11-14-97

U. S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 11/14/97

SUBJECT: Risk Assessment for Extension of Tolerances for Synthetic Pyrethroids

TO: George Larocca, PM Team 13
IB/RD (7505C)

FROM: P. Hurley, J. Whalan, J. Evans, G. Herndon, S. Knizner
RAB2/HED (7509C)

THRU: R. Loranger, Branch Senior Scientist
RAB2/HED (7509C)

Introduction

Tolerances for regulable residues of bifenthrin, cyfluthrin, lambda-cyhalothrin, cypermethrin, zeta-cypermethrin, deltamethrin, esfenvalerate, fenpropathrin, tefluthrin and tralomethrin in or on various commodities will expire on November 15, 1997. These tolerances were time-limited because of EFED concerns.

The registrants for these pyrethroids (AgrEvo, Bayer, Dupont, FMC, Valent and Zeneca) formed the Pyrethroid Working Group (PWG). OPP and the PWG have been engaged in discussions on how to conduct the human health exposure and risk assessments for these chemicals.

The HAZID Committee met on July 17 and 24, 1997, to determine appropriate toxicological endpoints for risk assessment purposes, to evaluate the FQPA aspects of these chemicals, and to stipulate which exposures should be considered in performing aggregate risk assessments. The report of the HAZID Committee is contained in Attachment 1.

Dietary (food) exposure analyses were conducted for the PWG by Novigen Sciences, Inc. Chronic and acute dietary exposure analyses were conducted according to appropriate Agency policies. Percent crop treated data for use in chronic and acute dietary exposure analyses were supplied by BEAD (see attached memos from D. Brassard dated 9/12/97 and 10/8/97). EFED supplied data concerning potential exposure from residues in drinking water (see attached memo of R.Matzner, undated).

The non-dietary exposure analysis was conducted by Risksciences.com, Inc., on behalf of the Pyrethroid Working Group (PWG). The approach used by Risksciences.com is based on discussions among representatives of PWG, California Department of Pesticide Regulation (CDPR) , and HED. The approach uses a wide variety of data and assumptions including the use of proprietary data, surrogate data and reports of studies found in the published literature.

A summary of dietary (food), drinking water, and aggregate exposures and risk estimates is presented in Attachment 2. Supporting documentation for the risk assessments for each pyrethroid is found in the other Attachments. This risk assessment document was reviewed by the HED Risk Assessment SARC on 10/29/97. Recommendations of this SARC have been incorporated into this document.

Summary

Acute and chronic aggregate dietary (food + water) risk estimates do not exceed HED's level of concern. Short- and intermediate-term aggregate (food + water + residential) risk estimates do not exceed HED's level of concern. Extension of the time limited tolerances should not pose an unacceptable aggregate risk to infants, children, or adults.

Therefore, HED has no objection to the extension of time limited tolerances for bifenthrin, cyfluthrin, lambda-cyhalothrin, cypermethrin, zeta-cypermethrin, deltamethrin, esfenvalerate, fenpropathrin, tefluthrin and tralomethrin.

2

Attachment 1

Synthetic Pyrethroids - Report of the Hazard Identification Assessment Review Committee

October 18, 1997 (Revised)

MEMORANDUM

SUBJECT: **SYNTHETIC PYRETHROIDS** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland
Branch Senior Scientist,
Science Analysis Branch, Health Effects Division (7509C)

THROUGH: K. Clark Swentzel
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

TO: Donna Davis
Chief, Registration Action Branch-2
Health Effects Division (7509C)
and
George Larocca
Product Manager, Registration Division

BACKGROUND: The existing time-limited tolerances for 10 synthetic pyrethroids are scheduled to expire in November 1997 and the Registrants are proposing to submit aggregate risk assessments in addition to requesting an extension of the tolerances for a period of 1-2 years. Therefore, the Health Effects Division's Hazard Identification Assessment Review Committee met on July 17 and 24, 1997, to evaluate the toxicology data base of these 10 synthetic pyrethroids.

The Hazard ID Committee : 1) evaluated the toxicology data base; 2) re-assessed the existing Reference Doses (RfDs); 3) selected doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments (TES) when appropriate; 4) addressed the sensitivity of infants and children as required by the Food Quality Protection Act of 1996; and 5) provided guidance for aggregate risk assessments.

The Committee's decisions are summarized below and documents providing the rationale for the Committee's decisions are presented in Attachments.

CC: Ed Zager, Chief, Registration Action Branch -1
Elizabeth Doyle, Chief, Chemical Exposure Branch-1
William Burnam, Chief, Science Analysis Branch
Rick Whiting, Science Analysis Branch
Caswell File

I. HAZARD IDENTIFICATION - *CHRONIC DIETARY* RISK ASSESSMENT

The dose and endpoint selected, the uncertainty factors (UF) used in deriving the RfD, and the RfD established for chronic dietary risk assessments are presented below. Details for each individual pyrethroid are provided in the Attachments .

CHEMICAL PC CODE	DOSE (mg/kg/day)	ENDPOINT SELECTED/ STUDY	RfD UF
Bifenthrin 128825	NOEL=1.5 LOEL=3.0	Tremors in both sexes of dogs in a chronic toxicity study.	RfD= 0.015 mg/kg/day UF= 100
Cyfluthrin 128831	NOEL=2.5 LOEL=6.2	Decreased body weight gain in males, and inflammatory foci in kidneys of female rats in a chronic toxicity/ carcinogenicity study.	RfD= 0.008 mg/kg/day UF= 300 (includes FQPA consideration)
lamba-Cyhalothrin 128867	NOEL=0.1 LOEL=0.5	Neurotoxicity, ataxia and convulsions in dogs in a chronic toxicity study .	RfD= 0.001 mg/kg/day UF= 100
Cypermethrin 109702	NOEL=1.0 LOEL=5.0	Gastrointestinal disturbances in dogs in a chronic toxicity study.	RfD= 0.01 mg/kg/day UF= 100
z-Cypermethrin 129064	NOEL=1.0 LOEL=5.0	Gastrointestinal disturbances in dogs in a chronic toxicity study with cypermethrin.	RfD=0.005 mg/kg/day UF=200 (to account for the differences in the percentage of the more biologically active isomers in the enriched technical product (z-cypermethrin)
Deltamethrin 209400 Tralomethrin 121501	NOEL=1.0 LOEL=2.5 (chronic rat with delta) NOEL=1.0 LOEL=3.0 (chronic dog with tralo)	Decreased body weight gain in both sexes of rats in a chronic toxicity/carcinogenicity study in deltamethrin supported by similar effects in rats and dogs in subchronic studies and by chronic study in dogs with tralomethrin: reduced body weight gain, tremors and ptyalism: 0.75 mg/kg/day raised to 1.0 mg/kg/day at 14 weeks with no effects.	RfD= 0.01 mg/kg/day UF= 100
Esfenvalerate 109303	Maternal NOEL=2.0 LOEL=2.5	Behavioral changes and clinical signs indicative of CNS in rat developmental study.	RfD= 0.02 mg/kg/day UF= 100
Fenpropathrin 127901	NOEL=2.5 LOEL=6.25	Tremors in both sexes in a chronic toxicity study in dogs	RfD= 0.025 mg/kg/day UF= 100

CHEMICAL PC CODE	DOSE (mg/kg/day)	ENDPOINT SELECTED/ STUDY	RfD UF
Tefluthrin 128912	NOEL=0.5 LOEL=2.0	Ataxia in both sexes of dogs in a chronic toxicity study.	RfD= 0.005 mg/kg/day UF= 100

II. HAZARD IDENTIFICATION - *ACUTE DIETARY* RISK ASSESSMENT

The doses and endpoints selected for acute dietary risk assessments are presented below. Details for each individual pyrethroid are provided in the Attachments .

CHEMICAL PC CODE	DOSE (mg/kg/day)	ENDPOINT SELECTED/ STUDY
Bifenthrin 128825	Maternal NOEL =1.0 LOEL=2.0	Tremors in dams observed during and post dosing period in developmental toxicity studies with rats. MOE = 100
Cyfluthrin 128831	Developmental NOEL =20.0 LOEL =60.0	Increased numbers of resorptions and percent incidence of postimplantation loss in rabbits in a developmental toxicity study. MOE = 300 (includes FQPA considerations)
lamba-Cyhalothrin 128867	Systemic NOEL=0.5 LOEL=3.5	Gait abnormalities on day 2 in dogs in a chronic toxicity study. MOE = 100
Cypermethrin 109702	Systemic NOEL=1.0 LOEL=5.0	Gastrointestinal disturbances in dogs seen during the first week in a chronic toxicity study MOE=100
z-Cypermethrin 129064	Systemic NOEL=0.5 LOEL=2.5	Gastrointestinal disturbances in dogs seen during the first week in a chronic toxicity study with Cypermethrin. The NOEL of 1.0 observed in the Cypermethrin study was selected with a correction factor of 2 to account for the biologically active isomer (z-cypermethrin) MOE = 100
Deltamethrin 209400 Tralomethrin 121501	Systemic NOEL=1.0 LOEL=3.0	Tremors and ptyalism and ataxia in dogs seen during study week 1 in chronic toxicity study with tralomethrin. Supported by subchronic/chronic dog studies with combined deltamethrin/tralomethrin database. MOE = 100
Esfenvalerate 109303	Maternal NOEL=2.0 LOEL=2.5 (rat) 3.0 (rabbit)	Behavioral changes and clinical signs indicative of CNS effects in rat and rabbit developmental studies MOE = 100
Fenpropathrin 127901	Maternal NOEL=6.0 LOEL=10.0	Clinical signs indicative of neurotoxicity in dams on the day of dosing in a developmental study in rats. MOE = 100

CHEMICAL PC CODE	DOSE (mg/kg/day)	ENDPOINT SELECTED/ STUDY
Tefluthrin 128912	Systemic NOEL=0.5 LOEL=2.0	Increased incidence of tremors in both sexes of dogs on study day 1 in a chronic toxicity study. MOE = 100

III. HAZARD IDENTIFICATION - *SHORT-TERM DERMAL* OCCUPATIONAL/ RESIDENTIAL EXPOSURE RISK ASSESSMENT

The doses and endpoints selected for Short-Term (1-7 days) occupational/residential dermal exposure risk assessments are presented below. A dermal absorption rate of 25% was derived based on the weight-of-the-evidence available for structurally-related pyrethroids. Details for each individual pyrethroid are provided in the Attachments .

CHEMICAL PC CODE	DOSE (mg/kg/day)	ENDPOINT SELECTED/ STUDY
Bifenthrin 128825	Maternal NOEL =1.0 LOEL =2.0	Tremors in dams during and post dosing period in a developmental toxicity studies in rats. Dermal absorption rate = 25%. MOE = 100
Cyfluthrin 128831	Developmental NOEL =20.0 LOEL =60.0	Increased numbers of resorptions and percent incidence of postimplantation loss in rabbits. Dermal absorption rate = 25% MOE = 300 (includes FQPA considerations)
lamba-Cyhalothrin 128867	Systemic NOEL=10.0 LOEL=100	Mortality, clinical signs and effects on body weight and food consumption in a 21-day dermal rat study. MOE = 100
Cypermethrin 109702	Systemic NOEL=5.0 LOEL=15	Neurotoxic clinical signs occurring as early as study week 1 in a chronic toxicity study in dogs. Dermal absorption rate =25% MOE = 100
z-Cypermethrin 129064	Systemic NOEL=2.5 LOEL=7.5	Neurotoxic clinical signs occurring as early as study week 1 in a chronic toxicity study in dogs with Cypermethrin; correction factor=2 Dermal absorption rate =25%. MOE = 100
Deltamethrin 209400	None	Risk assessment not required. No dermal or systemic toxicity at 1000 mg/kg/day in a 21-day study in rats.
Esfenvalerate 109303	Maternal NOEL=2.0 LOEL=2.5 (rat) 3.0 (rabbit)	Behavioral changes and CNS signs in rat and rabbit developmental studies. Dermal absorption rate=25%. MOE = 100
Fenpropathrin 127901	None	Risk assessment not required. No systemic toxicity at 3000 mg/kg/day in a 21-day study in rabbits

CHEMICAL PC CODE	DOSE (mg/kg/day)	ENDPOINT SELECTED/ STUDY
Tefluthrin 128912	Systemic NOEL=0.5 LOEL=2.0	Increased incidence of tremors in both sexes of dogs on study day 1 in a chronic toxicity study. Dermal absorption rate=25%. MOE = 100
Tralomethrin 121501	None	Risk assessment not required. No systemic toxicity at 1000 mg/kg/day in a 21-day study in rats.

IV. HAZARD IDENTIFICATION - *INTERMEDIATE-TERM DERMAL* OCCUPATIONAL/ RESIDENTIAL EXPOSURE RISK ASSESSMENT

The doses and endpoints selected as well as the dermal absorption rate (for use in risk assessments when the dose identified is from an oral study) for Intermediate-Term (one-week to several months) occupational/residential dermal exposure risk assessments are presented below. Details for each individual pyrethroid are provided in the Attachments .

CHEMICAL PC CODE	DOSE (mg/kg/day)	ENDPOINT SELECTED/ STUDY
Bifenthrin 128825	Maternal NOEL =1.0 LOEL =2.0	Tremors in dams during and post dosing period in developmental toxicity studies in rats. Dermal absorption rate=25%. MOE = 100
Cyfluthrin 128831	Developmental NOEL =20.0 LOEL =60.0	Increased numbers of resorptions and percent incidence of postimplantation loss in rabbits. Dermal absorption rate=25% MOE = 300 (includes FQPA considerations)
lamba-Cyhalothrin 128867	Systemic NOEL=10.0 LOEL=100	Mortality, clinical signs and effects on body weight and food consumption in a 21-dermal study in rats. MOE = 100
Cypermethrin 109702	Systemic NOEL=5.0 LOEL=15	Neurotoxic clinical signs occurring as early as study week 1 in a chronic toxicity study in dogs. Dermal absorption rate =25% MOE = 100
z-Cypermethrin 129064	Systemic NOEL=2.5 LOEL=7.5	Neurotoxic clinical signs occurring as early as study week 1 in a chronic toxicity study in dogs with Cypermethrin; correction factor=2. Dermal absorption rate =25%. MOE = 100

CHEMICAL PC CODE	DOSE (mg/kg/day)	ENDPOINT SELECTED/ STUDY
Deltamethrin 209400	None	Risk assessment not required. No systemic toxicity at 1000 mg/kg/day in a 21-day study in rats.
Esfenvalerate 109303	Maternal NOEL=2.0 LOEL=2.5 (rat) 3.0 (rabbit)	Behavioral changes and clinical signs indicative of CNS in rats and rabbits in developmental studies. Dermal absorption rate=25% MOE = 100
Fenpropathrin 127901	None	Risk assessment not required. No systemic toxicity at 3000 mg/kg/day in a 21-day study in rabbits
Tefluthrin 128912	Systemic NOEL=0.5 LOEL=2.0	Increased incidence of tremors in both sexes of dogs on study day 1 in a chronic toxicity study. Dermal absorption rate=25%. MOE = 100
Tralomethrin 121501	None	Risk assessment not required. No systemic toxicity at 1000 mg/kg/day in a 21-day study in rats.

V. HAZARD IDENTIFICATION - *CHRONIC DERMAL* OCCUPATIONAL/ RESIDENTIAL EXPOSURE RISK ASSESSMENT

The doses and endpoints selected as well as the dermal absorption rate (for use in risk assessments when the dose identified is from an oral study) for Chronic (several months to life-time) occupational/residential dermal exposure risk assessments are presented below. Details for each individual pyrethroid are provided in the Attachments .

CHEMICAL PC CODE	DOSE (mg/kg/day)	ENDPOINT SELECTED/ STUDY
Bifenthrin 128825	Systemic NOEL =1.5 LOEL =3.0	Tremors in both sexes of dogs in a chronic toxicity study. Dermal absorption rate=25%. MOE = 100
Cyfluthrin 128831	Systemic NOEL =2.5 NOEL =6.2	Decreased body weight in male and inflammatory foci in the kidney of female rats in a chronic toxicity/ carcinogenicity study. Dermal absorption rate=25%. MOE=300 (includes FQPA considerations)
lamba-Cyhalothrin 128867	Systemic NOEL=0.1 LOEL=0.5	Neurotoxic clinical signs in both sexes of dogs in a chronic toxicity study. Dermal absorption rate=25%. MOE=100

CHEMICAL PC CODE	DOSE (mg/kg/day)	ENDPOINT SELECTED/ STUDY
Cypermethrin 109702	Systemic NOEL=5.0 LOEL=15	Neurotoxic clinical signs occurring as early as study week 1 in a chronic toxicity study in dogs. Dermal absorption rate =25%. MOE = 100
z-Cypermethrin 129064	Systemic NOEL=2.5 LOEL=7.5	Neurotoxic clinical signs occurring as early as study week 1 in a chronic toxicity study in dogs with Cypermethrin; correction factor=2. Dermal absorption rate =25%. MOE = 100
Deltamethrin 209400	None	Risk assessment not required. No systemic toxicity at 1000 mg/kg/day in a 21-day study in rats.
Esfenvalerate 109303	Maternal NOEL=2.0 LOEL=2.5 (rat) 3.0 (rabbit)	Behavioral changes and clinical signs indicative of CNS in rats and rabbits in developmental studies. Dermal absorption rate=25%. MOE = 100
Fenpropathrin 127901	None	Risk assessment not required. No systemic toxicity at 3000 mg/kg/day in a 21-day study in rabbits
Tefluthrin 128912	Systemic NOEL=0.5 LOEL=2.0	Increased incidence of tremors in both sexes of dogs on study day 1 in a chronic toxicity study. Dermal absorption rate=25%. MOE = 100
Tralomethrin 121501	None	Risk assessment not required. No systemic toxicity at 1000 mg/kg/day in a 21-day study in rats.

VI. HAZARD IDENTIFICATION - *INHALATION (ANY TIME PERIOD)* OCCUPATIONAL/ RESIDENTIAL EXPOSURE RISK ASSESSMENT

The doses and endpoints selected for occupational/residential inhalation exposure risk assessments for any time period are presented below. Details for each individual pyrethroid are provided in the Attachments .

CHEMICAL PC CODE	DOSE	ENDPOINT SELECTED/ STUDY
Bifenthrin 128825	Oral NOEL = 1.0 mg/kg/day LOEL = 2.0 mg/kg/day rat developmental study	No appropriate studies are available. Risk assessment should be inclusive of oral and inhalation exposure components (100% absorption).
Cyfluthrin 128831	Short-Term: NOEL=0.44 µg/L LOEL=6 µg/L Intermediate/Chronic: NOEL= 0.09 µg/L LOEL=0.7 µg/L	Decreases in body and thymus weights, hypothermia and clinical pathology in rats in a 28-day study (short-term) and behavioral effects in rats in a 90-day study (intermediate/ chronic). UF=300 (includes FQPA considerations)

CHEMICAL PC CODE	DOSE	ENDPOINT SELECTED/ STUDY
l a m b a - Cyhalothrin 128867	NOEL=0.3 µg/L LOEL=3.3 µg/L	Neurotoxic clinical signs, alterations in clinical pathology and alveolitis in rats in a 21-day inhalation study. MOE=100
Cypermethrin 109702	NOEL=10 µg/L LOEL=50 µg/L	Decrease in body weight gains in rats in a 21-day inhalation study. MOE = 100
z - Cypermethrin 129064	NOEL=5.0 µg/L LOEL=25 µg/L	Decrease in body weight gains in rats in a 21-day inhalation study with Cypermethrin; correction factor=2. MOE = 100
Deltamethrin 209400	NOEL=3.0 µg/L LOEL=9.6 µg/L	Nerve stimulation, reduced body weight gain in males and elevated sodium levels in both sexes in a 21-day inhalation study. MOE = 100
Esfenvalerate 109303	Oral NOEL= 2.0 mg/kg/day LOEL=2.5 mg/kg/day	No appropriate studies are available. Risk assessment should be inclusive of dermal (25% absorption) and inhalation exposure components (100% absorption).
Fenpropathrin 12791	None	A separate risk assessment is not required. (Toxicity Category IV).
Tefluthrin 128912	None	No appropriate studies are available. Risk assessment should include oral and inhalation exposure components (100% absorption).
Tralomethrin 121501	None	No appropriate studies are available. Risk assessment should include oral and inhalation exposure components (100% absorption).

VII. AGGREGATE RISK ASSESSMENT

Committee's recommendation for aggregate risk assessments are presented below:

CHEMICAL PC CODE	RECOMMENDATIONS FOR AGGREGATE RISK ASSESSMENTS
Bifenthrin 128825	An aggregate systemic (oral) and dermal exposure risk assessment is not appropriate since a dermal toxicity study in the sensitive species (rat) was not available and thus toxicity via the dermal route could not be ascertained. An aggregate oral and inhalation risk assessment is appropriate due to the similarity in the toxicity endpoint (neurotoxicity) seen in rats via these routes.
Cyfluthrin 128831	An aggregate systemic (oral) and dermal exposure risk assessment is appropriate because of the concern for the developmental effects seen after oral exposure. An aggregate oral and inhalation exposure risk assessment is also appropriate due to the similarity in systemic toxicity observed in rats via these routes.

CHEMICAL PC CODE	RECOMMENDATIONS FOR AGGREGATE RISK ASSESSMENTS
lamba-Cyhalothrin 128867	An aggregate systemic (oral) and dermal exposure risk assessment is required . The "type"toxicity seen after dermal exposure could not be ascertained due to lack of details in the summary data provided. An aggregate oral and inhalation exposure risk assessment is appropriate due to the similarity in systemic toxicity observed in rats via these routes.
Cypermethrin 109702	An aggregate systemic (oral) and dermal exposure risk assessment is not appropriate due to differences in the toxicity endpoints observed between the oral (neurotoxicity) and dermal (hepatotoxicity) routes. An aggregate oral and inhalation risk assessment is appropriate due to the similarity of toxicity (neurotoxicity) observed in rats via these routes.
z-Cypermethrin 129064	An aggregate systemic (oral) and dermal exposure risk assessment is not appropriate due to differences in the toxicity endpoints observed between the oral (neurotoxicity) and dermal (hepatotoxicity) routes. An aggregate oral and inhalation risk assessment is appropriate due to the similarity of toxicity (neurotoxicity) observed in rats via these routes.
Deltamethrin 209400	An aggregate systemic (oral) and dermal exposure risk assessment is not appropriate due to lack of systemic toxicity via the dermal route. An aggregate oral and inhalation risk assessment is appropriate due to the similarity of toxicity (neurotoxicity) observed in rats via these routes.
Esfenvalerate 109303	An aggregate systemic (oral) and dermal exposure risk assessment is not required due to lack of appropriate dermal studies. An aggregate oral and inhalation risk assessment is appropriate because of the similarity of systemic toxicity observed in rats following oral and inhalation exposures.
Fenpropathrin 127901	An aggregate systemic (oral) and dermal exposure risk assessment is not required due to lack of systemic toxicity via the dermal route An aggregate oral and inhalation risk assessment is not required due to low inhalation toxicity. (Toxicity Category-IV).
Tefluthrin 128912	An aggregate systemic (oral) and dermal exposure risk assessment is not appropriate since dermal toxicity could not be ascertained. An aggregate oral and inhalation risk assessment is appropriate based on similarity in toxicity seen via these routes.
Tralomethrin 121501	An aggregate systemic (oral) and dermal exposure risk assessment is not required due to lack of systemic toxicity via the dermal route. An aggregate oral and inhalation risk assessment is appropriate due to the similarity of toxicity endpoints (neurotoxicity) seen in rats following oral and inhalation exposures.

