V. HAZARD CHARACTERIZATION

With the exception of the subchronic and developmental neurotoxicity studies, the toxicology database for 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 evidence of increased susceptibility of rats or rabbits to *in utero* or postnatal exposure to cyhalothrin.

Lambda-cyhalothrin is moderately acutely toxic via the oral, dermal and inhalation routes (Category II).

It is also a moderate eye irritant (Category II). It is neither irritating to the skin nor is it a sensitizer in the guinea pig. Acute toxicity studies conducted with cyhalothrin indicate that it is also Category II via the oral, dermal (rat) and inhalation routes. It is a moderate eye irritant without irrigation and a mild eye irritant with irrigation (Category III). It is a mild skin irritant in rats and not an irritant in rabbits (Category IV). Cyhalothrin is a skin sensitizer in guinea pigs.

The database on lambda-cyhalothrin and cyhalothrin indicates one major target for this chemical: the neuromuscular system. In studies where the liver is affected, it appears to be an adaptive response. The neuromuscular effects are consistently characterized by gait abnormalities and salivation. They are observed across species and across routes of administration (oral, dermal and inhalation). A comparison of the 90-day oral study in rats with the chronic feeding study in rats indicates that toxicity is not induced at lower dose levels when rats are exposed over a longer period of time. As with other pyrethroids, the dog appears to be the most sensitive species, exhibiting gait abnormalities as low as 0.5 mg/kg/day, starting at week 2. Neither sex appears to be more sensitive.

Several dermal penetration studies are available for lambda-cyhalothrin, one on humans and one in rats. The human study indicates a dermal absorption estimate of 1% whereas the rat study indicates a dermal absorption estimate of 16%.

The data demonstrate no indication of increased quantitative or qualitative sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to cyhalothrin. No developmental toxicity was observed in either of the developmental toxicity studies in rats and rabbits. Maternal toxicity was observed in the form of clinical signs of neurotoxicity and reduced body weight gain and food consumption in the rat study and reduced body weight gain and food consumption in the rabbit study. In the 3-generation reproduction study in rats, the parental/offspring NOAELs are the same based on decreased parental and pup body weight and body weight gain.

There is no evidence that lambda-cyhalothrin induces any endocrine disruption.

Although the HED RfD/Peer Review Committee noted increased incidences of mammary tumors in female mice when compared to the concurrent control group, they determined that because of the equivocal nature of the findings, and in view of the inadequacy of the dose levels tested, cyhalothrin should be classified as a Group D chemical. There was no evidence of tumor induction in rats.

Lambda-cyhalothrin tested negatively in 4 mutagenicity studies and cyhalothrin tested negatively in one mutagenicity study and inconclusively in 2 mutagenicity studies and in 1 cell culture transformation assay.

Cyhalothrin and lambda-cyhalothrin are type II pyrethroids (i.e. they have a cyano group at the α carbon position of the alcohol moiety and it is more effective when the ambient temperature is raised). Ware states, "pyrethroids initially stimulate nerve cells to produce repetitive discharges and eventually cause paralysis. Such effects are caused by their action on the sodium channel, a tiny hole through which sodium ions are permitted to enter the axon to cause excitation. These effects are produced in insect nerve cord, which contains ganglia and synapses, as well as in giant nerve fiber axons. The stimulating effect of pyrethroids is much more pronounced than that of DDT. The exact sites of action of pyrethroids at synapses are not known. It is probable that the toxic action of pyrethroids is primarily due to its blocking action on the nerve axon since this action shows a negative temperature coefficient. But because the

cockroach ganglion is affected by pyrethroid concentrations many fold less than are required to block conduction in giant fibers, its also seems likely that pyrethroids act on some aspect of synaptic function. The fast knockdown of flying insects could be the result of rapid muscular paralysis, suggesting that the ganglia of the insect central nervous system are affected."

VI. DATA GAPS / REQUIREMENTS

Subchronic mammalian neurotoxicity study (82-7, 870.6200)
Developmental neurotoxicity study (83-6, 870.6300)

VII. ACUTE TOXICITY

Acute Toxicity of Lambda-Cyhalothrin

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral (rat)	00151582	LD_{50} = 79 mg/kg (♂) 56 mg/kg (♀)	II
81-2	Acute Dermal (rat)	00151583	LD_{50} = 632 mg/kg (♂) 696 mg/kg (♀)	II
81-3	Acute Inhalation	40994701	LC_{50} = 0.065 mg/L (♂+♀)	II
81-4	Primary Eye Irritation	00151586	Mild irritant	II
81-5	Primary Skin Irritation (rabbits)	00151584	Not an irritant.	IV
81-6	Dermal Sensitization	00151585	Is not a sensitizer in the guinea pig	N/A

Acute Toxicity of Cyhalothrin

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral (rat)	00154865	LD_{50} = 243 mg/kg (♂) 144 mg/kg (♀)	II
81-2	Acute Dermal (rat)	00154865	LD_{50} > 1000 mg/kg (♂+♀)	II
	(rabbit)	00154865	LD_{50} > 2 g/kg (♂+♀)	III
81-3	Acute Inhalation (rat)	00150847	LC_{50} = 0.173 mg/L (♂) 0.183 mg/L (♀)	II
81-4	Primary Eye Irritation	00154868	Moderate irritant without irrigation; mild irritant with irrigation	III
81-5	Primary Skin Irritation (rabbits)	00154867	Mild dermal irritant.	IV
	(rats)	00154867	Not an irritant.	IV
81-6	Dermal Sensitization	00154866	Is a sensitizer in guinea pig	N/A

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicology Endpoint Selection for Cyhalothrin and Lambda-Cyhalothrin
(PC Codes 128867 and 128897)

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment	Study
Dietary Risk Assessments				
Acute Dietary general population including infants and children	NOAEL = 0.5 UF = 100 **Acute RfD** = 0.005 mg/kg	1	LOAEL = 3.5 mg/kg/day based on clinical signs of neurotoxicity (ataxia) observed from day 2, three to seven hours post-dosing.	Chronic oral study in the dog (lambda-cyhalothrin)
Chronic Dietary all populations	NOAEL= 0.1 UF = 100 **Chronic RfD** = 0.001 mg/kg/day	1	LOAEL = 0.5 based on gait abnormalities observed in 2 dogs	Chronic oral study in the dog (lambda-cyhalothrin)
Incidental Oral Short- and Intermediate- Term (1 - 30 Days and 1 - 6 Months) Residential Only	NOAEL= 0.1 **MOE**= 100	1	LOAEL = 0.5 based on gait abnormalities observed in 2 dogs	Chronic oral study in the dog (lambda-cyhalothrin)
Non-Dietary Risk Assessments				
Dermal (All Durations)	Dermal NOAEL= 10 mg/kg/day		LOAEL = 50 mg/kg/day based on clinical signs of neurotoxicity (observed from day 2) and decreased body weight and body weight gain	21-Day dermal toxicity study in the rat (lambda-cyhalothrin)
Residential	**MOE** = 100	1		
Occupational	**MOE** = 100	1		

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment	Study
Inhalation (All Durations)	Inhalation NOAEL= 0.3 µg/L (0.08 mg/kg/day)		LOAEL = 3.3 µg/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.	21-Day Inhalation Study in Rats (lambda-cyhalothrin)
Residential	**MOE** = 100	1		
Occupational	**MOE** = 100	1		
Cancer	**Classification:** Group D chemical. because of the equivocal nature of the findings and inadequacy of the dose levels tested.			