VIII. ASSESSMENT FOR ADDITIONAL SENSITIVITY FOR INFANTS AND CHILDREN (FQPA REQUIREMENT)

The Committee addressed the application of additional uncertainty factors for sensitivity to infants and children as required by the Food Quality Protection Act of 1996. The Committee's conclusions are summarized below. Details are provided in Attachment 3.

Bifenthrin, Lambda Cyhalothrin, Cypermethrin, z-Cypermethrin, Deltamethrin, Esfenvalerate, Fenpropathrin, Tefluthrin and

Tralomethrin : There are no data gaps for reproductive and developmental toxicity studies. No evidence of additional sensitivity to young rats or rabbits was observed following pre- or postnatal exposure to these synthetic pyrethroids. Based on these considerations, the Committee determined that there is no need for applying additional uncertainty factor(s) in risk assessments.

Cyfluthrin: There are no data gaps for reproductive and developmental toxicity studies. Evidence of increased sensitivity of young rats following pre-and/or postnatal exposure to cyfluthrin was observed in a two-generation reproduction study in rats. There was suggestive sensitivity of rats to *in utero* exposure based on bradypnea seen in dams. In addition, the reproductive NOEL of 2.5 mg/kg/day and the LOEL of 7.5 mg/kg/day established in the 2-generation reproduction study in rats are identical to the systemic NOEL/LOEL of 2.5 / 7.5 mg/kg/day established in the chronic toxicity/carcinogenicity study in rats. This NOEL (2.5 mg/kg/day) and a UF of 100 was used in deriving the RfD (0.025 mg/kg/day) and the RfD does not provide protection for infants and children.. Based on these considerations, the Committee determined that an additional UF of 3 is needed for risk assessments. An UF of 3 was selected because of the lack of severity of effects (reduced body weight gain in males in chronic toxicity study and decreased body weight gain in parental animals in the reproduction study) and the availability of acceptable reproduction (rat) and developmental (rats and rabbits) toxicity studies.

IX. DATA GAPS

Esfenvalerate: Data gaps - general metabolism (§85-1), (dermal penetration (§85-2) and 21-day dermal toxicity (§82-2) studies

Bifenthrin, Cypermethrin and Fenpropathrin: Although 21-day dermal toxicity studies in rabbits are available for these pyrethroids, the Hazard ID Committee has determined that rats are the most sensitive species to ascertain the dermal toxicity potential of synthetic pyrethroids. Therefore, the lack of 21-day dermal toxicity studies in rats (§82-2) is perceived as data gaps and should be reconsidered before permanent tolerances are granted.

Deltamethrin: An acceptable 3-generation reproduction study in rats is available, however, the highest dose tested (2.5 mg/kg/day) was not adequate to assess the effects of Deltamethrin on postnatal exposure; neither parental nor offspring toxicity was observed. Therefore, the 2-generation reproduction study (§83-4) is perceived to be a data gap and should be reconsidered before permanent tolerances are granted.

X. DATA CALL-IN NOTICE

The toxicology data base for the pyrethroids indicates that rats are the most sensitive species for pyrethroid-induced neurotoxicity. However, neither acute nor subchronic neurotoxicity studies are available. Neurotoxicity was also exhibited by dams in the reproductive and/or developmental studies conducted with rats and/or rabbits. Also, with some pyrethroids (e.g., Tefluthrin) the results of 21-day dermal studies are difficult to interpret as to whether the effects seen are a "local reaction" at the site of application or related to systemic neurological effects. Therefore, the Committee concluded that issuing a Data Call-In (DCI) notice should be considered for the studies listed below for all pyrethroids currently under reconsideration for time-limited tolerances.

1. Acute Neurotoxicity study in rats (§81-8)
2. Subchronic Neurotoxicity study in rats (§82-5)
3. Developmental Neurotoxicity study in rats (§83-6)

XI. CONCLUSIONS

The existing Referenced Doses (RfDs) are adequate. Doses and endpoints were selected for acute dietary as well as occupational and residential dermal and/or inhalation exposures for Bifenthrin, Lambda Cyhalothrin, Cyfluthrin, z-Cypermethrin, Deltamethrin, Fenpropathrin Tefluthrin and Tralomethrin; doses and endpoints selected previously were adequate for Cypermethrin and Esfenvalerate. Except for Cyfluthrin, an additional uncertainty factor was not warranted for the protection of infants and children from exposure to any of the pyrethroids evaluated. It is recommended that a DCI should be considered for the studies that are identified as data gaps for Bifenthrin, Cypermethrin, Esfenvalerate and Fenpropathrin (21-day dermal toxicity study in rats), Esfenvalerate (general metabolism and dermal penetration), and Deltamethrin (2-generation reproduction study in rats) as well as for acute, subchronic and developmental neurotoxicity studies for all pyrethroids.

Attachment 1
Appendix A

Clarification of Data Requirements for Pyrethroids

11/12/97

MEMORANDUM

SUBJECT: Clarification of Data Requirements for Pyrethroids and Documentation of Decision Logic Applied to Determination of Appropriate Uncertainty Factors for Infants and Children

FROM: Karl Baetcke
William Burnam
Pamela Hurley

TO: Donna Davis

The purpose of this memo is to clarify the statements made concerning the requirement for developmental neurotoxicity studies on pyrethroids as outlined in the HED Memorandum entitled "SYNTHETIC PYRETHROIDS - Report of the Hazard Identification Assessment Review Committee" dated 10/18/97 (Revised). In addition, information is provided to document the decision logic used in determining the appropriate uncertainty factor to protect infants and children from adverse effects due to pyrethroid exposure.

Under Section X of the cited document, the Hazard ID Committee indicated that acute and subchronic neurotoxicity studies should be conducted on a number of the pyrethroids. When required these studies should be considered as confirmatory in nature. The reasons for this designation are as follows:

1) A critical effect for most if not all pyrethroids is the occurrence of tremors. This effect can be observed in the standard studies typically required for registration (e.g. subchronic oral, developmental, reproductive, and chronic/oncogenicity studies). We have full confidence that evidence provided in the standard studies provides adequate data to determine both potential increased sensitivity of infants and children and to identify critical NOELs.

2) Pyrethroids do not produce neuropathology with the possible exception noted in one study involving a pyrethroid administered at high dose levels. Effects are transitory and as noted above, expressed as tremors. There is no evidence to support long-term or persistent effects on nervous tissue nor is there any evidence to indicate that an endpoint more sensitive than tremors would be observed in an acute or 90-day neurotoxicity study. However, HED is requesting acute and 90-day neurotoxicity studies to more fully characterize effects at high dose levels.

With respect to the requirement for a developmental neurotoxicity study, this data requirement is an upper tier study which would only be required if effects observed (e.g. lesions of the CNS) in the acute and 90-day neurotoxicity studies indicate concerns for increased sensitivity of the infant or neonate. Based on available data there is no indication that the developing fetus or

neonate is more sensitive than adult animals to the neurotoxic effects (e.g. tremors) of most pyrethroids. For some pyrethroids, however, results of developmental and/or reproduction studies have shown increased sensitivity for offspring. For such chemicals (e.g. cyfluthrin), the HAZID recommened for incorporation of an additional uncertainty factor to account for increased sensitivity in infants and children.

In summary, the requirement for acute and subchronic 90-day studies are considered to be confirmatory in nature since there is no reason to believe results of these studies will affect the overall risk assessments.

Attachment 2

Table 1. Chronic Dietary (Food) Exposure and Risk Estimates			
Chemcial	US Population and Most Highly Exposed Population Subgroup	Chronic Dietary Exposure (mg/kg/day)	%RfD Occupied
Bifenthrin	US Population Children 1-6 years	0.000019 0.000041	0.2 0.3
Cyfluthrin	US Population NNI[1]	0.000076 0.000151	1.0 1.9
lambda-Cyhalothrin	US Population Children 1-6 years	0.000068 0.000192	6.8 19.2
Cypermethrin	US Population Children 1-6 years	0.000025 0.000042	0.3 0.4
Zeta-cypermethrin	US Population Children 1-6 years	0.000018 0.000027	0.4 0.5
Deltamethrin and Tralomethrin	US Population Children 1-6 years	0.000021 0.000046	0.2 0.5
Esfenvalerate	US Population Children 1-6 years	0.000376 0.000911	1.9 4.6
Fenpropathrin	US Population Non-Hispanic other than Black or White	0.000020 0.000053	0.1 0.2
Tefluthrin	US Population Children 1-6 years	0.000007 0.000015	0.1 0.3
[1] NNI = Non-nursing infants <1 year old			

Table 2. Chronic Drinking Water Exposure and Risk Estimates			
Chemcial	US Population and Most Highly Exposed Population Subgroup	Chronic Drinking Water Exposure (mg/kg/day)	%RfD Occupied
Bifenthrin	US Population NNI	0.000001 0.000002	0.0 0.0
Cyfluthrin	US Population NNI	0.000001 0.000005	0.0 0.1
lambda-Cyhalothrin	US Population NNI	0.000000 0.000000	0.0 0.0
Cypermethrin	US Population NNI	0.000005 0.000021	0.0 0.2
Zeta-cypermethrin	US Population NNI	0.000005 0.000021	0.1 0.4
Deltamethrin/ Tralomethrin	US Population NNI	0.000000 0.000001	0.0 0.0
Esfenvalerate	US Population NNI	0.000001 0.000005	0.0 0.0
Fenpropathrin	US Population NNI	0.000086 0.000397	0.3 1.6
Tefluthrin	US Population NNI	0.000000 0.000002	0.0 0.0
NNI = Non-nursing infants <1 year old			

Table 3. Chronic Aggregate (Food and Water) Exposure and Risk Estimates			
Chemcial	US Population and Most Highly Exposed Population Subgroup	Chronic Dietary Exposure (mg/kg/day)	%RfD Occupied
Bifenthrin	US Population Children 1-6 years	0.000020 0.000042	0.2 0.3
Cyfluthrin	US Population NNI[1]	0.000076 0.000151	1.0 1.9
lambda-Cyhalothrin	US Population Children 1-6 years	0.000068 0.000192	6.8 19.2
Cypermethrin	US Population Children 1-6 years	0.000026 0.000044	0.3 0.4
Zeta-cypermethrin	US Population Children 1-6 years	0.000023 0.000034	0.5 0.6
Deltamethrin and Tralomethrin	US Population Children 1-6 years	0.000021 0.000046	0.2 0.5
Esfenvalerate	US Population Children 1-6 years	0.000377 0.000912	1.9 4.6
Fenpropathrin	US Population NNI	0.000106 0.000398	0.4 1.6
Tefluthrin	US Population Children 1-6 years	0.000007 0.000016	0.1 0.3
[1] NNI = Non-nursing infants <1 year old			

Table 4. Acute Dietary (Food) Exposure and Risk Estimates			
Chemcial	US Population and Most Highly Exposed Population Subgroup	Acute Dietary Exposure (mg/kg/day)	MOE (99.9th percentile)
Bifenthrin	US Population Children 1-6 years	0.002146 0.005192	466 193
Cyfluthrin	US Population NNI	0.004917 0.010687	4,068 1,871
lambda-Cyhalothrin	US Population NNI	0.001607 0.003594	311 139
Cypermethrin	US Population Children 1-6 years	0.004438 0.005465	225 183
Zeta-cypermethrin	US Population Children 1-6 years	0.003969 0.004776	126 105
Deltamethrin/ Tralomethrin	US Population Children 1-6 years	0.000728 0.001855	1,373 539
Esfenvalerate	US Population Children 1-6 years	0.011717 0.019445	171 103
Fenpropathrin	US Population Children 1-6 years	0.002847 0.007468	2,108 803
Tefluthrin	US Population NNI	0.000340 0.000724	1,469 691
NNI = non-nursing infants <1 year old			

Table 5. Acute Drinking Water Exposure and Risk Estimates			
Chemcial	Population Subgroup	Acute Drinking Water Exposure (mg/kg/day)	MOE (99.9th percentile)
Bifenthrin	US Population NNI	0.000060 0.000115	16,664 8,658
Cyfluthrin	US Population NNI	0.000054 0.000104	368,982 192,308
lambda-Cyhalothrin	US Population NNI	0.000022 0.000042	22,876 11,956
Cypermethrin	US Population NNI	0.000126 0.000242	7,965 4,138
Zeta-cypermethrin	US Population NNI	0.000126 0.000242	3,982 2,069
Deltamethrin/ Tralomethrin	US Population NNI	0.000014 0.000028	69,093 35,895
Esfenvalerate	US Population NNI	0.000039 0.000074	51,743 27,042
Fenpropathrin	US Population NNI	0.001042 0.001995	5,756 3,007
Tefluthrin	US Population NNI	0.000040 0.000078	12,362 6,439
NNI = Non-nursing infants <1 year old			

Table 6. Acute Aggregate (Food and Water) Exposure and Risk Estimates			
Chemcial	US Population and Most Highly Exposed Population Subgroup	Acute Dietary Exposure (mg/kg/day)	MOE (99.9th percentile)
Bifenthrin	US Population Children 1-6 years	0.002206 0.005243	453 191
Cyfluthrin	US Population NNI	0.004971 0.010791	4,023 1,853
lambda-Cyhalothrin	US Population NNI	0.001629 0.003636	307 138
Cypermethrin	US Population Children 1-6 years	0.004564 0.005572	219 179
Zeta-cypermethrin	US Population Children 1-6 years	0.004095 0.004883	122 102
Deltamethrin/ Tralomethrin	US Population Children 1-6 years	0.000742 0.001867	1,348 535
Esfenvalerate	US Population Children 1-6 years	0.011756 0.019477	170 103
Fenpropathrin	US Population Children 1-6 years	0.003889 0.008341	1,543 719
Tefluthrin	US Population NNI	0.000380 0.000802	1,316 623
NNI = non-nursing infants <1 year old			

Table 7. Short - and Intermediate-Term Aggreggate (Chronic Food, Chronic Water, Residential) Exposure and Risk Estimates.				
Chemcial	Population Subgroup	Aggregate Exposure (mg/kg/day)	MOE	Comments
Bifenthrin	Adult Infant Child	0.002359 0.005000 0.005106	417 200 196	Chronic dietary Chronic water Turf
Cyfluthrin	Adult Infant Child	0.005321 0.008255 0.007662	3800 2400 2600	Chronic dietary Chronic water Turf, Fogger
lambda-Cyhalothrin	Adult Infant Child	0.000725 0.001460 0.001580	14,000 6800 6300	Chronic dietary Chronic water Turf
Cypermethrin	Adult Infant Child	0.000082 0.002621 0.002451	61,000 1,900 2,000	Chronic dietary Chronic water Turf, Fogger
Zeta-cypermethrin	No residential uses			
Deltamethrin/ Tralomethrin	Adult Infant Child	0.000042 0.000057 0.000055	49,000 1,800 2,700	Chronic dietary Chronic water Turf, Carpet & Room

Esfenvalerate	Adult Infant Child	0.008200 0.009781 0.011470	244 204 174	Chronic dietary Chronic water Turf, Carpet & Room, Pet care
Fenpropathrin	No residential uses			
Tefluthrin	No residential uses			

Attachment 3

Percent of Crop Treated Data
D. Brassard, BEAD, 9/12/97
D. Brassard, BEAD, 10/8/97

September 12, 1997

NOTE

SUBJECT: Review of Pyrethroid Working Group Percent Crop Treated Estimates

FROM: David W. Brassard, Senior Entomologist
Biological Analysis Branch
Biological and Economic Analysis Division (7503W)

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

The following narrative and table represents BEAD's peer review of the Pyrethroid Working Group's (PWG) estimates of percent crop treated (%CT) by 10 pyrethroid insecticides. These estimates were developed by analysts from Novigen, RiskScience.com (industry consultants) and registrants. The percent crop treated estimates were based on usage estimates from Maritz, Doane, and Buckley (1994-1996 basis). The PWG also developed estimates of usage in Food Handling Establishments. These estimates are based on PCO survey data from NuVentures Consultants.

Because of the fast turnaround requested (we only had 2 days to work on this), our peer review should be considered preliminary in nature and subject to revision. Also because of the differences in methodology between PWG's estimates and ours (e.g. different data sources, different years) we accepted less than significant differences in their %CT estimates without comment. A major problem we had to deal with was the inaccuracy of many estimates in our QUA's due to a recently discovered glitch in the QUA SAS routine which caused us to overestimate %CT. These QUA's will be revised soon to better reflect reality.

Because of the above mentioned glitch, many of the estimates in the underlying QUA's are higher than the PWG estimates. I reconciled these discrepancies using Table 18 and Table 11 runs from Doane. When the PWG estimates were closer to reality than ours, I made no comment. When it looked like the PWG estimates were erroneous, I suggested revised estimates taking into account the actual base acres treated. In some cases the QUA did not reflect trend increases or decreases in use (e.g. esfenvalerate on sugarcane) as well as the PWG estimates did.

There is considerable uncertainty in our estimates of use in Food Handling Establishments (FHE's) since they are based on one source, CCPAS. The reliability of this survey has never been established and, since CCPAS reports usage in terms of pounds active ingredients applied, one has to make several assumptions regarding application rates and total area of Food Handling Establishments in order to estimate percent of FHE's treated. PWG's estimates appear to be based on NuVentures, a Pest Control Industry Survey that we have not seen. In general, their estimates appear to be significantly lower than ours but I don't have enough confidence in our estimates to say which is closer to the truth.

cc: Sherry Sterling
Susan Lawrence
Dennis Szuhay
Peter Caulkins
Steve Knizer
Jeff Herndon

PS: I'd like to extend special thanks to the seven economists (see list below) who graciously volunteered to drop everything they were working on to meet this deadline.

Art Grube
Ghulam Ali
Frank Hernandez
Steve Nako
Alan Halvorson
Ed Brandt
Sherry Wise

Table 1. Suggested revisions to Percent Crop Treated Estimates for Pyrethroids

Chemical/Crop	% crop treated				Degree of confidence in EPA estimate/Comments
	PWG		EPA		
	avg	max	avg	max	
BIFENTHRIN (CAPTURE®)					
cotton	4	5	4	6	high
CYFLUTHRIN (BAYTHROID®)					
carrots	0.8	0.9	1.4	2	medium: PWG estimates based on overstated estimate of acres of carrots grown (251,000). Actually area planted is 112,000 acres
radishes	0.8	0.9	1.4	7	medium PWG estimates based on overstated estimate of acres of radishes grown (251,000). Actually area planted is 29,000 acres
food handling est	3.8	--	11	22	low: our estimate is based on CCPAS, we don't have their NuVenture's data base to check the reliability of their estimate
CYPERMETHRIN (AMMO, CYMBUSH®)					
pecans	41	47	10	18	medium: PWG underestimated acres planted
DELTAMETHRIN (DECIS®): No Comments					
ESFENVALERATE (ASANA®)					
berries	1	3	2	6	low
cherries	12	15	16	24	medium
cole crops	32	36	45	60	medium
cotton	6	8	8	12	high
peaches	13	18	13	25	medium
vegetables, other	0	0	1	20	low
FENPROPATHRIN (DANITOL®) No Comments					
LAMBDA CYHALOTHRIN (KARATE®)					

Chemical/Crop	% crop treated				Degree of confidence in EPA estimate/Comments
	PWG		EPA		
	avg	max	avg	max	
lettuce	3.1	8.4	6	10	Medium
onions, dry	17	25	22	33	Medium: Lambda cyhalothrin use is increasing over time
rice	0.2	0.5	10	20	Medium: new registration, no usage data available; figures given are market projections based on company estimates and current usage of alternatives (e.g. carbofuran, malathion, carbaryl)
TEFLUTHRIN (FORCE®)					
field corn	27	--	8	10	High: No insecticide has ever treated more than 10% of field corn acreage
sweet corn	12	--	2	10	medium

Chemical/Crop	% crop treated				Degree of confidence in EPA estimate/Comments
	PWG		EPA		
	avg	max	avg	max	
TRALOMETHRIN (SCOUT®)					
sunflower	1	--	2	4	
ZETA-CYPERMETHRIN (FURY®)					
cole crops	0	0	1	2	
pecans	1	5	3	5	medium: PWG had an error in their calculation of %CT for 1995; they computed that 14,600/314,000 acres = 0.92%; their formula should have read 14,600/488,000 = 3%

October 8, 1997

NOTE

SUBJECT: Review of Pyrethroid Working Group Percent Crop Treated Estimates

FROM: David W. Brassard, Senior Entomologist
Biological Analysis Branch
Biological and Economic Analysis Division (7503W)

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

The following narrative and tables represents BEAD's revisions to estimates given in my September 12, 1997 note. These revisions are based on discussions with and new information provided by Lori Fix, Joel Kroenenberg, and Linda Mullen of the Pyrethroid Working Group (PWG).

FOOD HANDLING ESTABLISHMENTS

The most significant change to the previous analysis involves Food Handling Establishments (FHE's) (which include food processing plants, restaurants, and supermarkets). BEAD's previous estimates for cyfluthrin, were based on data from CCPAS (1993 Commercial/ Certified Pesticide Applicator Survey). Since CCPAS reports usage in terms of pounds active ingredients applied, BEAD used assumptions regarding application rates and total area of Food Handling Establishments to estimated that 11-22 percent of FHE's were treated.

The PWG used data from NuVentures, a Pest Control Industry Survey, to estimate that 3.8 percent of FHE's were treated with cyfluthrin. The PWG's estimate was based on cyfluthrin's current share of the pyrethroid Pest Control Operator (PCO) market (13.7 percent) times a multiplier of 28 percent (based on the pyrethroids' share of the residual dilutable PCO insecticide market (44.5%) times percent of all insecticides applied indoors (63%)). I disagree with the use of the second multiplier. I find it illogical to assume that only 63 percent of all food handling establishments are treated just because 37 percent of all PCO insecticide applications are made outdoors. The first multiplier is also problematic because not all pyrethroids are cleared for use in FHE's. Most notably, cypermethrin, which has the largest share of the PCO pyrethroid market, is not registered for use in FHE's. A reasonable upper bound estimate would be to assume that all FHE's are treated with some insecticide; therefore the use of all pyrethroids (registered for use in FHE's) should

add up to 44.5 percent of FHE's treated (the other 55.5% of FHE's would be treated with OP's, pyrethrins, IGR's, carbamates, etc.) (Table 1). It is likely, however, that less than 100 percent of FHE's are treated on a regular basis. Additionally, with the Delaney constraint removed, it is likely that more pyrethroids will be cleared for use in FHE's. Therefore, I propose using the current percentage of the pyrethroid residual insecticide market share as a lower bound estimate for percent of FHE's treated. This is still a conservative estimate, because it assumes that if al pyrethroids were registered they would treat 100 percent of FHE's. Using this methodology, our new estimates for cyfluthrin based on NuVentures data (13.7 to 22.8%) are surprisingly close to our old estimates using CCPAS (11 to 22 percent). The new methodology also allows us to make estimates for recently registered or pending pyrethroids that were not included in the 1993 CCPAS survey.

Note that Table 1 also includes revised estimates for deltamethrin, lambda cyhalothrin, and tralomethrin, which BEAD had not previously commented on.

AGRICULTURAL CROPS

In response to comments from Lori Fix and Linda Mullen of the PWG, I have revised estimates of percent crop treated (%CT) for cyfluthrin on radishes and esfenvalerate on cole crops. Refer to table 2 for a summary of these revisions

cc: Sherry Sterling
Susan Lawrence
Dennis Szuhay
Mark Dow
Peter Caulkins
Donna Davis
Steve Knizer
Jeff Herndon
Art Grube
Steve Nako
Alan Halvorson
Ghulam Ali
Sherry Wise

Table 1. Suggested Revisions to Estimates of the Percent of Food Handling Establishments Treated by Pyrethroids.

Chemical	% FHE treated estimates					Comments
	PWG	Old EPA		New EPA		
	avg	avg	max	avg	max	
cyfluthrin (Tempo)	3.8	11	22	13.7	22.8	average % FHE = cyfluthrin's current share of the total PCO residual insecticide market; max % FHE assumes that currently registered pyrethroids treat 44.5% of FHE's.
deltamethrin (Suspend)	--	--	--	4.2	7	PWG combined usage with tralomethrin
lambda cyhalothrin	0.7	--	--	2.6	4.3	
tralomethrin (Saga)	1.9	--	--	2.5	4.2	PWG estimate for tralomethrin plus deltamethrin
other FHE pyrethroids	--	--	--	3.8	6.3	includes other pyrethroids (e.g. fenvalerate) currently registered for use in FHE's
Current Total				26.8	44.5	Total for pyrethroids with current or pending FHE registrations
other non-FHE pyrethroids	--	--	--	73.2	--	Pyrethroids (e.g. cypermethrin, permethrin) that are not currently registered for use in FHE's. These currently occupy 73.2 percent of the PCO pyrethroid market.
Possible Future Total	--	--	--	100	--	Could only happen if pyrethroids supplanted all other insecticides; % FHE's treated with pyrethroids is more likely to remain under 50%.

Table 2. Suggested revisions to Percent Crop Treated Estimates for Pyrethroids

Chemical/ Crop	% crop treated						Comments
	PWG		Old EPA		New EPA		
	avg	max	avg	max	avg	max	
CYFLUTHRIN (BAYTHROID®)							
radishes	0.8	0.9	1.4	7	1	2	Old maximum estimate based on assumption that all root crop use was on radishes. Bayer claims that cyfluthrin is not currently used on radishes; that all cyfluthrin use reported for root crops was on carrots. Projections for use on radishes are based on extrapolation from carrot use
ESFENVALERATE (ASANA®)							
cole crops	32	36	45	60	32	36	Revised after recalculating for base acres treated.

Attachment 4

Estimates of Synthetic Pyrethroid Drinking Water Concentrations
R. Matzner, EFED, undated

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Preliminary Estimates of Synthetic Pyrethroid Drinking Water Concentrations

FROM: Robert Matzner, Hydrologist
Environmental Fate and Effects Division
Office of Pesticide Programs (7507C)

TO: Jeff Herndon
Steve Knizer
Health Effects Division (7509C)
Office of Pesticide Programs (7507C)

The following table includes pyrethroid exposure values which can be used as estimates of acute and chronic drinking water concentrations for FQPA. The values were generated with the PRZM I
and EXAMS 2.94 computer models in 1993 for comparative ecological risk assesment for these chemicals.

We may possibly be able to provide you with revised estimates by 10/10/97.

Pesticide Name	Instantan-eous Conc. (Zero day)	Chronic conc - Max 90 day ave
Cyhalothrin (Karate) ppt	95	3
Cyfluthrin (Baythroid)	236	44
Tralomethrin (Scout)	63	4

Cypermethrin (Ammo, Cymbush)	544	159
Esfenvalerate (Asana)	168	37
Fenpropathrin (Danitol)	4532	2954
Bifenthrin (Capture)	260	18
Permethrin (Ambush, Pounce)	1355	467

Table 1. Maximum Expected Environmental Concentration (EEC) expected one year in every ten years (conc in ppt).

Note: Subsequent to provideing the above infomration, EFED also supplied zero day and 90 average values for tefluthin, at 174 and 12 ppt respectively.

Attachment 5

Non-Dietary Exposure and Risk Assessment for the Synthetic Pyrethroids

NON-DIETARY EXPOSURE AND RISK ASSESSMENT FOR THE SYNTHETIC PYRETHROIDS

Attached please find the non-dietary and aggregate risk assessment approach for esfenvalerate and the synthetic pyrethroids. Esfenvalerate is one of 10 synthetic pyrethroids having their existing time-limited tolerances expire in November 1997. In order to reassess the tolerance for these chemicals under FQPA, dietary, non-dietary and aggregate risk assessments that include residential exposures must be conducted. To address these requirments, The registrant (DuPont) joined the Pyrethroid Working Group (PWG) to combine resources and develop a common approach for addressing the non-dietary and aggregrate risk assessments. The non-dietary and aggregrate risk assessment approaches are the result of discussions among representatives of the PWG, EPA, and the California Department of Pesticide Regulation (CDPR).

The focus of the aggregrate risk assessment is the use of sythetic pyrethroids to control fleas on pets, lawns, and indoor surfaces. Because of the wide variety of residential uses and the limited time to conduct the risk assessments, it was agreed between the EPA and the PWG that the flea control scenario was the most likely scenario for conducting an aggregate risk assessment.

This attachment presents the methods used to assess non-dietary exposure, provides an example risk assessment (esfenvalerate) and presents the non-dietary aggregate margins of exposure for the synthetic pyrethroids having non-dietary exposure potentials. Esfenvalerate has been chosen as the example aggregate risk assesment because it has all three uses: pet spray, turf treatment, and indoor spray. The other pyrethroids have either the turf and/or the indoor fogger/spray use but not the pet spray. The non-dietary methodology selected for conducting the esfenvalerate risk assessment is the same for all synthetic pyrethroids having non-dietary uses.

INTRODUCTION:

This risk assessment addresses adult exposure while applying the esfenvalerate to indoor surfaces (spray), and pets. Post-application exposure of adults, children (1-6 years), and infants (<1 year) to those applications as well as post-application exposure to turf treated by professional lawn care operators (LCO). Non-dietary exposure for adults will be addressed via the inhalation and dermal routes and exposure for infants and children will be addressed via the inhalation, dermal, and oral (hand-to-mouth) routes. The PWG are using a wide variety of data and assumptions including the use of propriarty data, surrogate data, a propriatary model (HouseModel) and reports of studies found in the published literature.

For estimating residential applicator exposure, the PWG is relying primarily on data presented in the Pesticide Handlers Exposure Database (PHED). Where homeowner applicator data are lacking, such as disposal of used fogger containers and hand exposure while incorporating pesticide spray into pet fur, dermal exposure was estimated using the film-thickness approach.

For post-application inhalation exposure, the PWG are citing data presented in two proprietary studies conducted by Bayer. These studies address post-application, airborne concentrations of cyfluthrin: Laser Room Fogger (Eberhart, 1987) and post-application inhalation exposure to turf treated with imidacloprid: Merit Turf Insecticide (Eberhart and Ellisor, 1994). A proprietary model (HouseModel), coupled with PHED inhalation values was used to estimate an emission rate for air concentration values following applications of esfenvalerate to pets and the use of hand-held carpet sprays.

Post-application dermal exposure to treated turfgrass and carpets will be assessed using "Jazzercise" studies. For carpets, the PWG are using transfer factors developed by the California Department of Pesticide Regulation (Ross, 1990 and 1991). For turf, the PWG are using transfer factors from the Bayer imidacloprid study (Eberhart and Ellisor, 1994) discussed above. Clothing penetration from the imidacloprid study were also used for certain clothing scenarios discussed later in this assessment.

For post-application oral (hand-to-mouth) exposure, the PWG are relying on hand transfer factors from (Ross 1990, 1991), and (Eberhart and Ellisor, 1994). The percent removal of the pesticide from hands as a result of mouthing is addressed by using the hand wash removal efficiency data presented in a published studies (Fenske and Lu, 1994; Bucks *et al.*, 1989; Webster *et al.*, 1990).

II. DETAILED CONSIDERATIONS:

METHODOLOGIES FOR ASSESSING LAWN, CARPET, AND PET TREATMENTS

Lawn Applications It should be noted, that during the techincal discussions held between EPA, the PWG, and Cal-DPR, lawn applications were assumed to be made by professional LCO's (lawn care operators) only. Applications by LCO's are considered "out of scope" for purposes of this risk assessment with respect to addressing residential exposure. However, in some PWG, submissions, adult exposure while applying lawn care pesticides was not conducted because "the **majority** of synthetic pyrethroids are applied by LCO's". It should be noted that the registrants of these products are members of the Outdoor Residential Exposure Task Force, which has recently completed the field portions of two homeowner applicator studies. These upcoming data are expected to be more robust than the current PHED data sets for these uses if needed.

Indoor Surface and Carpet Applications

The PWG used PHED to estimate dermal and Inhalation exposure while appling hand-held aerosols to carpets. The PHED data are based on a crack and crevice treatment. Dermal exposure while using total-release room foggers is expected to be negligable. However, the PWG utilized the film-thickness method to assess dermal exposure while disposing the fogger and the newspapers normally placed under the fogger (EPA 1987, Methods for Assessing Exposure to Chemical Substances, Vol. 7: Methods for Assessing Consumer Exposure to Chemical Substances, OTS, 560/5-85-007). When using this method, it is assumed that a uniform film covers the skin. The area of contact by the skin is represented by one-half the surface area of both hands (396.5 cm2), the film-thickness of the pesticide formulation is assumed to be that of water 0.002 cm. The product density of the particular pesticide is then used to calculate the exposure.

Pet Applications

The film-thickness method was also used to assess dermal exposure while treating pets. PHED was used to estimate inhalation exposure using the same crack and crevice spray subset as discussed above.

Post-Application

Dermal

The PWG, in cooperation with John Ross of Cal-DPR, generated unitless transfer factors to relate post-application dermal exposures to pesticide residues on indoor surfaces, pets, and lawns. The transfer factors are based on the "Jazzercise" routine in which dermal exposure was measured while adults participated in a Jazzercise routine. The unitless transfer factors developed by the PWG and Ross relate the dermal loading of dosimeters of adults while "Jazzercising" to transferrable residue measurements using the "CDPR Roller"; Ross *et al*,. (1990) and Ross *et al*,. (1991) respectively. In both studies, identical treatments of d-trans allethrin were made.

In Ross (1990), the Jazzercise routine was for twenty minutes, including the time spent entering and exiting the treated area. During the routine, approximately 90% of the time spent by the study cohorts was on their backs, sides, or stomachs. Two separate dermal dosimetry measurements of 5 adults in two rooms (one hour after treatment) were used for developing the unitless transfer factors. Dosimetry measurements were made for the upper body (shirt dosimeter representing 2/3 of the trunk and the arms - 5895 cm2), the lower body (tights dosimeter representing 1/3 of the trunk and the legs - 6817 cm2), the hands (glove dosimeters - 793 cm2), and feet (sock dosimeters - 1048 cm2).

For an example unitless transfer factor, consider the mean of 105 ug measured on the lower body dosimeters in Ross *et al*, (1990). This resulted in a lower body dosimeter loading of 0.0154 ug/cm2 (105 ug on dosimeter/6817 cm2 of body surface area represented by the dosimeter). To obtain the unitless transfer factor, the dermal loading of the dosimeter (0.0154 ug/cm2) is divided by the residue measured in the CDPR roller study (d-trans allethrin 0.0064 ug/cm2). This yields a unitless transfer factor of 2.4. The unitless transfer factors for the upper body, hands, and feet are 2.4, 12.6, and 13.6 respectively.

In Eberhart and Ellisor (1994), the Jazzercise routine was used in conjunction with the CDPR Roller method to measure post-application exposure to turf treated with imidacloprid. Unitless transfer factors of 6, 0.9, 1.6, and 6.6 were calculated for the hands, upper body, lower body, and feet respectively.

In the imidacloprid study (Eberhart and Ellisor, 1994) "to the skin" measurements were estimated using inner and outer dosimeters. These data can be used to estimate exposure for certain clothing scenarios. Therefore, unitless transfer factors were

also calculated for certain body parts based on comparing the inner and outer dosimeters.

Clothing assumptions for the carpet scenario are no clothes worn by infants or children and sleeveless shirts and short pants by adults.

Clothing assumptions for the turf scenario are sleeveless shirts and short pants for adults, children and infants.

The unitless transfer factors that represent clothing penetration for the upper body and lower body are 0.03 and 0.04 for the carpet scenario. This was calculated by dividing the measurements of the upper body inner dosimeter (ug/cm2) by the sum of the measurements of the upper body inner dosimeter and the upper body outer dosimeter then multiply the result by the 2.4 transfer factor extracted from Ross (1990, 1991).

For example:

$$\frac{\text{Inner dosimeter (7 ug)}}{\text{Inner dos.(7 ug)+ outer dos.(533 ug)}} \times 2.4 = 0.03$$

Inhalation

Post-applicaton inhalation exposure following treatments to lawns was estimated using TWA's from the imidacloprid study (Eberhart and Ellisor, 1994). In the study, air concentration measurements were taken in the vicinity of the volunteer subjects performing the Jazzercize routines.

Post-application inhalation exposure for the fogger treatments, will be assessed using time-weighted averages from the cyfluthrin room fogger study (Eberhart, 1987). The TWA's cover the period following 2.5 hours of ventilation as per label recommendations.

Post-application inhalation exposure for the use of aerosol spray treatments to carpets and from the spraying of pets uses air concentrations taken from the crack and crevice subset of PHED. HouseModel was then used to estimate an emission rate based on the dilution features of the model. HouseModel was used instead of MCCEM because MCCEM requires emission rate rather than the air concentration level reported in PHED.

Oral (hand-to-mouth)

For indoor surface and pet treatments, the PWG assessments rely on the high contact, dermal loading transfer factor (to the hands) taken from the Jazzercise data (Ross *et al.*, 1990, 1991). For lawn treatments, the hand transfers from the imidacloprid study (Eberhart and Ellisor, 1994) were used. For all hand-to-mouth scenarios it is assumed that 10 percent of those residues loaded on the skin will be available for oral injestion. The PWG cite Webster *et al.*, (1990) and Bucks *et al.*, (1989) data suggesting water rinsing of powdered stratum corneum with respect to lipophilic compounds such as alachor, PCB's, and chlorpyrifos results in less than 1 to 5 percent removal. Fenske and Lu (1994) suggest an efficiency of 20 to 30 percent when using ethanol or isopropanol/water hand rinses of chlorpyrifos. Given the low solubility of the pyrethroids, 10 percent transfer to the mouth is reasonably conservative.

BODY WEIGHTS, SURFACE AREAS, and BREATHING RATES

The PWG are citing mean body weights for male and female adults of 71.8 kg (male average 78.1 kg and female average 65.4 kg). The respective body weights for children

(1-6 years) and infants (< 1 year) are 18.9 kg and 11.3 kg (Exposure Factors Handbook, EPA, 1996).

The PWG are citing the following standard body surface areas matched with the above body weights (Exposure Factors Handbook, EPA, 1996). These are averages rather than the 50th percentile. However, they are matched to average body weights and therefore, will not underestimate exposure. In the Exposure Factors Handbook, it was determined that there is strong correlation (0.986) between body weight and surface area (Phillips *et al.*, 1993). The head and face were not included as they were not addressed in the Ross data (1990, 1991) or the imidicloprid data (Eberhart and Ellisor, 1994). Subsequent propriatary data using the "Jazzercise" method indicates less than 0.5 percent of the total exposure can be accounted for by the head and neck. Therefore the omission of head and neck values do not effect the results of the risk assessments.

Table 1 - Surface Areas (cm2)

	infants	*children*	*adults*
Upper Body - uncovered (arms)	744	1085	2190
Upper Body - covered (sleeveless shirt; 2/3 trunk)	1293	1615	3705
Lower Body - Uncovered (4/5 legs)	895	1650	3972
Lower Body - Covered (short pants; 1/3 trunk + 1/5 legs)	870	1220	2845
Hands	288	452	793
Feet	355	553	104

Table 2 - Breathing rates m3/hr

Setting	**Adults**	**Children**	**Infants**
Indoor	0.71	0.47	0.34
Outdoor	1.43	0.93	0.69

The grand mean breathing rates for indoor settings are for light activity and for outdoors settings, for moderate activity.

APPLICATION RATES

The PWG are using concentration correction factors to adjust product specific AI's to the amount of active ingredient used in the surrogate studies. This assumes residues and subsequent exposures are directly proportionate to the application rate. The concentration correction factor is calculated by dividing the active ingredient of the

compound that is the subject of the risk assessment by the amount of active ingredient used in the surrogate monitoring study.

EXPOSURE DURATION

Exposure durations will be discussed in the example equations as follows.

EXPOSURE FORMULAS

Total Release Foggers

Formula 1 - home fogger application using the film-thickness approach.

$$\text{Dose} = \frac{(\text{Surface Area}) \times (\text{Density}) \times (\text{Film Thickness}) \times (\text{Weight Fraction}) \times (\text{Fraction Absorbed}) \times (\text{Use Frequency})}{(\text{Body Weight})}$$

For Density, the PWG has assumed a default value of 800 mg/cm3 or 0.80g/ml as representative of organic solvent-based sprays (Residential SOP's, EPA 1997). The value is based on a comparison of various organic solvents used in aerosol foggers.

The use frequency assumes the use of one can. It should be noted, that for fleas or other pests, it is likely more than one fogger would be used. However, the use of the film thickness approach should account for the clean-up of additional cans and underlying newspapers.

Formula 2 - Post-application inhalation of airborne aerosols.

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

The concentration (Conc) is the TWA from Eberhart (1987) and is adjusted for the concentration of the active ingredient being evaluated by the use of the concentration correction factor.

The exposure duration (8 hours) is an upper bound estimate of the time spent in any given room (other than sleeping). The Agency default assumption of 100 percent pulmonary absorption also provides additional measure of overestimation.

Formula 3 - Post-application dermal exposure to treated surfaces .

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{Trans Res}) \times (\text{Surface Area})] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

The transfer factor and transferrable residues are derived from Ross *et al.*, (1991) in which d-trans allethrin residues were collected with the CDPR roller. The correction factor is used to adjust the concentration of d-trans allethrin transferable residues, at time zero, to the amount of active ingredient being evaluated.

It should be noted that this formula does not consider a duration of exposure. Cal-DPR and the PWG believe the twenty minute "Jazzercise" routine provides a bounding estimate of dermal exposure for the variety of potential activites in and around the residence. The routine is a well defined floor activity that has shown considerable consistency between subjects in the studies conducted thus far. The method was designed to distinguish the exposure potential of toddlers (due to their higher activity levels) from estimates in previous studies by Vacarro *et al.*, (1991) in which adults performed the activites of infants for 4 hours (crawling, playing with blocks etc). In fact, the twenty minute routine produced similar results to that of Vacarro *et al.*, (1991). In a paper presented to ILSI, titled Experimental Method to Estimate Indoor Pesticide Exposure to Children, Ross *et al.*, the results of Ross and Vacarro were presented both exposure in terms of mg/kg. The respective exposure estimates for chlorpyrifos by Vacarro and Ross were 0.021 - 0.031 mg/kg and 0.007 - 0.025 mg/kg. Again, the Ross data were collected over a 20 minute period vs Vacarro which was collected over a four hour period. Hand data, which is more important for hand-to-mouth estimates, was also comparable (Ross, mean of 0 and 6 hour measurements - 0.43 mg vs Vacarro 0.47 mg). This suggests that exposure assessments that assume exposure is accumulated over time may in fact overestimate exposure. In fact it appears that residues and dermal skin loading may come into equlibrium. Durkin *et al.* (1996), addressed this issue while comparing harvester hand loading levels to concurrent dislodgeable field residues (for 16 different pesticides). These data show residue levels on harvesters' hands coming into equilibrium with the residue levels in fields in which they were harvesting.

The issue of the Jazzercise exposure duration period was discussed among a subgroup of HED's Exposure SAC. The group concluded (with some dissention) that the PWG approach was reasonable, but more data were needed in the future, to totally understand the dynamics of indoor exposure.

There is still sufficient conservatism built into the formula. That is, the use of zero hour residues; the assumption of no clothing protection for infants and children; and the assumption of 25 percent dermal absorption. The PWG cite studies by Wollen *et al.*, (1992) and Rabbe *et al.*, (1989) indicating dermal absorption of synthetic pyrethroids to be less than 2 percent. The use of 25 percent dermal absorption overides any concerns regarding the selection of the dermal post-application scenario. Finally, according to the Hazard ID document, dermal exposures were not to be included in four of the six aggregate assessments.

Formula 4 - Post-application incidential ingestion exposure (hand to mouth).

$$\text{Dose} = \frac{\text{(Dermal Hand Exp) x (Correction Factor) x (Hand-to-Mouth Trans Factor) x (Oral Absorption Frac)}}{\text{(Body Weight)}}$$

The dermal hand exposure is based on the hand transfer factor and the mean transferrable residues from Ross *et al.*, (1991). The correction factor is the same as discussed in the previous formulas. Also as previously discussed, the hand-to-mouth transfer factor is an estimate based on the studies conducted by Fenske and Lu (1994), Bucks *et al.*, (1989), Webster *et al.*, (1990). These data collectively suggest 1 - 5 percent hand wash efficiency using water and 10 to 30 percent using isopropanol and isopropanol/water rinses. The 10 percent transfer from mouthing appears to be a conservative estimate considering the low solubility of sythetic pyrethroid compounds.

The oral absorption is an Agency default value believed by the PWG to overestimate exposure via this route. The PWG cite World Health Orginization data (1990) in which an oral human volunteer study showed urinary and fecal excretion of 59 and 26 percent respectively.

Lawn Care Products

Formula 5 - Post-application inhalation exposure to airborne aerosols.

$$\text{Dose} = \frac{\text{(Conc) x (Inhalation Rate) x (Conc Correction Factor) x (Pulmonary Absorption) x (Expo Duration)}}{\text{(Body Weight)}}$$

This formula relies on the time weighted average air concentrations measured in the Imidacloprid study (Eberhart and Ellisor, 1994). The TWA is adjusted for the amount of active ingredient, in the chemical being evaluated, by use of the concentration correction factor. The duration of exposure matches the Jazzercise duration (1/3 hour). The PWG selected a moderate breathing rates based on Layton 1993, presented in the Exposure Factors Handbook. For example, the mean for males and females is 1.43 m3/hr. Assumptions regarding the default of 100 percent inhalation absorption and the low volatility of synthetic pyrethroids ensures that the formula is protective.

Formula 6 - Post-application dermal exposure to treated lawns.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{Trans Res}) \times (\text{Surface Area})] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

This formula is the same as **formula 3.** However, rather than using the Ross data, the imidacloprid turf data (Eberhart and Ellisor, 1994) was used instead.

Formula 7 - Post-application incidential ingestion exposure (hand to mouth).

$$\text{Dose} = \frac{(\text{Dermal Hand Exp}) \times (\text{Correction Factor}) \times (\text{Hand-to-Mouth Trans Factor}) \times (\text{Oral Absorption Frac})}{(\text{Body Weight})}$$

The dermal hand exposure is based on the hand transfer factor and the mean transferrable residues from Eberhart and Ellisor (1994). The correction factor is the same as discussed in the previous formulas. Also as previously discussed, the hand-to-mouth transfer factor is an estimate based on the studies conducted by Fenske and Lu (1994), Bucks *et al.*, (1989), Webster *et al.*, (1990). These data collectively suggest 1 - 5 percent hand wash efficiency using water and 10 to 30 percent using isopropanol and isopropanol/water rinses. The 10 percent transfer from mouthing appears to be a conservative estimate considering the low solubility of sythetic pyrethroid compounds.

Formula 8 - Inhalation exposure while using a hand-held aerosol sprayer.

$$\text{Dose} = \frac{(\text{Inhal Unit Exp}) \times (\text{Amt Formulation Used}) \times (\text{Weight Fraction}) \times (\text{Inhalationl Absorption}) \times (\text{Use Frequency})}{(\text{Body Weight})}$$

The unit exposure for this scenario is from the Pesticide Handlers Exposure Database (PHED)- 15 replicates (A + B grades), use of aerosol spray. The user is expected to apply the entire contents of a 16 ounce aerosol container. Although the PHED data set are from a crack and crevice spray, the scenarios appear similar enough to address this scenario. This is because both carpet spray and the crack and crevice spray require the user to apply the spray against a solid surface. A breathing rate of 13.8 liters/minute was assumed. An inhalation absorption rate of 100 percent is used which is viewed by the PWG as conservative given the low volatility of synthetic pyrethroids. The use of the entire contents of the container is also assumed to be conservative. The weight fraction of the active ingredient in the formulation is based on the percent.

Formula 9 - Dermal exposure while using a hand-held aerosol sprayer.

$$\text{Dose} = \frac{(\text{Dermal Unit Exp}) \times (\text{Amt Formulation Used}) \times (\text{Weight Fraction}) \times (\text{Dermal Absorption}) \times (\text{Use Frequency})}{(\text{Body Weight})}$$

The unit exposure for this scenario is from the PHED data set discussed above. The scenario is for total deposition (no clothing penetration). The use of one entire can, the assumption of total deposition and 25 percent dermal absorption ensure the formula is conservative.

Formula 10 - Post-application inhalation exposure following the use of a hand-held aerosol sprayer to treat carpets.

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

This formula requires the input of an inhalation concentration from the PHED aerosol use, and the use of an indoor air dilution model (HouseModel). The model is a two chamber proprietary model that include as parameters a 60 cubic meter room and an air exchange rate of 0.5 air exchanges per hour. The exchange rate is that of the air exchanged between two rooms separated by a door with the windows closed in both rooms. This is based on a national average exchange rate of residences during winter (THERdbASE - 1997). HouseModel was used to assume an 8 hour TWA with a starting concentration of 0.0229 mg/m3. The TWA is 0.00377

mg/m3. The Exposure duration is 8 hours. For post-application inhalation exposure following the use of a total release fogger, a TWA from data presented in Eberhart 1987 was used.

Formula 11 - Post-application incidential ingestion exposure (hand-to-mouth).

$$\text{Dose} = \frac{\text{(Dermal Hand Exp) x (Correction Factor) x (Hand-to-Mouth Trans Factor) x (Oral Absorption Frac)}}{\text{(Body Weight)}}$$

See **Formula 4** for additional information

Pet Care Products

Formula 12 - Inhalation exposure while using a hand-held aerosol sprayer (PHED).

$$\text{Dose} = \frac{\text{(Inhal Unit Exp) x (Amt Formulation Used) x (Weight Fraction) x (Inhalationl Absorption) x (Use Frequency)}}{\text{(Body Weight)}}$$

Formula 13 - Dermal exposure while using a hand-held aerosol sprayer to treat pets.

$$\text{Dose} = \frac{\text{(Surface Area) x (Density) x (Film Thickness) x (Weight Fraction) x (Fraction Absorbed) x (Use Frequency)}}{\text{(Body Weight)}}$$

This formula relies on the film thickness approach for estimating dermal exposures resulting from coming in contact with the spray and wet residues during treatment. Although the label recommends using gloves during treatment, this formula assumes that gloves are not worn. A film thickness of 0.002 cm (water) is assumed and the density is assumed to be 0.8g/cm3.

Formula 14 - Post-application inhalation exposure following the use of a hand-held aerosol sprayer to treat pets.

$$\text{Dose} = \frac{\text{(Conc) x (Inhalation Rate) x (Conc Correction Factor) x (Pulmonary Absorption) x (Expo Duration)}}{\text{(Body Weight)}}$$

This formula relies on a TWA generated from the inhalation PHED assessment above (**Formula 12**) and an air dilution model (HouseModel).

Formula 15 - Post-application dermal exposure following the use of the pet care spray.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{S Area}) \times (\text{Cloth Penetration}) \times \text{Depos on Dog})\ ] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

The transferability of residues from dogs is unknown. Dermal exposure will be estimated using the Jazzercise data, but in a different way than used for the lawn and indoor surface treatments. Rather than use transfer factors derived from transferable residues, mean percent transfers will be used from the gauze fallout samples taken in the Ross data (1990). The percents represent ug/cm2 clothing per ug/cm2 fallout gauze. In the Ross (1990) study, the mean percent hand transfer factors were 22.4 percent. Its use in the formula is as follows: 0.224 x 0.00283 mg/cm2 (deposits on dog) and 396.5 cm2 (surface area of hands) = 0.251 mg. This assumption should overestimate exposure since the Jazzercise cohorts were presumably exposed to the majority of residues on the surface of the carpet. In a pet scenario, most of the residues will be under the lay of the fur.

The pet surface area was estimated assuming an 80 pound dog and body weight to surface area ratios reported in Klaassen *et al.* (1986). The surface area used is 11.300 cm2. This value is similar to one you could calculate for mammals, using Stahl (1967) as presented in EPA's Wildlife Exposure Factors Handbook. The dosage of 32 grams was used as an application rate to the dog and it assumes there was no overspray.

The human surface area exposed includes the hands and the upperbody (uncovered - 50% arms and covered 50% chest). For areas of the body covered by clothing, the PWG cite a clothing penetration rate of 0.49% from Snodgrass (1992). In the Snodrgass study permethrin penetration through cotton clothing was measured.

Formula 16 - Post-application, incidental oral exposure (hand-to-mouth).

$$\text{Dose} = \frac{(\text{Trans Fact hand}) \times (\text{S Area}) \times \text{Depos on Dog}) \times (\text{Corr Fact}) \times (\text{Hand-to-Mouth}) \times (\text{Oral Abs})}{(\text{Body Weight})}$$

This formula addresses the hand-to-mouth exposure as discussed in previous formulas. However it utilizes the same concept of transfer factors as percents as discussed in **Formula 15.**

ESFENVALERATE NON-DIETARY ASSESSMENT

Lawn Care Treatment - Adults

Adult post-application inhalation exposure to airborne aerosols following the lawn care application.

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

Concentration of surrogate (TWA) - 0.0066 mg/m3

Inhalation rate - 1.43 m3/hr

Concentration Corection Factor - 0.066

Pulmonary Absorption Factor - 1

Exposure Duration - 0.33 hr/day

Body Weight - 71.8 kg

Adult Inhalation Dose = 2.86E-06

Adult post application dermal exposure to transferable residues from the lawn treatment.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{Trans Res}) \times (\text{Surface Area})] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

Sum of the transfer factors x transferable residues x body surface area - 1.49 mg

Correction factor - 0.066

Dermal absorption - 0.25

Body weight - 71.8 kg

Adult Dermal Dose = 3.4E-04

Lawn Care Treatment - Children (1-6)

1 to 6 Year Old Child post-application inhalation exposure to airborne aerosols following the lawn care application.

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

Concentration of surrogate (TWA) - 0.0066 mg/m3

Inhalation rate - 0.93 m3/hr

Concentration Corection Factor - 0.066

Pulmonary Absorption Factor - 1

Exposure Duration - 0.33 hr/day

Body Weight - 18.9 kg

1 to 6 Year Old Child Inhalation Dose = 7.07E-06

1 to 6 Year Old Child post application dermal exposure to transferable residues from the lawn treatment.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{Trans Res}) \times (\text{Surface Area})] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

Sum of the transfer factors x transferable residues x body surface area - 0.741 mg

Correction factor - 0.066

Dermal absorption - 0.25

Body weight - 18.9 kg

1 to 6 Year Old Child Dermal Dose = 6.47E-04

1 to 6 Year Old Child Incidential Oral Ingestion exposure (hand to mouth), post application exposure to transferable residues from the lawn treatment.

$$\text{Dose} = \frac{(\text{Dermal Hand Exp}) \times (\text{Correction Factor}) \times (\text{Hand-to-Mouth Trans Factor}) \times (\text{Oral Absorption Frac})}{(\text{Body Weight})}$$

Daily dermal exposure to the hands - 0.2 mg

Hand-to-mouth transfer - 0.1

Oral Absorption Fraction - 1

Correction factor - 0.066

Body weight - 18.9 kg

1 to 6 Year Old Child Oral Dose = 7.01E-05

Lawn Care Treatment (infants <1)

<1 Year Old Child post-application inhalation exposure to airborne aerosols following the lawn care application.

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

Concentration of surrogate (TWA) - 0.0066 mg/m3

Inhalation rate - 0.69 m3/hr

Concentration Corection Factor - 0.066

Pulmonary Absorption Factor - 1

Exposure Duration - 0.33 hr/day

Body Weight - 11.3 kg

<1 Year Old Child Inhalation Dose = 8.78E-06

<1 Year Old Child post application dermal exposure to transferable residues from the lawn treatment.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{Trans Res}) \times (\text{Surface Area})] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

Sum of the transfer factors x transferable residues x body surface area - 0.459 mg

Correction factor - 0.066

Dermal absorption - 0.25

Body weight - 11.3 kg

<1 Year Old Child Dermal Dose = 6.70E-04

<1 Year Old Child Incidential Oral Ingestion exposure (hand to mouth), post application exposure to transferable residues from the lawn treatment.

$$\text{Dose} = \frac{(\text{Dermal Hand Exp}) \times (\text{Correction Factor}) \times (\text{Hand-to-Mouth Trans Factor}) \times (\text{Oral Absorption Frac})}{(\text{Body Weight})}$$

Daily dermal exposure to the hands - 0.128 mg

Hand-to-mouth transfer - 0.1

Oral Absorption Fraction - 1

Correction factor - 0.066

Body weight - 11.3 kg

<1 Year Old Child Oral Dose = 7.47E-05

Carpet Care - Adult Applicator Exposure

Adult Application Inhalation Exposure during application of hand-held carpet care spray.

$$\text{Dose} = \frac{\text{(Normalized Exp) x (Weight Fraction) x (Amount Used) x (Pulmonary Absorb) x (Use Frequency)}}{\text{(Body Weight)}}$$

Normalized exposure by amount used - 1.34 mg/kg

Weight fraction of AI in formulation - 0.0005

Amount of formulation used - 0.45 kg

Use frequency - 1

Pulmonary absorption factor - 1

Body weight - 71.8

Adult Applicator Inhalation Dose = 4.23E-06

Adult Application Dermal Exposure during application of hand-held carpet care spray.

$$\text{Dose} = \frac{\text{(Normalized Exp) x (Weight Fraction) x (Amount Used) x (Dermal Absorb) x (Use Frequency)}}{\text{(Body Weight)}}$$

Normalized exposure by amount used - 1056 mg/kg

Weight fraction of AI in formulation - 0.0005

Amount of formulation used - 0.45 kg

Use frequency - 1

Dermal absorption factor - 0.25

Body weight - 71.8

Adult Applicator Dermal Dose = 8.34E-06

Carpet Care - Adult Post-Application

Adult post-application inhalation exposure to airborne aerosols following the carpet care application.

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

Concentration of surrogate (TWA) - 0.00337 mg/m3

Inhalation rate - 0.71 m3/hr

Concentration Corection Factor - 0.05

Pulmonary Absorption Factor - 1

Exposure Duration - 8 hr/day

Body Weight - 71.8 kg

Adult Post-Application Inhalation Dose = 1.33E-05

Adult post application dermal exposure to transferable residues from the carpet care treatment.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{Trans Res}) \times (\text{Surface Area})] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

Sum of the transfer factors x transferable residues x body surface area - 0.25 mg

Correction factor - 2.13

Dermal absorption - 0.25

Body weight - 71.8 kg

Adult Post-Application Dermal Dose = 1.87E-03

Carpet Care - Children Post-Application

1 to 6 Year Old Child post-application inhalation exposure to airborne aerosols following the carpet care application.

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

Concentration of surrogate (TWA) - 0.00337 mg/m3

Inhalation rate - 0.47 m3/hr

Concentration Corection Factor - 0.05

Pulmonary Absorption Factor - 1

Exposure Duration - 8 hr/day

Body Weight - 18.9 kg

1 to 6 Year Old Child Inhalation Dose = 3.35E-05

1 to 6 Year Old Child post application dermal exposure to transferable residues from the carpet care treatment.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{Trans Res}) \times (\text{Surface Area})] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

Sum of the transfer factors x transferable residues x body surface area - 0.17 mg

Correction factor - 2.13

Dermal absorption - 0.25

Body weight - 18.9 kg

1 to 6 Year Old Child Dermal Dose = 4.8E-03

1 to 6 Year Old Child Incidential Oral Ingestion exposure (hand to mouth), post application exposure to transferable residues from the carpet care treatment.

$$\text{Dose} = \frac{\text{(Dermal Hand Exp) x (Correction Factor) x (Hand-to-Mouth Trans Factor) x (Oral Absorption Frac)}}{\text{(Body Weight)}}$$

Daily dermal exposure to the hands - 3.64E-02 mg

Hand-to-mouth transfer - 0.1

Oral Absorption Fraction - 1

Correction factor - 2.13

Body weight - 18.9 kg

1 to 6 Year Old Child Oral Dose = 4.11E-04

Carpet Care - Infants

<1 Year Old Child post-application inhalation exposure to airborne aerosols following the carpet care application.

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

Concentration of surrogate - 0.00337 mg/m3

Inhalation rate - 0.34 m3/hr

Concentration Corection Factor - 0.05

Pulmonary Absorption Factor - 1

Exposure Duration - 8 hr/day

Body Weight - 11.3 kg

<1 Year Old Child Inhalation Dose = 4.06E-05

<1 Year Old Child post application dermal exposure to transferable residues from the carpet care treatment.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{Trans Res}) \times (\text{Surface Area})] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

Sum of the transfer factors x transferable residues x body surface area - 0.112 mg

Correction factor - 2.13

Dermal absorption - 0.25

Body weight - 11.3 kg

<1 Year Old Child Dermal Dose = 5.28E-03

<1 Year Old Child Incidential Oral Ingestion exposure (hand to mouth), post application exposure to transferable residues from the carpet care treatment.

$$\text{Dose} = \frac{(\text{Dermal Hand Exp}) \times (\text{Correction Factor}) \times (\text{Hand-to-Mouth Trans Factor}) \times (\text{Oral Absorption Frac})}{(\text{Body Weight})}$$

Daily dermal exposure to the hands - 2.32E-02 mg

Hand-to-mouth transfer - 0.1

Oral Absorption Fraction - 1

Correction factor - 2.13

Body weight - 11.3 kg

<1 Year Old Child Oral Dose = 4.38E-05

Pet Care - Adult Applicator Exposure

Adult Application Inhalation Exposure during application of hand-held pet care spray.

$$\text{Dose} = \frac{\text{(Normalized Exp) x (Weight Fraction) x (Amount Used) x (Pulmonary Absorb) x (Use Frequency)}}{\text{(Body Weight)}}$$

Normalized exposure by amount used - 1.34 mg/kg

Weight fraction of AI in formulation - 0.0002

Amount of formulation used - 0.16 kg

Use frequency - 1

Pulmonary absorption factor - 1

Body weight - 71.8

Adult Applicator Inhalation Dose = 5.97E-07

Adult Applicator Dermal Exposure during application of hand-held pet spray.

$$\text{Dose} = \frac{\text{(Surface Area) x (Density) x (Film Thickness) x (Weight Fraction) x (Fraction Absorbed) x (Use Frequency)}}{\text{(Body Weight)}}$$

Skin surface area - 2983 cm2

Density of formulation - 800 mg/cm3

Film thickness of formulation on human skin - 0.002 cm

Weight fraction of AI in formulation - 0.002

Dermal absorption fraction - 0.25

Use frequency - 1

Body weight - 71.8

Adult Applicator Dermal Dose = 3.32E-03

Pet Care - Adult Post-Application

Adult Post-Application Inhalation exposure following the use of a pet care spray

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

Concentration of AI from(PHED), (TWA) - 0.00377 mg/m3

Inhalation rate - 0.71 m3/hr

Concentration correction factor - 0.00705

Pulmonary Absorption - 1

Exposure duration - 8 hr

Body weight - 71.8

Adult Post-Application Inhalation Dose = 2.10E-06

Adult Post-Application Dermal Exposure following the use of the pet care spray.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{S. Area}) \times (\text{Cloth Penetration}) \times \text{Depos on Dog})\ ] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

Sum (Transfer Factor x Surface Area x Clothing Penetration Factor) - 148.44 cm2

Deposition on dog - 0.0028 mg/cm2

Correction Factor - 1

Dermal absorption - 0.25

Body weight - 71.8

Adult Post Application Dermal Dose = 1.46E-03

Pet Care - Children

1 to 6 Year Old Post-Application Inhalation exposure following the use of a pet care spray

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

Concentration of AI (TWA) - 0.00377 mg/m3

Inhalation rate - 0.47 m3/hr

Concentration correction factor - 0.00705

Pulmonary Absorption - 1

Exposure duration - 8 hr

Body weight - 18.9 kg

1 to 6 Year Old Post-Application Inhalation Dose = 5.29E-06

1 to 6 Year Old Post-Application Dermal Exposure following the use of the pet care spray.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{S. Area}) \times (\text{Cloth Penetration}) \times (\text{Depos on Dog})] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

Sum (Transfer Factor x Surface Area x Clothing Penetration Factor) - 80.13 cm2

Deposition on dog - 0.0028 mg/cm2

Correction Factor - 1

Dermal absorption - 0.25

Body weight - 71.8

1 to 6 Year Old Post Application Dermal Dose = 3.00E-03

1 to 6 Year Old Child Incidential Oral Ingestion exposure (hand to mouth), post application exposure to transferable residues from the pet care treatment.

$$\text{Dose} = \frac{\text{(Hand Transfer Factor) x (Skin SA) x (Depo on Dog) x (Expo Cor Fact) x (Hand-to-Mouth) x (Oral Abs)}}{\text{(Body Weight)}}$$

Transfer Factor for hand (as fraction) - 0.224

Skin surface area - 226 cm2

Deposition on dog - 0.00283 mg/cm2

Correction factor - 1

Hand-to-mouth transfer fraction - 0.1

Oral absorption fraction - 1

Body weight - 18.9 kg

1 to 6 Year Old Child Oral (Hand-To-Mouth) Dose = 7.59E-04

Pet Care - Infants (<1 Year)

<1 Year Old Post-Application Inhalation exposure following the use of a pet care spray

$$\text{Dose} = \frac{(\text{Conc}) \times (\text{Inhalation Rate}) \times (\text{Conc Correction Factor}) \times (\text{Pulmonary Absorption}) \times (\text{Expo Duration})}{(\text{Body Weight})}$$

Concentration of AI (TWA) - 0.00377 mg/m3

Inhalation rate - 0.34 m3/hr

Concentration correction factor - 0.00705

Pulmonary Absorption - 1

Exposure duration - 8 hr

Body weight - 11.3 kg

<1 Year Old Post-Application Inhalation Dose = 6.40E-06

1 to 6 Year Old Post-Application Dermal Exposure following the use of the pet care spray.

$$\text{Dose} = \frac{\sum[(\text{Trans Fact}) \times (\text{S. Area}) \times (\text{Cloth Penetration}) \times \text{Depos on Dog})] \times (\text{Correction Factor}) \times (\text{Dermal Absorption})}{(\text{Body Weight})}$$

Sum (Transfer Factor x Surface Area x Clothing Penetration Factor) - 52.52 cm2

Deposition on dog - 0.0028 mg/cm2

Correction Factor - 1

Dermal absorption - 0.25

Body weight - 11.3 kg

<1 Year Old Post Application Dermal Dose = 3.25E-03

<1 Year Old Child Incidential Oral Ingestion exposure (hand to mouth), post application exposure to transferable residues from the pet care treatment.

$$\text{Dose} = \frac{\text{(Hand Transfer Factor) x (Skin SA) x (Depo on Dog) x (Expo Cor Fact) x (Hand-to-Mouth) x (Oral Abs)}}{\text{(Body Weight)}}$$

Transfer Factor for hand (as fraction) - 0.224

Skin surface area - 144 cm2

Deposition on dog - 0.00283 mg/cm2

Correction factor - 1

Hand-to-mouth transfer fraction - 0.1

Oral absorption fraction - 1

Body weight - 11.3 kg

<1 Year Old Child Oral (Hand-To-Mouth) Dose = 8.08E-04

Please note: The PWG only addressed the aggregate risk by presenting aggregate MOE's. Route specific MOE's are also presented in the following Exposure/MOE summaries.

SUMMARY EXPOSURE TABLE FOR ESFENVALERATE(mg/kg/day)
Lawn

Scenario	Individual	Inhalation	Dermal	Oral
Lawn Application	Adult	not conducted	not conducted	not conducted
Post-Application Lawn	Adult	2.86E-06	3.42E-04	not conducted
Post-Application Lawn	Child (1-6)	7.07E-06	6.47E-04	7.01E-05
Post-Application Lawn	Infant (<1)	8.78E-06	6.70E-04	7.47E-05

Endpoints for risk assessment:

Short and intermediate term dermal exposure - 2 mg/kg/day;
The respective dermal MOE's for adults, children and infants are 5,900, 3,100 and 3,000.

Systemic Oral - 2 mg/kg/day;

Aggregate inhalation and incidental oral.

Total Lawn Aggregate (inhalation + incidental oral)

Adult 2.86E-06 MOE = 700,000
Child 7.72E-05 MOE = 26,000
Infant 8.35E-05 MOE = 24,000

SUMMARY EXPOSURE TABLE FOR ESFENVALERATE (mg/kg/day)
Carpet

Scenario	Individual	Inhalation	Dermal	Oral
Carpet Application	Adult	4.23E-06	8.34E-04	not conducted
Post-Application Carpet	Adult	1.33E-05	1.78E-03	not conducted
Post-Application Carpet	Child (1-6)	3.35E-05	4.80E-03	4.11E-04
Post-Application Carpet	Infant (<1)	4.06E-05	5.31E-03	4.39E-04

The respective dermal MOE's for adults, children and infants are 740, 420 and 380.

Total Carpet Aggregate (inhalation + incidental oral)

Adult 1.76E-05 MOE = 110,000
Child 4.45E-04 MOE = 4,500
Infant4.79E-05 MOE = 4,200

SUMMARY EXPOSURE TABLE FOR ESFENVALERATE (mg/kg/day)
Pet

Scenario	Individual	Inhalation	Dermal	Oral
Pet Application	Adult	5.97E-07	3.32E-03	not conducted
Post-Application Pet	Adult	2.10E-06	1.46E-03	not conducted
Post-Application Pet	Child (1-6)	5.29E-06	3.00E-03	7.58E-04
Post-Application Pet	Infant (<1)	6.40E-06	3.29E-03	8.08E-04

The respective dermal MOE's for adults, children and infants are 420, 670 and 610.

Total Pet Aggregate (inhalation + incidental oral)

Adult 2.70E-06 MOE = 740,000
Child 7.64E-04 MOE = 2,600
Infant8.15E-05 MOE = 2,500

TOTAL AGGREGATE NON-DIETARY EXPOSURE INCLUDING LAWN, CARPET, AND PET USES (MG/KG/DAY)

Scenario	**Adult**	**Child (1-6)**	**Infant (<1)**
Lawn	2.86E-06	7.72E-05	8.35E-05
Carpet	1.76E-05	4.45E-04	4.79E-04
Pet Care	2.70E-06	7.64E-04	8.15E-04
Total	2.30E-05	1.29E-03	1.38E-03

SUMMARY EXPOSURE TABLE FOR DELTAMETHRIN/TRALOMETHRIN (mg/kg/day)
Lawn (expressed as deltamethrin equivalents)

Scenario	Individual	Inhalation	Dermal	Oral
Lawn Application	Adult	not conducted	not conducted	not conducted
Post-Application Lawn	Adult	6.00E-06	not conducted	not conducted
Post-Application Lawn	Child (1-6)	1.48E-05	not conducted	1.47E-04
Post-Application Lawn	Infant (<1)	1.84E-05	not conducted	1.56E-04

Endpoints for Risk Assessment:

Short and intermediate term dermal - none;

Systemic oral - 3.3 mg/kg/day (maternal);

Inhalation - 3 mg/m3; the MOE's for inhalation are 3,300.

Aggregate inhalation and incidential oral.

Total Lawn Aggregate (inhalation + incidental oral)

Adult 5.99E-06 MOE = 550,000
Child 1.62E-04 MOE = 20,000
Infant 1.75E-04 MOE = 19,000

SUMMARY EXPOSURE TABLE FOR DELTAMETHRIN/TRALOMETHRIN (mg/kg/day) Carpet (Expressed as Deltamethrin equivalents)

Scenario	Individual	Inhalation	Dermal	Oral
Carpet Application	Adult	3.22E-06	not conducted	not conducted
Post-Application Carpet	Adult	1.13E-05	not conducted	not conducted
Post-Application Carpet	Child (1-6)	2.85E-05	not conducted	3.13E-04
Post-Application Carpet	Infant (<1)	3.45E-05	not conducted	3.33E-04

The MOE's for inhalation are adults (16,000), children and infants (21,000).

Total Carpet Aggregate (inhalation + incidental oral)

Adult 1.46E-05 MOE = 230,000
Child 3.41E-04 MOE = 9,700
Infant3.68E-04 MOE = 9,000

TOTAL AGGREGATE NON-DIETARY EXPOSURE INCLUDING LAWN, AND CARPET USES (MG/KG/DAY) (Expressed as Deltamethrin Equivalents)

Scenario	**Adult**	**Child (1-6)**	**Infant (<1)**
Lawn	6.00E-06	1.62E-04	1.75E-04
Carpet	1.46E-05	3.41E-04	3.68E-04
Total	2.00E-05	5.03E-04	5.43E-04

SUMMARY EXPOSURE TABLE FOR LAMDA-CYHALOTHRIN (mg/kg/day)
Lawn

Scenario	Individual	Inhalation	Dermal	Oral
Lawn Application	Adult	not conducted	not conducted	not conducted
Post-Application Lawn	Adult	5.46E-06	6.52E-04	not conducted
Post-Application Lawn	Child (1-6)	1.35E-05	1.24E-03	1.34E-04
Post-Application Lawn	Infant (<1)	1.68E-05	1.28E-03	1.43E-04

Endpoints for Risk Assessment:

Short and intermediate term dermal - 10 mg/kg/day; the respective dermal MOE's for an adult, child and infant are 3800, 2000 and 1950.

Systemic oral - 10 mg/kg/day;

Inhalation - 0.3 mg/m3; the MOE's for and adult, child and infant are 365, 360 and 366.

Aggregate inhalation, dermal, incidental oral.

Total Lawn Aggregate (inhalation + dermal + incidental oral)

Adult	6.57E-04	MOE = 15,000
Child	1.39E-03	MOE = 7,200
Infant	1.44E-03	MOE = 7,000

SUMMARY EXPOSURE TABLE FOR BIFENTHRIN (mg/kg/day)
Lawn

Scenario	Individual	Inhalation	Dermal	Oral
Lawn Application	Adult	not conducted	not conducted	not conducted
Post-Application Lawn	Adult	1.94E-05	2.32E-03	not conducted
Post-Application Lawn	Child (1-6)	4.80E-05	4.39E-03	4.76E-04
Post-Application Lawn	Infant (<1)	5.96E-05	4.55E-03	5.07E-04

Endpoints for Risk Assessment:

Short and intermediate term dermal - 1 mg/kg/day (maternal);The dermal MOE for adults is 646.

Systemic oral - 1 mg/kg/day

Aggregate inhalation and incidental oral.

Total Lawn Aggregate (inhalation + incidental oral)

Adult 1.94E-05 MOE = 51,000
Child 5.24E-04 MOE = 1,900
Infant5.67E-04 MOE = 1,800

SUMMARY EXPOSURE TABLE FOR CYFLUTHRIN (mg/kg/day)
Lawn

Scenario	Individual	Inhalation	Dermal	Oral
Lawn Application	Adult	not conducted	not conducted	not conducted
Post-Application Lawn	Adult	1.16E-05	1.39E-03	not conducted
Post-Application Lawn	Child (1-6)	2.78E-05	2.63E-03	2.85E-04
Post-Application Lawn	Infant (<1)	3.56E-05	2.72E-03	3.03E-04

Endpoints for Risk Assessment:

Short and intermediate term dermal - 20 mg/kg/day (developmental); the dermal MOE for adults is 14,300.

Systemic oral - 20 mg/kg/day;

Inhalation - 0.44 mg/m3; the inhalation MOE's for adults, children and infants is 250.

Aggregate inhalation, dermal and incidental oral.

Total Lawn Aggregate (inhalation + dermal + incidental oral)

Adult 1.40E-03 MOE = 14,000
Child 2.94E-03 MOE = 6,800
Infant3.06E-03 MOE = 6,500

SUMMARY EXPOSURE TABLE FOR CYFLUTHRIN (mg/kg/day)
Carpet fogger

Scenario	Individual	Inhalation	Dermal	Oral
Carpet Application	Adult	not conducted	8.84E-03	not conducted
Post-Application Carpet	Adult	3.40E-05	1.63E-03	not conducted
Post-Application Carpet	Child (1-6)	8.56E-06	4.20E-03	3.60E-04
Post-Application Carpet	Infant (<1)	1.04E-05	4.65E-03	3.84E-04

The respective applicator and post-application dermal MOE's for adults are 2,260 and 12,300. The respective inhalation MOE's for adults, children and infants are 2600, 2600, and 2,500.

Total Carpet Aggregate (inhalation + dermal + incidental oral)

Adult 3.84E-03 MOE = 5,200
Child 4.57E-03 MOE = 4,400
Infant5.04E-03 MOE = 4,000

TOTAL AGGREGATE NON-DIETARY EXPOSURE INCLUDING LAWN, AND CARPET USES (MG/KG/DAY)

Scenario	**Adult**	**Child (1-6)**	**Infant (<1)**
Lawn	1.40E-03	2.94E-03	3.06E-03
Carpet	3.84E-03	4.57E-03	5.04E-03
Total	5.24E-03	7.51E-03	8.10E-03

The inhalation MOE (249) for children and infants for the lawn treatment is below the Agency's level of concern (300). The decision to regulate this compound with a MOE of 300 was decided on September 30, 1997. The LOEL for inhalation is an order of magnitude higher than the NOEL.

SUMMARY EXPOSURE TABLE FOR CYPERMETHRIN (mg/kg/day)
Lawn

Scenario	Individual	Inhalation	Dermal	Oral
Lawn Application	Adult	not conducted	not conducted	not conducted
Post-Application Lawn	Adult	3.09E-05	4.65E-03	not conducted
Post-Application Lawn	Child (1-6)	9.62E-05	8.81E-03	9.54E-04
Post-Application Lawn	Infant (<1)	1.19E-04	9.12E-03	1.02E-03

Endpoints for Risk Assessment:

Short and intermediate term dermal - 5 mg/kg/day; the respective dermal MOE's for adults, children and infants are 1,100, 570 and 550.

Inhalation - 10 mg/m3; the inhalation MOE's for adults, children and infants are 1,700.

Systemic oral - 5 mg/kg/day;

Aggregate inhalation and incidental oral.

Total Lawn Aggregate (inhalation + incidental oral)

85

Adult 3.90E-05 MOE = 130,000
Child 1.05E-03 MOE = 4,800
Infant1.14E-03 MOE = 4,400

SUMMARY EXPOSURE TABLE FOR CYPERMETHRIN (mg/kg/day)
Carpet fogger

Scenario	Individual	Inhalation	Dermal	Oral
Carpet Application	Adult	not conducted	3.79E-02	not conducted
Post-Application Carpet	Adult	1.25E-05	6.00E-03	not conducted
Post-Application Carpet	Child (1-6)	3.15E-05	1.54E-02	1.32E-03
Post-Application Carpet	Infant (<1)	3.81E-05	1.71E-02	1.41E-03

Total Carpet Aggregate (inhalation + incidental oral)

Adult 1.25E-05 MOE = 400,000
Child 1.36E-03 MOE = 3,700
Infant1.45E-03 MOE = 3,500

The dermal MOE's for adult applicators and post-application exposure are 130 and 830 respectively. The respective dermal MOE's for children and infants are 330 and 300.

The inhalation MOE's for adults, children and infants are 16,800.

TOTAL AGGREGATE NON-DIETARY EXPOSURE INCLUDING LAWN, AND CARPET USES (MG/KG/DAY)

Scenario	Adult	Child (1-6)	Infant (<1)

Lawn	3.90E-05	1.05E-03	1.14E-03
Carpet	1.25E-05	1.36E-03	1.45E-03
Total	5.15E-05	2.41E-03	2.59E-03

Attachment 6

Bifenthrin

Toxicology and Residue Chemistry Details

Bifenthrin

1. Hazard Assessment

a. Acute Toxicity

Acute Toxicity of Bifenthrin

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral Acceptable	Accession # 251726	LD_{50} (M): 70.1 mg/kg (F): 53.8 mg/kg	II
81-2	Acute Dermal - rabbits Acceptable	Accession # 251726	LD_{50} (M&F) > 2000 mg/kg	III
81-3	Acute Inhalation Study not available on technical			II
81-4	Primary Eye Irritation Acceptable	Accession # 251726	Not an eye irritant	IV
81-5	Primary Dermal Irritation Acceptable	Accession # 251726	Non-irritating.	IV
81-6	Dermal Sensitization Acceptable	Accession # 251726	Not a sensitizer	N/A
81-7	Acute Delayed Neurotoxicity Supplementary	Accession: 254405	5000 mg/kg given on days 0 & 21. Unsteadiness, jerking head movements after 1st dose. 2nd dose: violoent movements of head & legs, unable to stand, weight loss. No histological evidence of delayed neurotox., however hens that died were not examined.	N/A

b. Subchronic Toxicity

<u>90-day feeding study in rats</u>

In an oral toxicity study in rats (MRID 00141199), bifenthrin (91.4% a.i.) was administered for 90 days in the diet to Sprague-Dawley rats (15/sex/dose) at dose levels of 0, 12, 50, 100, and 200 ppm (calculated by the reviewer to be equivalent to 0, 0.6, 2.5, 5, or 10 mg/kg/day). An additional 10 rats/sex were administered the diet containing bifenthrin at 0 or 10 mg/kg/day for 90 days, and then fed a recovery (control) diet for an additional 28 days. There was no mortality during the study. There were no

90

treatment-related changes noted in hematological, organ weight, and gross and microscopic data. In addition, there were no ophthalmological changes observed that were related to dietary levels of bifenthrin. Tremors were noted during the first 2 weeks of the study at 5 mg/kg/day and throughout the study at 10 mg/kg/day. At 10 mg/kg/day, the tremors were reversible within 3 days after discontinuation of dosing. Body weight gains were decreased at 10 mg/kg/day in both males and females relative to controls, although the changes were not statistically significant. Food consumption for males at 5 mg/kg/day was increased significantly during weeks 1 to 3. Serum potassium levels were significantly lower (6%, $p \leq 0.05$) in males at 2.5-10 mg/kg/day relative to controls. Females at 10 mg/kg/day had significantly higher serum potassium (↑6%, $p \leq 0.05$) and calcium (data not submitted) levels relative to controls. The LOEL for this 90-day study is 5 mg/kg/day based on the increased incidence of tremors in both sexes. The NOEL is 2.5 mg/kg/day. This 90-day toxicity study in rats is classified core minimum.

13-week feeding study in dogs

In an oral toxicity study in dogs (MRID 00141200), bifenthrin (88.35% a.i.) was administered via capsule to beagle dogs (4/sex/dose) at nominal dose levels of 0, 2.5, 5, 10, or 20 mg/kg/day (equivalent to 2.21, 4.42, 8.84, and 17.7 mg/kg/day, based on % a.i.) for 13 weeks. There was no mortality during the study. There were no treatment-related changes noted in food consumption, hematology, clinical chemistry, organ weight, gross or microscopic parameters. In addition, there were no treatment-related ophthalmological changes. Tremors were noted in 3 dogs/sex at 4.42 mg/kg/day and in 4/sex at 8.84 and 17.7 mg/kg/day. Ataxia was noted in 4/sex at 8.84 and 17.7 mg/kg/day and in one female at 4.42 mg/kg/day. Languidness occurred primarily at 17.7 mg/kg/day in both sexes, but also occasionally at 8.84 mg/kg/day. All of these symptoms occurred more frequently during the last 3 weeks of the study. Other dose-related clinical signs included blinking, mydriasis, nystagmus, lacrimation, and polypnea. One high-dose female appeared thin and/or dehydrated during the final weeks of the study. A non-statistically significant, but possibly treatment-related reduction in body weight gain was noted in females at 17.7 mg/kg/day (0.6 kg) relative to the controls (1.3 kg). None of the females at 8.84 or 17.7 mg/kg/day showed cyclic activity or signs of estrus, but cyclic activity was observed in 2, 2, and 1 female at 0, 2.21, and 4.42 mg/kg/day, respectively and 4/5 showed signs of estrus. The LOEL for this 13-week study is 4.42 mg/kg/day based on the increased incidence of tremors in both sexes. The NOEL is 2.21 mg/kg/day. This 13-week toxicity study is classified core minimum.

21-day dermal study in rabbits

In a repeated dose dermal toxicity study in rabbits (MRID 00141198), bifenthrin (88.35% a.i.) was administered by dermal application to the shaved dorsal trunk area of New Zealand White rabbits (6/sex/dose) at dose levels of 0, 25, 50, 100, or 500 mg/kg/day) for 21 days. There were no treatment-related differences in body weights, food consumption, hematology, clinical chemistry, and gross and microscopic pathology. Tremors were noted in 3/6 males and 2/6 females at 500 mg/kg/day. Tremors were also noted in 1/6 females at 100 mg/kg/day, on the day this animal died after presumably ingesting the test substance. Loss of muscle coordination was noted in all males and

91

females at 500 mg/kg/day. This toxic sign appeared as early a 2 days after dosing began and persisted to the end of the study period. The systemic LOEL is 500 mg/kg/day based on the loss of muscle coordination in both sexes. The systemic NOEL is 100 mg/kg/day. This 21-day dermal toxicity study in rabbits is classified core minimum.

c. Chronic Toxicity/Carcinogenicity

52-week feeding study in dogs

In an oral toxicity study (MRID 00163065), bifenthrin (88.35% a.i.) was administered for 52 weeks via capsule to beagle dogs (4/sex/dose) at dose levels of 0, 0.75, 1.5, 3, or 5 mg/kg/day. No mortality occurred during the study and there were no treatment-related effects on body weight, food consumption, organ weights, and gross or microscopic pathology. In addition, there were no treatment-related ophthalmological changes. Tremors were noted in all males and females at 5 mg/kg/day during weeks 15-29 and in 1/4 males and 2/4 females at 3 mg/kg/day during weeks 16-23. A significant increase in platelets was noted at 52 weeks in 5 mg/kg/day males. Serum sodium levels were significantly increased in males at 3 and 5 mg/kg/day and serum chloride was increased in males at 5 mg/kg/day. The LOEL for this 52-week study is 3 mg/kg/day based on the increased incidence of tremors in both sexes. The NOEL is 1.5 mg/kg/day. This 52-week toxicity study is classified core minimum.

Chronic/carcinogenicity study in mice

In a chronic/carcinogenicity study (MRID 00157227), bifenthrin (88.35% a.i.) was administered in the diet to Swiss-Webster, Tac(SW)fBR mice (50/sex/dose) at dose levels of 0, 50, 200, 500, or 600 ppm (calculated by the reviewer to be equivalent to 0, 2.5, 10, 25, or 30 mg/kg/day) for 87 weeks (males) or 92 weeks (females). There were no treatment-related differences in survival. Tremors were noted in all males and females at 25 and 30 mg/kg/day during the first 3 months of the study. Tremors were also noted in 2 males and 2 females at 10 mg/kg/day and in 1 male at 2.5 mg/kg/day. However, tremors in the 2.5 mg/kg/day male occurred late in the study and this animal died soon after with fluid detected in the lungs. A statistically significant increased trend ($p=0.054$) for hemangiopericytomas (originally reported as leiomyosarcomas) of the urinary bladder was noted in males. Combined bronchioalveolar adenomas and adenocarcinomas were increased in dosed females, with statistically significant ($p<0.05$) increases at 2.5, 10, and 30 mg/kg/day. Males had a significant dose-related increasing trend ($p=0.022$) in combined hepatocellular adenomas and adenocarcinomas. Males and females at 30 mg/kg/day had slight increases in glandular hyperplasias of the stomach and retinal atrophy, and males in this group also had an increased incidence in cortical atrophy of the adrenal gland. Males at 2.5, 10, and 30 mg/kg/day also had significantly ($p\leq0.05$) increased incidences of bilateral germinal epithelial degeneration of the testes. The chronic LOEL is 10 mg/kg/day based on the incidence of tremors in both sexes. The chronic NOEL is 2.5 mg/kg/day. Carcinogenic potential was evidenced by a statistically significant increased trend for hemangiopericytomas in the urinary bladders of males, a significant dose-related trend for combined hepatocellular adenomas and carcinomas in males, and a significantly higher incidence of combined

lung adenomas and carcinomas in females. This chronic/carcinogenicity study in mice is classified core minimum for both chronic toxicity and carcinogenicity.

Chronic/carcinogenicity study in rats

In a chronic/carcinogenicity study (MRID 00157226), bifenthrin (88.35% a.i.) was administered for 734 days in the diet to Sprague-Dawley rats (50/sex/dose) at dose levels of 0, 12, 50, 100, or 200 ppm (calculated by reviewer to be equivalent to 0, 0.6, 2.5, 5, or 10 mg/kg/day). There were no treatment-related differences in survival. Tremors were noted in all males at 10 mg/kg/day during days 4-28 and in all females at 10 mg/kg/day during days 4-30. Body weights of females at 10 mg/kg/day were significantly lower (↓8-10%, $p<0.05$ or 0.01) during weeks 13-96. Males at 10 mg/kg/day had higher, although not statistically significant, mean liver (↑11%) and kidney (↑28%) weights at 24 months. Males and females at 10 mg/kg/day and males at 5 mg/kg/day also had higher, although not statistically significant, liver and kidney organ-to-body weight ratios. Three of 28 females at 10 mg/kg/day had retinal atrophy compared with 0/40 controls. The incidences of pancreatic cell adenoma and fibrosarcoma in males at 10 mg/kg/day were increased (3/50 vs 1/47 for the controls, and 3/50 vs 0/50 vs the controls, respectively), but statistical significance was not achieved and historical control data indicated that these are not rare tumors in this strain. The chronic LOEL is 5 mg/kg/day based on the increased incidence of tremors in both sexes and possible increases in organ-to-body weight ratios in males. The chronic NOEL is 2.5 mg/kg/day. Under the conditions of this study, there was no evidence of carcinogenic potential. This chronic/carcinogenicity study in rats is classified core minimum for both chronic toxicity and carcinogenicity.

d. Developmental Toxicity

Pilot developmental study in rats

In a pilot developmental study (MRID 00154482), bifenthrin (88.35% a.i.) in corn oil was administered via gavage to mated female Sprague-Dawley rats (10/sex/dose) at dose levels of 0, 0.5, 1.0, 2.0, or 2.5 mg/kg/day during days 6-15 of gestation. Three of 10 rats at 2.5 mg/kg/day died on days 14-15. Tremors were noted in all 10 rats at 2.5 mg/kg/day and in 9/10 at 2.0 mg/kg/day. Mean body weight gains were depressed at 2.5 mg/kg/day throughout the study, and food consumption was lower (↓20%) at this dose level during days 6-13. There were no differences in mean body weight gains or food consumption in the lower dose groups with respect to the controls. There were no treatment-related differences from controls in the number of implantations or litter size. The mean number of resorptions was similar in the lower dose groups; at 2.5 mg/kg/day it was somewhat higher, but this was attributable to an excessive number of resorptions in a single rat. The maternal LOEL is 2.0 mg/kg/day based on sporadic tremors (gestation days 7-18) and 30% mortality at 2.5 mg/kg/day. The maternal NOEL is 1.0 mg/kg/day. The developmental LOEL and NOEL were not determined; fetuses were not examined. This pilot developmental study is classified core supple

Developmental study in rats

In a developmental study in rats (MRID 00141201), bifenthrin (88.35% a.i.) in corn oil was administered via gavage to pregnant female Sprague-Dawley rats (25/dose) at dose levels of 0, 0.5, 1.0, or 2.0 mg/kg/day or with 250 mg/kg/day aspirin (positive control) in 2% carboxymethylcellulose during days 6-15 of gestation. Maternal toxicity was characterized as tremors in 18/25 dams at 2.0 mg/kg/day during days 10-19. There were no deaths during the study, and no significant differences between groups or dose-related trends with respect to mean maternal body weight gains or food consumption were noted. The maternal LOEL is 2.0 mg/kg/day based on the incidence of tremors. The maternal NOEL is 1.0 mg/kg/day. Developmental toxicity was noted at 2.0 mg/kg/day and was characterized as an increased fetal and litter incidence of hydroureter. Although not statistically significant, the incidence of hydroureter was double that of the vehicle control and the lower dose groups. Also, 5 fetuses from dams at 2.0 mg/kg/day had hydroureter without hydronephrosis, a finding which was not present in controls or any of the other exposure groups. There were no other treatment-related malformations or variations noted at any dose level. There were no group differences or dose-related trends with respect to pregnancy rates, numbers of corpora lutea, implantation sites and resorptions, litter sizes, sex ratios, fetal body weights, or viability. The positive control gave the appropriate responses of increased early resorptions, depressed fetal body weights, external, visceral, and skeletal malformations and variations. The developmental LOEL is 2.0 mg/kg/day based on the increased fetal and litter incidence of hydroureter. The developmental NOEL is 1.0 mg/kg/day. This developmental study is classified core guideline.

Developmental study in rabbits

In a developmental study (MRID 00145997), bifenthrin (88.35% a.i.) in corn oil was administered via gavage to pregnant female New Zealand White rabbits (20/dose) at dose levels of 0, 2.67, 4.0, or 8.0 mg/kg/day or with 3.0 g/kg/day 6-aminonicotinamide (positive control) in 2% carboxymethylcellulose via IP injection during days 7-19 of gestation. Maternal toxicity was characterized at 8.0 mg/kg/day as tremors in 17/20 rabbits and twitching of the head and forelimb in 14/20 rabbits. At 4.0 mg/kg/day head and forelimb twitching was noted in 4/20 rabbits. There were no treatment-related differences in mean body weight gains in the does or pregnancy rates. There were no treatment-related deaths in the does; however, 10 rabbits died during the study and 9 of these deaths (including 3 vehicle control animals) were attributed to Pasteurella multocida. There were no gross or microscopic findings attributable to exposure to the test material. The maternal LOEL is 4.0 mg/kg/day based on the treatment-related incidence of head and forelimb twitching. The maternal NOEL is 2.67 mg/kg/day. There was no developmental toxicity demonstrated at any dose level. There were no treatment-related effects on the number of live fetuses, fetal weights, implantations, resorptions, external, visceral or skeletal malformations and variations. The positive control gave the appropriate responses of increased early resorptions, reduced number of live fetuses, increased external, visceral, and skeletal malformations and variations. A developmental LOEL was not observed. The developmental NOEL is ≥8.0 mg/kg/day. This developmental study is classified core minimum.

e. Reproductive Toxicity

2-generation reproduction study in rats

In a 2-generation study (MRID 00157225), liquified bifenthrin (88.35% a.i.) mixed with acetone was administered in the diet to TAC(SD)fBR rats (25/sex/dose) at dose levels of 0, 30, 60, or 100 ppm (calculated by the reviewer to be equivalent to 0, 1.5, 3 or 5 mg/kg/day). For the P generation, dosing began 8 weeks prior to mating and for the F_1 generation, 11 weeks prior to mating. P generation animals were bred twice and F_1 parental animals were selected from the F_1b pups. There was no treatment-related mortality in either the P or F_1 generation. Tremors were noted only in females of both generations at 5 mg/kg/day with one P generation rat observed to have clonic convulsions. The tremors occurred during days 9-35 following delivery in the P generation and during days 3-35 following delivery in the F_1 generation. Premating body weights were comparable to the controls for both sexes of both generations at all dose levels. P generation females at 5 mg/kg/day had lower mean body weights (↓4%, $p<0.05$) at week 17 (after gestation and lactation), and lower body weight gains during the second gestation and lactation periods (statistically significant only on lactation day 14, ↓5%, $p<0.01$). Similar results were noted for the F_1 generation. There was no correlation between lower body weight and frequency of tremors. Lower body weights in females at 3 mg/kg/day (although not statistically significant) frequently paralleled body weight depression at 5 mg/kg/day. There were no clinical signs or effects on body weight at 1.5 mg/kg/day. Mean absolute ovary weights were decreased (↓9%, $p<0.05$ or ↓12%, $p<0.01$) at 3 and 5 mg/kg/day, respectively, in the F_1 parental generation; however, ovary-to body-weight ratios were unaffected. There were no treatment-

related effects on reproductive parameters or fetal toxicity, and there were no treatment-related gross or microscopic findings in either sex. The original DER, dated January 31, 1986, states that the LOEL is 3 mg/kg/day, based on dose-related lower body weights in P_1 and F_1 females during the first and second lactation periods, as well as for the second gestation, and significantly decreased mean absolute ovarian weights in F_1 females at 3 and 5 mg/kg/day. However, none of the differences in body weights shown at 3 mg/kg/day were statistically significant. In addition, the pre-mating body weights wee comparable to the controls at all dose levels. The differences noted in body weights at the high dose were small (↓2-5% from controls) and only occasionally statistically significant. A range-finding study summarized in the DER indicates that excessive fetotoxicity occurred at 10 mg/kg/day (all pups from 2 of the 4 litters at 10 mg/kg/day died within 14 days of birth) and body weight gains were decreased during lactation at 2.5, 5, and 10 mg/kg/day. The 2-generation rat study indicates that systemic toxicity occurred at 5 mg/kg/day as demonstrated by tremors and slightly lowered body weights during lactation and gestation. Overt systemic toxicity was not demonstrated at 3 mg/kg/day. The systemic LOEL is 5 mg/kg/day based on the incidence of tremors and marginally lower body weights in P and F_1 generation females during gestation and lactation. The systemic NOEL is 3 mg/kg/day. A reproductive LOEL was not observed. The reproductive NOEL is 5 mg/kg/day. This 2-generation reproduction study is classified core minimum.

f. Mutagenicity

The submitted studies satisfy both the pre-1991 and the new mutagenicity test batteries. No further testing is required at this time. Bifenthrin was tested in 8 acceptable mutagenicity assays; a Salmonella typhimurium reverse gene mutation assay, a mouse lymphoma forward gene mutation assay (HGPRT locus), a mouse lymphoma $TK^{\pm}$ assay, a CHO/HGPRT assay, an in vitro chromosomal aberration assay in CHO cells, a rat bone marrow cytogenetic assay, and 2 unscheduled DNA synthesis assays in primary rat hepatocytes. Bifenthrin tests positively both with and without metabolic activation in the mouse lymphoma forward gene mutation assay ($TK^{\pm}$). There is also presumptive evidence that bifenthrin is mutagenic with metabolic activation in the CHO gene mutation assay. However, this study appears to be unacceptable at this time. All the other studies tested negatively.

g. Metabolism

A number of metabolism studies have been reviewed. The following summarizes the results from all the studies. Some of the studies were graded as supplementary, some were acceptable. When rats were administered either 3.9 mg/kg or 7.0 mg/kg, absorption from the GI tract was very slow with a half-life of 1.5 hours with ½ hour lagtime. The low dose follows with first order kinetics while the high dose exceeds it. When 5 mg/kg was adminstered, nearly all the radioactivity was excreted by 7 days. When rats are administered either 4 or 35 mg/kg, the metabolic route appears to be hydrolysis of the ester linkage with oxidation of the resulting alcohol to the acid. Protein binding of the radioactive components appears to increase with time. When the carbons are labelled in either the acid or the alcohol positions, $^{14}C\text{-}CO_2$ accounts for very little of the total radioactivity recovered. Approximately 70% of the dose is recovered in the feces, with 20% recovered in the urine. There is very little breakage of the ester

96

linkage of the parent compound. The majority of the radioactivity in the feces was the parent and its intact hydroxylated metabolites. Much of the radioactivity excreted in the urine was hydrolytic and hydrolytic/oxidative degradation product of the parent. When 0.5 mg/kg was administered, significant bioaccumulation occurs in tissues with high fat content such as skin. The half-lives in these tissues are approximately 50 days. Metabolites in the fat were identified. After administration of 5 mg/kg, major deposits of radioactivity after 7 days are skin and fat in males and females and gonads in females.

h. Neurotoxicity

No neurotoxicity studies are available.

i. Dermal Absorption

In a dermal absorption study, the following doses of ^{14}C bifenthrin were administered dermally in aqueous suspension: 49.2, 514 or 5253 μg/rat. Bifenthrin is rapidly absorbed into and through the skin, with a direct correlation between the doses applied and the amount absorbed. Most of the label was recovered within the skin at the application site. Average amounts of activity absorbed at the skin site for each of the doses at the 0.5 hour sacrifice were 54.47%, 56.42% and 52.54%; and at the 24 hour sacrifice were 71.34%, 45.33% and 53.63%.

j. Other Toxicological Considerations (special studies)

No special studies are available.

2. Dose/Response Assessment

a. Reference Dose (RfD)

The RfD value has been established at 0.015 mg/kg/day based on a 1-year oral study in the dog with a NOEL of 1.5 mg/kg/day and an uncertainty factor of 100. The LEL of 3 mg/kg/day was based on intermittent tremors. In this study, the dogs were administered bifenthrin in capsules at 0, 0.75, 1.5, 3.0 or 5.0 mg/kg/day for 52 weeks. Tremors were intermittant in one male and 2 females at 3.0 mg/kg/day between weeks 15 and 23. All of the high dose group dogs displayed tremors between weeks 15 and 29. Males appeared to be more sensitive. The tremors did not persist after week 29. The maternal and developmental NOELs in the rat developmental study are lower than the NOEL chosen to establish the RfD. However, it was concluded that the RfD is sufficiently low to account for developmental effects (RfD Committee 11/06/8

b. Carcinogenic Classification and Risk Quantification

Bifenthrin has been classified as a group C with Q* carcinogen by the Cancer Peer Review Committee based on urinary bladder tumors in male mice (5/3/90). The Q_1^* is 5.4×10^{-2} mg/kg/day in human equivalents.

c. Developmental Concerns

97

Bifenthrin is not considered to be a developmental toxicant. In the rat developmental study, the maternal and developmental NOELs are equivalent at 1 mg/kg/day. Maternal toxicity (tremors) and developmental toxicity (increased incidence of hydroureter) were observed at 2 mg/kg/day (highest dose tested). In rabbits, there was no evidence of developmental toxicity up to and including the highest dose tested (8 mg/kg/day). Head and forelimb twitching was observed in does at 4.0 mg/kg/day. The maternal NOEL was established at 2.67 mg/kg/day. In the two-generation reproduction study in rats, no evidence of toxicity was observed in the offspring at dietary levels up to 5 mg/kg/day. Parental toxicity (decreased body weights and decreased ovarian weights) was observed at 3 and 5 mg/kg/day with a NOEL of 1.5 mg/kg/day.

98

d. Determination of Safety for Infants and Children

An acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits have been submitted to the Agency, meeting basic data requirements. There are no data gaps for the assessment of the effects of bifentrhin following *in utero* or early postnatal exposure. The data demonstrated no indication of increased sensitivity of rats or rabbits *in utero* and/or postnatal exposure. Based on these considerations, the Hazard ID Committee (7/24/97) determined that the 10x factor to account for enchanced sensitivity of infants and children (as required by FQPA) should be removed.

e. Dermal Absorption

The TES Committee (4/16/96, no official memo) did not use the dermal penetration value of 71% from the available rat dermal absorption study (MRID # 00264639) due to the absence of report details regarding the percent of internally absorbed dose. A comparison of the rat oral LD_{50} of 70 mg/kg for males (MRID # 00251726) and the rabbit dermal LD_{50} of >= 2000 mg/kg (MRID # 00251726) provided an apparent dermal penetration estimate of 4% for bifenthrin. Discussion of this issue with the Hazard ID Committee on 7/24/97 led to the weight-of-the-evidence decision that a dermal penetration value of 25% (similar to other pyrethroids) should be employed for worker MOE calculations. The dermal absorption rate of 25% was selected based on the 6-45% dermal absorption observed with the structurally related pyrethroids permethrin (22-45%), deltamethrin (15%) and tralomethrin (6-25%). A range of dermal absorption factors were presented for permethrin and tralomethrin because the studies indicated higher absorption at lower exposure doses but not for deltamethrin.

f. Other Toxicological Endpoints

i. Acute Dietary

The TES Committee on 4/16/96 recommended the maternal NOEL value of 1 mg/kg/day from the oral developmental toxicity study in rats (MRID # 00254409). The maternal LEL of 2 mg/kg/day was based on tremors from gestation day 7-17 of dosing (observed at this dose level in the pilot study). In comparison to the other studies, tremors were observed at the earliest time period with the lowest dose level in this study. An MOE of 100 was recommended.

ii. Short and Intermediate Term Occupational and Residential

For the dermal endpoint, the TES Committee again recommended the maternal NOEL value of 1 mg/kg/day from the oral developmental study in rats (MRID # 00254409). The maternal LEL of 2 mg/kg/day was based on tremors from gestation day 7-17 of dosing (observed at this dose level in the pilot study). In comparison to the other studies, tremors were observed at the earliest time period with the lowest dose level in this study. An estimated dermal absorption factor of 25% will be used. An MOE of 100 was recommended.

A 21-day dermal study in rabbits is available in which they were dermally exposed to 0, 25, 50, 100, 500 mg/kg, 6 hrs/day for 21 days. The systemic NOEL = 100 mg/kg/day and the systemic LEL= 500 mg/kg/day (tremors (day 19) and loss of muscle control (starting at day 2)). Erythema was observed in both sexes at all dose levels. The 21-day dermal study in the rabbit was not used because the rat is considered to be more sensitive than the rabbit based on a comparison of the maternal NOELs and LELs in the developmental studies. The maternal NOEL for the rat developmental study is 1 mg/kg/day and the maternal LEL is 2 mg/kg/day based on tremors from gestation day 7-17 of dosing. In the rabbit developmental toxicity study, the maternal NOEL is 2.67 mg/kg/day and the maternal LEL is 4.0 mg/kg/day based on head and forelimb twitching in 4/20 animals.

For the inhalation endpoint, the Hazard ID Committee (7/24/97) found that no appropriate studies were available. They determined that the risk assessment should be inclusive of oral & inhalation exposure components assuming 100% absorption via the inhalation route. An aggregate oral and inhalation risk assessment is appropriate due to the similarity in the toxicity endpoint (neurotoxicity) seen in rats via these routes. The inhalation study used for comparison purposes was an acute toxicity study in rats on the 25.1% formulation where tremors, convulsions and loss of hindlimb motor control was observed among other clinical signs of toxicity.

iii. Chronic Occupational and Residential (Non-Cancer)

For chronic dermal occupational and residential exposure, the Hazard ID Committee (7/24/97) recommended the NOEL of 1.5 mg/kg/day from the chronic oral study in the dog with a dermal absorption rate of 25%. The LEL for the dog study was 3.0 mg/kg/day based on intermittent tremors. The recommended MOE is 100.

For the inhalation endpoint, again, the Hazard ID Committee (7/24/97) found that no appropriate studies were available. They determined that the risk assessment should be inclusive of oral & inhalation exposure components assuming 100% absorption via the inhalation route. An aggregate oral and inhalation risk assessment is appropriate due to the similarity in the toxicity endpoint (neurotoxicity) seen in rats via these routes. The inhalation study used for comparison purposes was an acute toxicity study in rats on the 25.1%

100

formulation where tremors, convulsions and loss of hindlimb motor control was observed among other clinical signs of toxicity.

TABLE x. Summary of Toxicological Endpoints for Bifenthrin

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Acute	Dietary	NOEL: 1.0 mg/kg/day (tremors in dams during & post dosing in rat developmental study) MOE = 100
Short-Term (1-7 days) Occupational/Residential	Dermal [Inhalation]	NOEL: 1.0 mg/kg/day (tremors in dams during & post dosing in rat developmental study) Dermal absorption rate: 25%. MOE = 100
Intermediate-Term (one week to several months) Occupational/Residential	Dermal [Inhalation]	NOEL: 1.0 mg/kg/day (tremors in dams during & post dosing in rat developmental study) Dermal absorption rate: 25%. MOE = 100
[All time periods]	[Inhalation]	Oral NOEL: 1.0 mg/kg/day. No appropriate studies available. Risk assessment should be inclusive of oral & inhalation exposure components (100% absorption).
Cancer	Dietary/Dermal/Inhalation	Q with Q*. Urinary bladder tumors in mice.
Chronic (non-cancer)	Dietary	RFD: 0.015 mg/kg/day based on NOEL of 1.5 mg/kg/day (tremors in M&F dogs in chronic oral study). UF=100.

102

2. Dietary Exposure

Background

Tolerances have been established under 40 CFR 180.442 for residues of bifenthrin, [2-methyl-(1,1'-biphenyl)-3-yl]methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropane-carboxylate in numerous plant commodities with tolerances ranging from 0.05 to 10.0 ppm; in the fat of cattle, goats, hogs, horses, and sheep at 1.0 ppm; in the meat of cattle, goats, hogs, horses, and sheep at 0.5 ppm; in the meat byproducts of cattle, goats, hogs, horses, and sheep at 0.1 ppm; milkfat at 1.0 ppm (reflecting 0.1 ppm in whole milk); and poultry fat, meat, meat byproducts, and eggs at 0.05 ppm. No food/feed additive tolerances have been established for bifenthrin.

Product Chemistry

The manufacturing process for technical bifenthrin has been detailed in PP#5G3201 (R. Loranger, 6/4/85). Technical bifenthrin is 90% pure. Residue problems with impurities in the technical product are not expected (PP#6F3454, R. Loranger, 4/1/89).

Nature of the Residue

Nature of the residue studies in corn, ruminants and poultry for bifenthrin have been previously submitted and reviewed. In a meeting held on 7/27/93, the HED Metabolism Committee concluded that only the parent compound should appear in the tolerance expression for corn grain, forage, fodder and ruminant and poultry commodities. No special concern was expressed about the principal metabolite in corn, 4'-hydroxy bifenthrin. The metabolite typically is found in corn forage or fodder at about one-tenth the concentration of parent and is also a rat metabolite of bifenthrin. Similarly, no concern was raised over biphenyl alcohol, the only metabolite predicted to be present in ruminant tissue in detectable concentrations. CBTS estimated that the maximum concentration of this metabolite in ruminant tissue would be 0.04 ppm in fat. Neither bifenthrin nor its metabolites are likely to be present in poultry and eggs in detectable concentrations.

Analytical Methods

An enforcement method (GLC/ECD) for the determination of residues of bifenthrin in cottonseed has been sent to the FDA for inclusion in PAM II (see our correspondence of 7/31/89, to A. Marcotte, FDA from C. Deyrup, EPA, PP#6F3453). Additionally, CBTS has recently concluded that another method (Method P-2550M, GLC/ECD/large bore fused silica column) is suitable as an enforcement method for the determination of bifenthrin residues in corn matrices (see our memo of 03/07/96, W.D. Wassell, PP#7F3546).

The petitioner has previously submitted data concerning the recovery of bifenthrin residues by the FDA Multiresidue Methods of PAM I (see our memo of 2/1/93, M. Flood, PP#7F3546). Residues of bifenthrin are recoverable under Protocols D and E of the methods.

Magnitude of the Residue

103

A report entitled "Revisions to Dietary Exposure Analyses for Bifenthrin" (Report by Judith L. Kidwell at Novagen Sciences, Inc., dated 10/10/97, MRID# not yet available) contains revisions to the originally submitted report: "Dietary Exposure and Risk Assessment for Bifenthrin Residues in/on Artichokes, Cotton, Field Corn, Hops, Strawberries, Brassica (Head and Stem) Vegetables, Cucurbits, Canola, and Raspberries" (Report by Judith L. Kidwell at Novagen Sciences, Inc., dated 8/15/97, MRID# 443532-04). The 10/10/97 report contains a list of all residue values used in the chronic and acute dietary exposure analyses (including drinking water). The residue values have been verified by HED and are appropriate.

Plant Commodities

Field Trial Studies

For the purposes of dietary risk assessment, residue data generated from residue field trials conducted at maximum application rates and minimum pre-harvest intervals were used to estimate chronic and acute dietary exposure to potential residues of bifenthrin. For chronic dietary exposure analyses, mean anticipated residue values were calculated, substituting one-half the limit of detection for those samples for which residues were reported as non-detectable. For acute dietary exposure analyses, the entire range of field trial residue data which reflected the current labeled maximum rate and minimum PHI for single serving commodities were used (Tier 3 modeling, as outlined in "Final Office Policy for Performing Acute Dietary Exposure Assessment", D. Edwards, 6/13/96). For those foods considered to be blended, mean field trial residues were calculated, substituting the full limit of detection for those samples for which residues were reported as non-detectable (Tier 2 modeling) used residue distributions from field trial studies

Monitoring Data

In FDA's surveillance enforcement program database, there were sufficient numbers of observations for field corn (304) and strawberries (273). To calculate a mean residue for use in the chronic assessment, one-half the weighted LOD value was assigned to the appropriate number of samples reported as nondetect. For example, none of the 273 strawberry samples analyzed for bifenthrin in the FDA surveillance monitoring program contained detectable bifenthrin residues. Assuming 17% of the crop would have been treated, one would expect 46 samples with detectable bifenthrin residues. Thus 46 of the nondetect samples were assigned a value of one-half the weighted LOD; the remaining samples wetre assumed to be 0 ppm.

Percent Crop Treated Data

The percent crop treated data that were used in the dietary analyses were verified by BEAD (see attached memos from D. Brassard).

Animal Commodities

For chronic dietary analyses, dietary burdens were calculated using mean field trial residues, adjusted for percent of crop treated and applying appripriate processing factors, for all feed items. For acute dietary analyses, mean field trial residues (with no adjustment for percent of crop treated) were used for those feed items that are processed or blended, while the highest field trial residue values were used for the remaining feed items.

The secondary residue levels in animal tissues were then calculated by multiplying the total dietary burden by the tissue-to-feed rario calculated from the lactating ruminant or laying hen feeding studies.

International Tolerances/Maximum Residue Limits

Codex MRLs for bifenthrin have been established which are in harmony with the U.S. tolerances for cattler meat (0.5 ppm), corn grain (0.05 ppm), poultry fat (0.05 ppm), poultry meat (0.05 ppm), and poultry meat byproducts (0.05 ppm). Codex MRLs have been established which exceed the U.S. tolerances for horse fat (10.0 vs. 1.0 ppm). Codex MRLs have been established which are below their U.S. counterparts for cattle fat (0.5 vs. 1.0 ppm), cattle meat byproducts (0.05 vs. 0.10 ppm), corn forage (0.05 vs. 2.0 ppm), corn fodder (0.2 vs. 5.0 ppm), eggs (0.01 vs. 0.05 ppm), and whole milk (0.05 vs. 0.1 ppm).

No Canadian MRLs have been established for residues of bifenthrin. Mexico has established a tolerance for residues of bifenthrin on cottonseed (0.5 ppm) which is in harmony with the U.S. tolerance.

Exposure Characterization

The dietary exposure estimates calculated in this memo are based on extensively refined residue estimates. Percent of crop treated data were used for all commodities and monitoring data used for two commodities (in place of using field trial residue data) both with (acute) and without (chronic) Monte Carlo modeling. Additional sources of more refined data would include additional use of monitoring data (if available). Additionally, for the acute dietary analyses, the livestock dietary burdens could have been constructed using Monte Carlo techniques, which would likely have reduced exposure estimates from meat, milk, poultry, and eggs.

Attachment 7

Cyfluthrin

Toxicology and Residue Chemistry Details

Cyfluthrin

1. Hazard Assessment

a. Acute Toxicity

Acute Toxicity of Cyfluthrin

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	00131499 00131518	LD_{50} (M)=16.2 mg/kg (cremophor)	I
	(Minimum)		LD_{50} (M)=254 mg/kg (acetone)	II
			LD_{50} (M)=500-1000 mg/kg (N-methyl pyrollidon)	III
81-2	Acute Dermal	00131499 00131518	LD_{50} (M&F) > 5000 mg/kg (cremophor)	IV
	(Minimum)		LD_{50} (M&F)> 5000 mg/kg (0.9% NaCl)	IV
			LD_{50} (M&F)> 5000 mg/kg (undiluted)	IV
81-3	Acute Inhalation	00131509	LC_{50} (M) > 0.735 LC_{50} (F) = 0.468 mg/L (aqueous cremophor)	II
	(Minimum)		LC_{50} (M) = 0.575 LC_{50} (F) = 0.490 mg/L (DMSO/polyethylene glycol)	II
81-4	Primary Eye Irritation Acceptable (Minimum)	00131499	No corneal opacity; transient irritation for 3 days.	III
81-5	Primary Dermal Irritation Acceptable (Minimum)	00131499	Non-irritating. Primary irritation score = 0	IV
81-6	Dermal Sensitization	00131512	Not a sensitizer (Draize test)	N/A
	Acceptable (Minimum: both studies together)	00131513	Not a sensitizer (Maximization test)	
	Acceptable (guideline)			

107

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-7	Acute Delayed Neurotoxicity Acceptable	00131544	Oral doses of 5000 mg/kg (2 doses, 7 days apart) caused no behavioral or microscopic changes in nerve tissue.	N/A
	Acceptable	00131545	Dermal applications of 5000 mg/kg (5 daily doses, 23 hrs/day) caused no neuro toxic effects.	N/A
	Acceptable	Accession # 264955	Oral doses of 4300 mg/kg (1-2 doses) or of 1500 mg/kg (5 doses) were mildly neurotoxic, but did not cause classic delayed neurotoxic signs; a single oral dose of 4300 mg/kg did not inhibit NTE activity.	N/A

b. Subchronic Toxicity

28-day Oral Toxicity Study in Rats

In a 28-day oral toxicity study (accession no. 072008, MRID 00131523?), cyfluthrin (85% a.i.) in polyethylene glycol was administered to SPF-Wistar rats (20/sex/dose) via gavage at 0, 5, 20, or 80 (40) mg/kg/day. The high dose was 80 mg/kg/day during the first and third weeks and 40 mg/kg/day during the second and fourth weeks. After 4 weeks 10 rats/sex/dose (or one half of the survivors) were sacrificed and the remainder were allowed a 6-week recovery period prior to sacrifice. No rats died in the 5 or 20 mg/kg/day groups. In the 80 (40) mg/kg/day dose group, six males and one female died. Clinical signs of toxicity observed in the 80 (40) mg/kg/day group were "apathy, ruffled coat, dyspnea, salivation, hyperkinesis, ataxia, and athetotic and choreiform movements." Body weight gain in 80 (40) mg/kg/day males was reduced (↓12-13%); body weight gain in females was unaffected. There were no treatment induced changes in hematology parameters. Alanine aminotransferase was elevated in the 80 (40) mg/kg/day males. There were no treatment-related urinalysis findings. Liver weights in 80 (40) mg/kg/day females were elevated (↑24%); following the 6 week recovery, liver weights were reduced (↓32%) in females at 20 and 80 (40) mg/kg/day. In the 80 (40) mg/kg/day males kidney weights were reduced (↓12%) and adrenal weights were elevated (↑15%). Adrenal weights were also increased (↑19%) in 80 (40) mg/kg/day females. There were no dose-related gross necropsy or histopathologic findings. The LOEL in this 28-day oral toxicity study in rats is 80 (40) mg/kg/day in both sexes based on clinical signs of nerve toxicity, decreases in body weight gain, and changes in liver and adrenal weights. The NOEL is 20 mg/kg/day. This study is classified as core minimum.

28-day Oral Toxicity Study in Rats

108

In a 28-day feeding study in rats (MRID 00131525; strain unspecified; 18/sex/dose) were dosed with cyfluthrin (% a.i. not reported) in the diet at 0, 100, 300, or 1000 ppm (equivalent to 0, 5, 15, or 50 mg/kg/day). After 4 weeks, 12 rats/sex/dose were sacrificed and the remainder were allowed a 4-week recovery period. At the 50 mg/kg/day dose, the following abnormalities were observed: behavioral reactions (straddle gait, salivation, and/or nervousness) early in the study; decreases in body weight and food and water consumption; urobilinogen and ketone bodies in urine; decreased RBC count, hematocrit, and hemoglobin; decreased total serum protein and glucose in blood; increased weight of the submaxillary glands, increased relative liver and kidney weights (organ weight changes returned to normal after the recovery period). Also at 50 mg/kg/day there was cytoplasmic swelling of the glandular epithelium in the submaxillary glands and single nerve fiber degeneration of the sciatic nerve (minimal, disappeared after the 4-week recovery period). Serum glucose was decreased (↓12%) at the 15 mg/kg/day dose. The LOEL for this 28-day rat feeding study is 15 mg/kg/day in both sexes based on decreased blood glucose. The NOEL is 5 mg/kg/day. This study is classified core supplementary.

Three-Month Feeding Study in Rat

In an oral toxicity study (MRID 00131524) SPF Wistar (TNO W.74 strain) rats (30/sex/dose) were dosed with cyfluthrin (84.2% a.i.) in the diet at 0, 30, 100, or 300 ppm (equivalent to 0, 1.5, 5, or 15 mg/kg/day) for 3 months. There were two unscheduled deaths attributed to ether overdose during blood collection. There were no abnormal clinical signs reported and no consistent treatment-related effects on body weight or feed and water consumption. No treatment-related changes in hematology parameters, blood biochemistry, or urinalysis. There were no treatment-related organ weight changes, nor gross or microscopic histopathology findings. After 7 days of dosing, there were elevations in activities of N-demethylase in males from all treated groups, O-demethylase in females at 5 and 15 mg/kg/day, and cytochrome P450 in males at 15 mg/kg/day. At 1 and 3 months of dosing, all three enzymes were equivalent to activities in control groups. The NOEL for this 3-month rat feeding study is ≥15 mg/kg/day for both sexes. This study is classified core minimum.

Six-Month Dog Feeding

In a 6-month dog feeding study (MRID 00131530), cyfluthrin (84.8% a.i.) was administered in the diet to six dogs/sex/group at 0, 65, 200, or 600 ppm (equivalent to 0, 1.62, 5 or 15 mg/kg/day) for 26 weeks. The test material had no effect on survival. In the high dose dogs hind-limb abnormalities were observed developing during the later weeks of the study. The 15 mg/kg/day group also exhibited vomiting and diarrhea. Body weight decreased in the 5 and 15 mg/kg/day groups, although statistical significance was not attained for the high dose group. Treatment did not affect food or water consumption. There were no test chemical effects on hematology, clinical chemistry, or urinalysis findings. There were no ophthalmoscopic effects. Liver weights were not affected by the test substance. Absolute thymus weights were reduced in males at 5 and 15 mg/kg/day (↓35 and 34%, respectively) and in high dose females (↓28%); relative thymus weights in these groups were similarly affected. The only gross pathology findings were two incidences of atrophied thymus in high dose females. There were no treatment-related histopathological findings. No effects were noted on

109

activity of N-demethylase or cytochrome P450 in liver homogenates. The LOEL for this 6-month dog feeding study is 15 mg/kg/day for both sexes, based on neurological effects (hindlimb abnormalities) and gastrointestinal disturbances. The NOEL is 5 mg/kg/day for males and females. This study is classified as core minimum.

21- Day Dermal Study in Rats

In a 21-day repeated dose dermal toxicity study (MRID 44066001), groups of 8 male and 8 female Sprague-Dawley rats were treated with Technical grade Baythroid (≥95.5%, lot 2030025/ BF9140-23) in acetone by dermal occlusion at target doses of 0, 100, 340, or 1000 mg/kg/day for 6 hours/day. (Average actual dose levels were 0, 113, 376 or 1077 mg/kg/day). Males received 17 applications and females received 18 applications within a total period of 22 and 23 days, respectively. Additionally, control and high concentration recovery dose groups were similarly treated and observed for at least 2 weeks to assess potential reversibility of effects. No mortality was observed, and there were no treatment-related effects on body weight, opthalmology, organ weights, clinical biochemistry, or hematology. Decreased food consumption ($p \leq 0.05$) (10-17%) was observed in high-dose males and females during the first week of the study. Treatment-related clinical signs included scabbing at the application site in mid-dose females and high-dose males and females. High-dose males exhibited a red nasal discharge, while high-dose females exhibited urine staining. Epidermal and dermal changes were observed grossly and histologically. Ulceration with adjacent epidermis thickened by acanthosis and hyperkeratosis were observed in three high-dose males and seven high-dose females and one animal of each sex from the mid-dose group. The LOEL for dermal effects was 376 mg/kg/day for male and female Sprague-Dawley rats based on gross and histological skin lesions. The NOEL for dermal effects was for technical Baythroid was 113 mg/kg/day. The LOEL for systemic effects was 1077 mg/kg/day based on decreased food consumption, red nasal discharge and urine staining. The NOEL for systemic effects was 376 mg/kg/day. This study is classified as acceptable and satisfies the guideline requirements for a 21-day dermal study (82-2) in rats.

3-Week Inhalation Toxicity Studies in Rats

Study I - In a subacute inhalation toxicity study (MRID 131527), Wistar TNO/W 74 rats (10/sex/dose) were dynamically exposed by nose-only inhalation to cyfluthrin (85.3% a.i.) in ethanol/polyethylene glycol 400 (1:1) at concentrations of 0, 2.3, 11.5, or 69.6 mg/m^3 for 6 hours/day, 5 consecutive days/week for 3 weeks (total of 15 exposures). A single high-dose female died following the fifth exposure; all other animals survived the 3-week study. No treatment-related abnormalities were observed in clinical chemistry parameters, organ weights, gross pathology, and histopathology. No effects were noted on liver enzyme levels (N-demethylase, O-demethylase, and Cytochrome P450). Clinical signs of toxicity were observed in the mid- and high-dose rats following exposure that included ungroomed coats, abnormal gaits, and increased salivation. Treatment-related effects on body weight were observed in all exposure groups; mid- and high-dose groups exhibited overall decreases in body weight. Decreases in body temperatures were observed in all dose and control groups; decreases were dose-dependent and were most severe after the first exposure (change of -7.5 °C in the high-dose females), and milder after the tenth and fifteenth exposures. A mild neutrophilia

110

was seen in the mid- and high-dose groups. The LOEL was 2.3 mg/m^3, based on the treatment-related effects on body weight and temperature observed during the 3-week exposure period. A NOEL was not established; therefore, this study was repeated using lower doses.

Study II - Wistar TNO/W 74 rats (MRID 00131528; 10/sex/dose) were dynamically exposed by nose-only inhalation to cyfluthrin (85.3% a.i.) in ethanol/polyethylene glycol 400 (1:1) at concentrations of 0, 0.4, 1.4, or 10.5 mg/m^3 for 6 hours/day, 5 consecutive days/week for 3 weeks (total of 15 exposures). No mortality was observed during the study. Unspecified behavioral disorders were observed in the high-dose rats during the third week of exposure. In addition, high-dose males exhibited a mild decrease in overall weight gain. Absolute and relative spleen weights were mildly decreased in the high dose males and females. No compound-related abnormalities were observed upon gross or microscopic examination. Bone marrow smears did not reveal any evidence of hematopoietic effect. Hematology, clinical chemistry, and urinalysis measurements were not performed. The LOEL is 10.5 mg/m^3, based on the treatment-related behavioral effects as well as effects on body and organ (spleen) weights. The NOEL is 1.4 mg/m^3. These studies were classified as core minimum.

4-Week Inhalation Toxicity Study in Rats

In a subacute inhalation toxicity study (MRID 41842601), Bor:WISW (SPF-Cpb) rats (10/sex/dose) were dynamically exposed by inhalation (nose only) to cyfluthrin (93.8% a.i.) in ethanol/polyethylene glycol 400 (1:1) at concentrations of 0, 0.44, 6.04, or 46.6 mg/m^3 for 6 hours/day, 5 consecutive days/week for 4 weeks (total of 20 exposures). No mortality was observed during the 4-week study. There were no treatment-related effects on ocular abnormalities, blood gases, or gross pathology. Clinical signs of toxicity were observed in high-dose rats, such as piloerection and bradypnea following each exposure, and reduced activity during Week 1 followed by hyperactivity starting at Week 2. Final body weights of mid- and high-dose males were significantly reduced (↓10-14%, $p<0.01$). Steady hypothermia was observed directly following exposure in mid-dose rats beginning at Day 13 and in high-dose rats throughout the 4-week exposure period. Small reductions in leukocytes counts were observed in mid-dose females and in high-dose males; no other hematological effects were noted. Low serum protein was also observed in mid-dose rats in conjunction with an increase in chloride concentration and a decrease in calcium concentration. A significant acidification of the urine also occurred in high-dose rats. In addition, there was a compound-related reduction in the respiratory rate after the start of exposure, with respiration starting to return to normal after approximately 3 hours of exposure. Thymus weights were reduced in mid-dose and high-dose rats, with a significant reduction (↓43%, $p<0.01$) occurring in high-dose males. The LOEL is 6.04 mg/m^3 based on the decrease in body and thymus weights, hypothermia, reduction in leukocytes counts (females), and low serum protein. The NOEL is 0.44 mg/m^3. This subacute inhalation toxicity study in rats is classified as supplementary as the study was conducted for only 4 weeks, food consumption and histopathological data were not provided, and urine and clinical chemistry parameters were incomplete.

13-Week Inhalation Toxicity Study in Rats

In a subchronic inhalation toxicity study (MRID 00157793), Bor:WISW (SPF-Cpb) rats (10/sex/dose) were dynamically exposed by head-only inhalation to cyfluthrin (94.9% a.i.) in ethanol/polyethylene glycol 400 (1:1) at concentrations of 0, 0.09, 0.71, or 4.51 mg/m^3 for 6 hours/day, 5 consecutive days/week for 13 weeks. All animals survived the 13-week study, and no treatment-related changes were observed in organ weight, gross pathology, and histopathology. Clinical signs of toxicity were observed as lethargy and unthriftiness/unkempt fur in mid-dose females following exposures on unspecified days, and in high-dose rats between Weeks 2 and 13. In addition, high-dose animals were agitated with "erect tails" following exposures between Weeks 6 and 13. High-dose males exhibited dose-related decreases (10-15%) in body weight gain from Week 2 to termination. Decreased urinary pH in high-dose males and increased urinary protein in mid- and high-dose males were observed at 6 and 12 weeks; however, no corresponding lesions were found to verify nephritic damage. No signs of toxicity were observed in animals from the low-dose group. The LOEL is 0.71 mg/m^3, based on the treatment-related behavioral effects in females as well as the increased urinary protein in males. The NOEL is 0.09 mg/m^3. This study is classified as core minimum.

c. Chronic Toxicity/Carcinogenicity

Twelve-month Dog Feeding Study

In a 12-month feeding study, cyfluthrin (MRID 00151358; purity not reported) was administered in the feed to six beagle dogs/sex/dose group at 0, 40, 160, or 640 ppm (equivalent to 0, 1, 4, or 16 mg/kg/day) for 52 weeks (accession no. 073256). The test material had no effect on survival. There were no treatment-related effects on ophthalmology, hematology, clinical chemistry, or urinalysis findings. Increased spleen weight and spleen/body weight ratio in high-dose females were not corroborated by gross or microscopic abnormalities and were considered a random finding. There were no test-related histopathology findings. Clinical signs of toxicity were observed in two dogs dosed at 16 mg/kg/day, each on a single occasion at weeks 36 or 37, exhibited a "swaying, slightly clumsy gait primarily in the hindquarters." Animals in the high-dose group showed increased frequency of vomiting and diarrhea, compared with controls and lower dose groups. There was a treatment-related decrease in body weights in high-dose males; body weight in females was unaffected. Body weight gain was reduced 30% in high-dose males, but was unaffected by dose in females. A reduction in food consumption in high-dose males was attributed to poor eating habits of one animal. There was no change in food consumption among females or in water consumption by either sex. The LOEL for this 12-month dog feeding study is 16 mg/kg/day for both sexes, based on slight ataxia in two dogs on single occasions, decreased body weight in males, and on observations of increased vomiting and diarrhea at the high dose. The NOEL is 4 mg/kg/day. This study is classified as core minimum.

Chronic/Oncogenicity-rat

In a chronic/oncogenicity study (MRID 00137303), cyfluthrin (purity not reported) was administered for 24 months in the diet to Wistar SPF rats (65/sex/dose) at dose levels of 0, 50, 150, or 450 ppm (equivalent to 2.02, 6.19, or 19.20 mg/kg/day in males and

2.71, 8.15, or 25.47 mg/kg/day in females based on food consumption and body weights). There were no treatment related deaths and no treatment-related changes noted in the clinical observations, food consumption, hematology, urinalysis, and the gross and microscopic data. No ophthalmologic examinations were performed. The mean body weights of the high-dose males and females were lower (↓5-10%; $p<0.01$) than the controls throughout the study. The mean body weights of the mid-dose males were also lower than the controls during the first year of the study (↓4-5%; $p<0.05$), but the animals recovered thereafter. Significant ($p<0.05$) increases were observed in the incidences of inflammatory foci of the kidneys in the mid-dose females (7/50 treated vs 1/50 controls) and the high-dose females (7/49 treated) and in hyperplastic nodules of the adrenals in the high-dose animals (Males: treated - 20/50, control - 10/48; Females: treated - 18/49, control - 9/49; $p<0.05$). Medullary hyperplasia was also observed in high-dose males (14/50 treated vs 4/48 controls). In addition compared to concurrent controls, the following were observed: (i) increased (↑75%; $p<0.01$) liver N-demethylase activity in the high-dose females after 7 days of dosing; and (ii) increased fluoride levels in the bones of the mid- and high-dose males (11-21%; $p<0.05$) and the high-dose females (19%; $p<0.01$), as well as in the teeth of the high-dose males (20%); $p<0.01$). The chronic LOEL is 150 ppm (equivalent to 6.19 mg/kg/day in males and 8.15 mg/kg/day in females) based on decreased body weights in the high-dose animals and the mid-dose males. The chronic NOEL is 50 ppm (equivalent to 2.02 mg/kg/day in males and 2.71 mg/kg/day in females). Under the conditions of this study, there was no evidence of carcinogenic potential. This chronic/oncogenicity toxicity study in rats is classified core minimum for both chronic toxicity and oncogenicity.

Chronic/oncogenicity-mouse

In a chronic/oncogenicity study (MRID 00137304), cyfluthrin (purity not reported) was administered in the diet for 23 months to SPF mice (50/sex/dose) at dose levels of 0, 50, 200, or 800 ppm (equivalent to 11.6, 45.8, or 194.5 mg/kg/day in males and 15.3, 63.0, or 259.9 in females based on food consumption and body weights). There were no treatment related changes noted in the clinical observation, food consumption, hematology, gross observation, organ weight, and microscopic data. No ophthalmologic examinations or urinalyses were performed. Fluoride did not accumulate in teeth or bones of mice as observed in the rat study. The mortality data were equivocal with respect to treatment. The incidence of mortality in the mid- and high-dose females was somewhat higher than the controls throughout the study. However, only the mid-dose at termination was significantly ($p \leq 0.05$) different from controls. At termination, excess mortality in the females was 8, 22, and 16% for the low-, mid-, and high-dose groups, respectively, compared to controls. Excess mortality in the high-dose males was 8% at termination. The mean body weight differences were as high as 11% for mid- and high-dose males and 8% and 12% for the mid- and high-dose females throughout the study. The mean body weights of the treated groups however, were not significantly different at termination, possibly due to the mortality differences in the dosed groups compared to the concurrent controls. In the clinical chemistry data, the dose-response of alkaline phosphatase activity in treated males compared to controls was clearly evident at month 6 (↑43-230%; $p \leq 0.01$), 12 (↑37-73%; $p \leq 0.01$) and 18 (↑61-114%; $p \leq 0.01$). At termination, there was evidence that the samples were hemolyzed, leading to spurious results. The histopathology data did not confirm the liver as a target organ. The chronic LOEL is 50 ppm (equivalent to 11.6 mg/kg/day in males and 15.3 mg/kg/day in females) based on increased alkaline phosphatase activity in the dosed males. A chronic NOEL was not established in male and female mice. Under the conditions of this study, there was no evidence of carcinogenic potential. This study is classified core minimum for oncogenicity and supplementary for chronic toxicity.

d. Developmental Toxicity

Developmental study in rats (oral)

In a developmental study (MRID 00157794), cyfluthrin (93.4% a.i.) in distilled water containing 1% Cremophor EL was administered via gavage to pregnant female Wistar KFM-Han rats (25/dose) during days 6-15 of gestation at dose levels of 0, 1, 3, or 10 mg/kg/day. There were no maternal deaths during the study and no clinical signs of toxicity, except for vaginal bleeding, abortion, and weight loss in one mid-dose dam on gestation day 18, which was not considered to be treatment-related. There were no treatment-related effects on weight gain or food consumption. There were no treatment-related differences in the number of corpora lutea, resorptions, implantations, live litters and fetuses, sex ratios, or fetal weights. There were no treatment-related external, visceral, or skeletal malformations or variations noted at any dose level. A maternal LOEL was not observed. The maternal NOEL is >10 mg/kg/day. A developmental LOEL was not observed. The developmental NOEL is >10 mg/kg/day. An EPA ad hoc committee meeting (memorandum, dated May 26, 1993) that reviewed

154

a previously conducted range-finding study (also MRID 00157794) concluded that the results of the range-finding study supported the dose selection for the developmental study. In the range-finding study, maternal toxicity was noted at 10 mg/kg/day and included decreased body weight gain from day 6-11 post coitus, decreased food consumption during the treatment period, and single instances of slight dyspnea after dosing at 3 and 10 mg/kg/day. This developmental study in rats is classified core guideline.

Developmental Study in Rabbits (oral)

In a developmental study (MRID 42675401), cyfluthrin (96% a.i.) in corn oil was administered via gavage to pregnant female Chinchilla (CHbb: CH, Hybrids, SPF Quality) rabbits (25/dose) during days 6-18 of gestation at dose levels of 0, 20, 60, or 180 mg/kg/day. There were no maternal deaths or clinical signs of toxicity during the study, and no treatment-related gross pathology was observed. Mean body weight gains were decreased (↓373% and 483%, $p \leq 0.01$) relative to the controls at 60 and 180 mg/kg/day, respectively, during the dosing period. At 180 mg/kg/day, food consumption was decreased during days 6-15 (↓41-48%, $p \leq 0.01$) and days 15-19 (↓27%). At 60 mg/kg/day, food consumption was decreased during days 6-19 (↓24-29%). Both food consumption and body weight gains at 60 and 180 mg/kg/day increased during the post-dosing period. There were no treatment-related effects on the number of live litters, fetal weights, implantations, external, visceral or skeletal malformations and variations. Postimplantation loss was increased significantly at 60 mg/kg/day ($p \leq 0.05$) and 180 mg/kg/day ($p \leq 0.01$). Resorptions were significantly increased ($p \leq 0.05$) and the number of fetuses was significantly decreased ($p \leq 0.05$) at 60 and 180 mg/kg/day. The maternal LOEL is 60 mg/kg/day based on decreased body weight gain and food consumption during the dosing period. The maternal NOEL is 20 mg/kg/day. The developmental LOEL is 60 mg/kg/day based on increased numbers of resorptions and percent incidence of postimplantation loss. The developmental NOEL is 20 mg/kg/day. This developmental study in rabbits is classified core guideline.

115

Developmental Study in Rats via Inhalation

Two developmental toxicity studies via inhalation (MRID 40780401) were conducted. In the first study, 4 groups of 30 female Bor:WISW (SPF Cpb) rats were inseminated by being housed overnight with males. The presence of sperm in the vaginal smears following mating established gestation day 0. They were exposed head-only to cyfluthrin dissolved in a 1:1 mixture of Lutrol and ethanol at analytical concentrations of 0, 1.1, 4.7 or 23.7 mg/M^3/day for 6 hours/day on gestation days 6 through 15. In the second study, the dams were exposed to analytical concentrations of 0, 0.09, 0.25, 0.59 or 4.2 mg/M^3 of the test material. An oxygen enriched atmosphere (30%) was provided for the 4.7 mg/M^3 group to see if the embryotoxic effects seen in the first study at this concentration could be lessened. The rats were observed several times on the exposure days except during the exposures (because of restraint for head-only exposure). They were weighed on gestation days 0, 6, 9, 12 and 20. The dams were sacrificed on day 20 and their pups removed by caesarian section. Their ovaries and uteri were examined for implantations, live young, embryonic and fetal deaths, fetal sex and weights, and external fetal abnormalities. Combining the results of the two studies, maternal effects were observed at 4.7 mg/M^3 and above: reduced motility, dyspnea, piloerection, ungroomed coats and eye irritation. Effects in the pups were observed at 1.1 mg/M^3 and above. At 1.1 mg/M^3 and above, a dose-related increase in the incidence of runts and skeletal anomalies in the sternum were observed. At 4.7 mg/M^3 and above, increases in post-implantation losses and decreases in pup weights were observed. At 23.7 mg/M^3, increased incidences of late embryonic deaths and in skeletal anomalies in the extremities, pelvis and skull were observed as well as microphthalmia. The maternal NOEL is 1.1 mg/M^3 and the maternal LOEL is 4.7 mg/M^3 (reduced motility, dyspnea, piloerection, ungroomed coats and eye irritation. The developmental NOEL is 0.59 mg/M^3 and the developmental LOEL is 1.1 mg/M^3 (increases in the incidence of runts and skeletal anomalies in the sternum (1.1 mg/M^3 and above); increases in post-implantation losses and decreases in pup weights (4.7 mg/M^3 and above) and increased incidences of late embryonic deaths, in skeletal anomalies in the extremities, pelvis and skull and in microphthalmia (23.7 mg/M^3). An ad hoc committee met on 4/22/93 to discuss the developmental toxicity data base for cyfluthrin. At that time, the Committee recommended that due to deficiencies that were mentioned in the review of the study, this study should be re-examined if it is to be used as a regulatory endpoint. Although the study had been graded Core Minimum and NOELs and LOELs had been established for maternal and developmental toxicity, comments had also been made that developmental anomalies in the study had not been adequately reported.

Developmental Study in Rats via Inhalation

In a developmental toxicity study via inhalation (MRID 43393401), FCR 1272 (cyfluthrin) was administered to 25 female Wistar rats per group for air control, vehicle control (polyethylene glycol-400: 50% ethanol), 0.46, 2.55, 11.9 or 12.8 mg/M^3 plus 39% oxygen (analytically determined) exposure levels for gestational days 6 through 15 in a nose only inhalation chamber. The rats were exposed to the test material 6 hours per day, 7 days per week. The particle sizes in the inhalation chambers had a MMAD +/- geometric standard deviation of 1.1 +/- 1.5 micrometers for all the test groups. Additional satellite rats (5 per group) were exposed similarly from gestational day 6

116

through day 13 to determine the effect of cyfluthrin exposure on body temperature, ventilation rate and plasma cyfluthrin levels. Mean maternal body weight gain was statistically significantly decreased at 0.46 mg/M^3 and above for the interval gestational day 6 to 15 and gestational day 0 to 20. The relative efficiency of food utilization appeared to be decreased at 0.46 mg/M^3 and above. Placental (>=7% from the vehicle control) and fetal weights (>=11% from the vehicle control) were decreased at 2.55 mg/M^3 and above. Developmental toxicity was also expressed in the form of retarded skeletal ossification in the phalanx, metacarpals, cervicla vertebrae, sacral and caudal arches at 2.55 mg/M^3 and above. Dose related total fetal malformations such as microphthalmia and skeletal dysplasia were evident at 11.9 mg/M^3 (8.8% in fetuses/43% in litters vs. vehicle controls with 1.0% in fetuses/14% in litters). The weight of the evidence would suggest that the cyfluthrin exposure at 11.9 and 12.8 mg/M^3 caused the developmental toxicity indirectly through the bradypnea in dams. While the bradypnea in dams at 2.55 mg/M^3 may have caused the reduced fetal and placental weight and retarded ossification, the data presented was insufficient to draw this conclusion. The maternal NOEL/LOEL were < 0.46/<0.46 mg/M^3 based on decreased body weight gain and reduced relative food efficiency. The developmental NOEL/LOEL were 0.46/2.55 mg/M^3 based on reduced fetal and placental weight, reduced ossification in the phalanx, metacarpals and vertebrae. Core classification: Guideline. The study is acceptable under Guideline 83-3 for a developmental toxicity study in rats via inhalation.

e. Reproductive Toxicity

Multigeneration Reproduction Study in Rats

In a 3-generation reproduction study (MRID 00131532) cyfluthrin (% a.i. not indicated) was administered in the diet to 10 male and 20 female BOR:WISW SPF rats/dose at dose levels of 0, 50, 150, or 450 ppm (calculated by the reviewer to be 0, 2.5, 7.5, or 22.5 mg/kg/day). Six sets of litters were bred: F1a and F1b from the F0 parental groups; F2a and F2b from the F1b parental groups; F3a and F3b from the F2b parental groups. For each mating one male rat was mated with 2 female rats. Parental toxicity was demonstrated at 22.5 ppm for all parental generations as a treatment-related decrease in body weight gains. There were no treatment-related deaths, gross pathology, or histopathology. Reproductive toxicity was demonstrated as treatment-related decreases in the viability indices (no. of live pups after 5 days/no. of pups born) at 7.5 and 22.5 mg/kg/day for the F1a, F2a, F3a, and F3b generations. The F3a and F3b generation were most noticeably affected; viability indices for the F3b generation were 99.0, 92.3, 89.0, and 77.4 for the control, low-, mid-, and high-dose groups, respectively. Lactation indices (no. of live pups after 4 weeks/no. of live pups at day 5 after culling) were also decreased at the mid- and high-doses for the F1a, F1b, F2a, F2b, and F3b litters. The maximum differences were found for the F2a and F2b groups which were 75.8 and 72.4% for the mid- and high-dose levels verses 93.1% for the controls. In addition at the mid- and high-doses, pup body weight gains were decreased. There were no treatment-related effects on fertility indices, gestation indices, sex ratios of the pups, number of pups, stillbirths, pup body weights at birth, gross pathology, or histopathology. The LOEL for parental toxicity is 450 ppm (22.5 mg/kg/day) based on decreased body weight gains. The NOEL for parental toxicity is 150 ppm (7.5 mg/kg/day). The LOEL for reproductive toxicity is 150 ppm (7.5

117

mg/kg/day) based on decreased viability and lactational indices and decreased pup body weight gains. The reproductive NOEL is 50 ppm (2.5 mg/kg/day). The multigeneration reproductive study in the rat is classified core minimum.

f. Mutagenicity

There is no mutagenicity concern. The submitted studies satisfy the pre-1991 mutagenicity test battery. There are seven acceptable studies: 3 reverse mutation assays (Salmonella typhimurium, E. coli and Saccharomyces cerevisiae); 1 reverse mutation, mitotic recombination and conversion assay in Saccharomyces cerevisiae (Accession No. 72009); 1 CHO/HGPRT assay; 1 sister chromatid exchange assay in CHO cells; and 1 UDS assay in primary rat hepatocytes (Accession No. 261771). All these studies were negative.

g. Metabolism

Study No. 1

In a general metabolism study, ^{14}C-cyfluthrin was administered to Sprague Dawley rats and the absorption, plasma levels, distribution, excretion and organ/tissue levels of radioactivity were studied. Male and female rats were given a single oral dose of 0.5 or 10 mg/kg of ^{14}C-cyfluthrin, 14 daily oral doses of 0.5 mg/kg of unlabeled cyfluthrin followed by a single oral dose of radiolabeled cyfluthrin of 0.5 mg/kg, or a single intravenous dose of 0.5 mg/kg of ^{14}C-cyfluthrin. Either 4 or 5 rats/sex were dosed in each treatment regimen. In addition, 5 male rats with bile fistulas were given single duodenal doses of 0.5 mg/kg of radiolabeled cyfluthrin.

Following oral administration, the test material was rapidly and nearly completely absorbed. Peak plasma levels of radioactivity were observed at about 2 hours after dosing. Greater than 95% of the administered radioactivity was excreted within 48 hours. Radioactivity was excreted in the urine and feces with virtually none being excreted in expired air. By 48 hours after dosing, >98% of the total retrieved radioactivity was recovered in the urine and feces. The ratio of radioactivity in urine/feces was higher in males than in females. About 50% of the total urinary radioactivity was recovered during the first 6-8 hours after dosing and about 90% within the first 24 hours. At 48 hours, only the fat tissue (renal fat) contained levels of radioactivity that clearly exceeded the overall mean body level, being 6-11X higher. Levels of radioactivity in brain were quite low, being 15-20X lower than the overall mean body level. Different dose levels (0.5 or 10 mg/kg) or pretreatment (14X) did not appreciably affect the above findings. Some sex differences, however, were observed as indicated by higher urine/feces ratios in males and slightly higher organ/tissue levels of redioactivity in females (except for fat tissue).

Following intravenous administration, a 2 phase plasma elimination pattern was observed with plasma half-lives of about 2.1 and 20 hours. The apparent volume of distribution (Vd) was about 17% of the total body volume, corresponding to the "readily diffusable part of the extracellular fluid". Greater than 90% of the administered radioactivity was excreted within 48 hours. By 48 hours after dosing, about 93-94% of the total retrieved radioactivity was recovered in the urine and feces. Residual levels of radioactivity in the body and in individual organs/tissues were higher than after oral administraiton. In other respects, the results following intravenous dosing were quite similar to those described for oral dosing. Studies in male rats with bile fistulas indicated an enterhepatic circulation of test material.

119

Study No. 2

The excretion and metabolic transformation of ^{14}C-cyfluthrin was studied in Sprague Dawley rats. The rats were treated in the same manner as in a companion biokinetic study (see above) as follows: a single oral dose of 0.5 or 10 mg/kg of ^{14}C-cyfluthrin, 14 daily doses of 0.5 mg/kg of unlabeled cyfluthrin followed by a single oral dose of radiolabeled cyfluthrin of 0.5 mg/kg, or a single intravenous dose of 0.5 mg/kg of ^{14}C-cyfluthrin. Four rats/sex were dosed in each treatment regimen.

Excretion of radioactivity was rapid. Following oral administration, >95% of the administered radioactivity was excreted within 48 hours, and following intravenous injection, >90% within 48 hours. Most of the radioactivity was excreted in urine, the urine/fecal ratio being about 2-3X in males and about 1.6-1.8X in females following oral administration and about 2.5X in males and about 2.6X in females following intravenous injection. Parent cyfluthrin is cleaved at the ester bond and then oxidized to yield 3-phenoxy-4-fluorobenzoic acid. This intermediate is then either hydroxylated and subsequently conjugated and excreted or first bound to glycine and then hydroxylated, conjugated and excreted. Identified metabolites and parent cyfluthrin (in urine, feces and body) accounted for 65-73% of the recovered radioactivity after a single oral or intravenous dose of 0.5 mg/kg and about 82-83% of the recovered radioactivity after a single oral dose of 10 mg/kg or after 14 daily oral doses.

h. Neurotoxicity

Subacute Oral Neurotoxicity in Rat

In a subacute neurotoxicity study (MRID 00157801), Wistar Bor:WISW (SPF-Cpb) rats (5/sex/dose) were orally dosed by gavage with cyfluthrin (96.5% a.i.) in polyethylene glycol 400 at 0, 50 (males only), or 60 mg/kg/day for 14 days. The animals were observed for an additional 14 days, then necropsied. Four high-dose males died on treatment Days 6 through 9. The mid- and high-dose males weighed significantly less than the concurrent controls. Clinical signs commenced on Day 2 in all treated animals and included non-specific disturbed behavior, rolling, tremors, stretched gait, uncoordinated gait, and excessive salivation. The high-dose males occasionally phonated. The LOEL for neurotoxicity is 50 mg/kg/day based on the clinical signs observed. A NOEL was not observed. This subacute oral neurotoxicity study was originally classified as supplemental. However, upon submission of additional data/information it was upgraded to core guideline.

Subacute oral neurotoxicity-rat

In a subacute neurotoxicity study (MRID 00157801?), Male SD rats (number/dose, not specified) were orally dosed with cyfluthrin (95% a.i.) in polyethylene glycol 400 at 0 or 80 mg/kg/day for 14 days (reduced to 40 mg/kg/day after 5 doses). The animals were observed through the 14-days of dosing and a 3-month observation period. The treated rats had slight to moderate straddled gait, slow leg movements, and titubation; some rats also salivated and had red tears. These clinical signs were most severe several hours after dosing. A reversal in these clinical signs occurred within 2 weeks after

decreasing the dose to 40 mg/kg/day. Body weights of the treated rats were similar to controls at the end of the study. Light microscopic examination revealed minimal axonal degeneration (myelin swelling and desquamation) in a single fiber of the sciatic nerve on day 1 (6/8), day 5 (3/8), month 1 (3/8), and month 2 (2/9). Electron microscopic lesions included microtubular dilatation with proliferation of neurofilaments and mitochondria degeneration in the sciatic nerve at days 1 and 5, and at one month. These same lesions were also observed in the femoral nerve of a rat on day 5. An equivocal LOEL for neurotoxicity is 80 mg/kg/day based on the clinical signs observed at this dose. An equivocal NOEL is 40 mg/kg/day based on reversal of the clinical signs observed at 80 mg/kg/day. This subacute oral neurotoxicity study was originally classified as supplemental. However, upon submission of a revised report it was upgraded to core guideline.

Neurotoxicity in Rat

In a neurotoxicity study (MRID 131529), Wistar TNO/W74 albino rats (15/sex/dose) were dosed via stomach tube with cyfluthrin (83.3% a.i.) in polyethylene glycol 400 at 0 or 60-80 mg/kg/day for 5 months. No treatment related effects on liver enzymes (N-demethylase, O-demethylase, and cytochrome P-450), gross pathology, or histopathology were observed. Hematology and urinalysis were not performed. Ten treated and 4 control rats died during the study. Clinical signs observed in the treated rats included apathy, out-of-condition coat, troubled respiration, digging and grooming, tremors, gait abnormalities, and salivation. In males relative to controls, lower body weight gains and decreased liver (↓11%) and kidney (↓19%) weights were observed. Liver weights were increased in the females compared to controls (↑16%). It was stated that the dose range was chosen "..so that the rats always showed symptoms." The LOEL for neurotoxicity is 60 mg/kg/day based on the clinical signs observed at the 60-80 mg/kg/day doses. The NOEL is <60 mg/kg/day. This neurotoxicity study is classified as core minimum.

i. Other Toxicological Considerations

In a 7-day inhalation toxicity study (MRID 44373401) technical cyfluthrin (96.8%) was administered to groups of SPF-bred NMRI mice, 5 dams/dose with 8 pups each (4 males and 4 females, 10 days old). The dams were exposed together with their offspring in a dynamic whole-body chamber at concentrations of 0, 0.006, 0.015 or 0.058 mg/L for 6 hours per day for 7 consecutive days. During the recovery period, the dams were maintained and housed with their pups until weaning, at which time the offspring were housed with their same sex litter mates (4/cage) for 14 weeks. At week 15, the offspring were tested for spontaneous motor activity and hematological and selected clinical chemistry parameters were examined. Brains from the offspring were either processed for microscopic examination or prepared for determination of muscarinic receptors in different brain regions. At 0.006 mg/L, no effects were observed in either the pups or the dams when compared to the control group. At 0.015 mg/L, clinical signs of toxicity were observed in both sexes of pups during the period right after exposure (exposure days 0-6; decreased motility, poor general condition, tonic seizures and temporary scratching (direct sensory irritation)). No clinical signs were observed in the dams. Adult female offspring showed higher scores for horizontal and vertical

activity, total distance and movement time when compared to the control group. At 0.058 mg/L, all pups except one died during the first exposure period. The one surviving pup was killed in extremis. No deaths were observed in any of the dams. The LOEL for pups is 0.015 mg/L based on clinical signs of toxicity and increased spontaneous motor activity in females 4 months after exposure. The NOEL for pups is 0.006 mg/L. The parental LOEL (dams) is greater than 0.058 mg/L (HDT). No effects were observed at any dose level. The parental NOEL is 0.058 mg/L (HDT). This 7-day inhalation study is acceptable nonguideline.

2. Dose/Response Assessment

a. Reference Dose (RfD)

The RfD value has been established at 0.008 mg/kg/day based on a chronic/carcinogenicity feeding study in the rat with a NOEL of 2.5 mg/kg/day and an uncertainty factor of 300 (includes FQPA considerations). The LEL of 6.2 mg/kg/day was based on decreased body weights in males and inflammatory foci in the kidneys of females. In this study, rats were administered cyfluthrin in the diet at 2.02, 6.19, or 19.20 mg/kg/day in males and 2.71, 8.15, or 25.47 mg/kg/day in females (RfD Committee 3/14/86).

b. Carcinogenic Classification and Risk Quantification

Cyfluthrin is classified as a group E chemical. Carcinogenicity studies in rats and mice were negative.

c. Developmental Concerns

Cyfluthrin is not considered to be a direct developmental toxicant. However, there are concerns for extra sensitivity of the pups when compared to the dams. A 1982 inhalation developmental toxicity study in rats provided a developmental NOEL of 0.00059 mg/l (based upon sternal anomalies and increased incidence of runts at 0.0011 mg/l) which was less than the maternal NOEL of 0.0011 mg/l (based upon reduced motility, dyspnea, piloerection, ungroomed coats, and eye irritation). However, in a subsequent (1994) inhalation developmental toxicity study in rats, developmental toxicity occurred only in the presence of maternal toxicity. Reduced placental and fetal weight, and reduced ossification of the phalanx, metacarpals, and metatarsals were observed in fetuses at 2.55 mg/m^3; the developmental NOEL was 0.46 mg/m^3. Maternal toxicity (decreased body weight gain and reduced relative food efficiency) was observed at all exposure levels tested (NOEL <0.46 mg/m^3). It was hypothesized that the developmental anomalies observed in the inhalation studies may have been caused, or at least exacerbated, by bradypnea in the dams, and may not have been the direct result of cyfluthrin exposure.

In the oral (gavage) developmental toxicity study in rats, no developmental toxicity was observed at doses up to the HDT of 30 mg/kg/day, while maternal toxicity (behavioral

changes in gait and coordination) was observed at 10 mg/kg/day (maternal NOEL = 3 mg/kg/day).

In the gavage prenatal developmental toxicity study in rabbits, evidence of developmental toxicity (increased resorptions and postimplantation loss) occurred only in the presence of maternal toxicity (decreased body weight gain and food consumption during treatment) at the LOEL of 60 mg/kg/day. Both the maternal and developmental NOELs were 20 mg/kg/day.

In the two-generation reproduction study in rats, reduced pup weights were observed at dietary levels of 7.5 mg/kg/day and above with a NOEL of 2.5 mg/kg/day. Parental systemic toxicity (decreased body weights) was observed at 22.5 mg/kg/day with a NOEL of 7.5 mg/kg/day.

In a 7-day inhalation toxicity study in mice, dams were exposed together with their 10-day old offspring at concentrations of 0, 0.006, 0.015 or 0.058 mg/L for 6 hours per day for 7 consecutive days. The LOEL for pups was 0.015 mg/L based on clinical signs of toxicity and increased spontaneous motor activity in females 4 months after exposure. At the highest dose tested, all the pups died during the first exposure period. The NOEL for pups was 0.006 mg/L. The parental NOEL (dams) is 0.058 mg/L (HDT). No effects were observed at any dose level.

d. Determination of Safety for Infants and Children

An acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats (via gavage and inhalation) and rabbits (via gavage) have been submitted to the Agency. In addition, a 7-day inhalation study conducted with mouse dams and their offspring has been submitted. There are no data gaps for the assessment of the effects of cyfluthrin following *in utero* or early postnatal exposure. Suggested sensitivity of rats to *in utero* exposure to cyfluthrin was hypothetically linked to bradypnea in the dams and was judged not to be a valid consideration in the calculation of risk. However, evidence of increased sensitivity of young rats following pre- and/or postnatal exposure to cyfluthrin was observed in the two-generation reproduction study and in the 7-day inhalation study in mice

Based upon these considerations, the Hazard ID Committee (7/24/97) determined that the 10 x factor to account for enchanced sensitivity of infants and children (as required by FQPA) may be reduced to 3 x because of the lack of severity of the effect (reduced body weight), but offspring were more sensitive). The 7-day inhalation study was received after the decision to use the 3 x factor. This study was examined by a subsequent subcommittee of the Hazard ID Committee and it was determined that for inhalation endpoints, the 3 x factor adequately protects infants and children because the inhalation endpoints are based on rat studies which have NOELs that are at least 10 times lower than the pup NOEL in the 7-day study.

e. Dermal Absorption

The Hazard ID Committee recommended using a dermal absorption rate of 25% for cyfluthrin based on weight-of-the-evidence available for structurally-related pyrethroids.

A dermal absorption rate of 25% was selected based on the 6-45% dermal absorption observed with the structurally related pyrethroids permethrin (22-45%), deltamethrin (15%) and tralomethrin (6-25%). A range of dermal absorption factors were presented for permethrin and tralomethrin because the studies indicated higher absorption at lower exposure doses but not for deltamethrin. Since no study is available with cyfluthrin, a value of 25% is assumed.

f. Other Toxicological Endpoints

i. Acute Dietary

The Hazard ID Committee considered the NOEL of 20 mg/kg/day from the rabbit developmental study to be the appropriate endpoint due to resorptions at the LEL of 60 mg/kg/day. The NOEL from rat study (10 mg/kg/day) is lower; however this was the highest dose tested and there were some effects at 10 mg/kg/day in the pilot rat study.

ii. Short and Intermediate Term Occupational and Residential

For the **short and intermediate term dermal endpoints**, the Hazard ID Committee considered the NOEL of 20 mg/kg/day from the rabbit developmental study to be the appropriate endpoint due to resorptions and increase in % incidence of postimplantation loss at the LEL of 60 mg/kg/day. The dermal absorption rate is 25% and the recommended MOE is 300, which includes FQPA considerations.

For the **short term inhalation endpoint**, the Committee recommended the NOEL of 0.00044 mg/L based on decreases in body and thymus weights, hypothermia, and clinical pathology at 0.00604 mg/L in a 28-day inhalation study. The recommended MOE is 300 which includes FQPA considerations. The additional FQPA uncertainty factor was included for inhalation because an inhalation study is available in the mouse which indicates increased sensitivity of the pups in comparison to the dams.

For the **intermediate term inhalation endpoint**, the Committee recommended the NOEL of 0.00009 mg/L based on behavioral effects in rats at 0.00071 mg/L in a 90-day inhalation study. The recommended MOE is 300 which includes FQPA considerations.

iii. Chronic Occupational and Residential (Non-Cancer)

For the chronic dermal endpoint, the Committee recommended using the NOEL of 2.5 mg/kg/day from the chronic feeding/carcinogencity study in the rat with a dermal absorption factor of 25%. As stated before in the RfD section, the LEL of 6.2 mg/kg/day was based on decreased body weights in males and inflammatory foci in the kidneys of females. The recommended MOE is 300 (including FQPA considerations).

Cyfluthrin

2. Dietary Exposure Assessment

Background

Tolerances have been established under 40 CFR §180.436 for residues of cyfluthrin [cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate] in numerous plant commodities with tolerances ranging from 0.05 to 4.0 ppm; in the fat, meat and meat byproducts of cattle, goats, hogs, horses and sheep at 0.40 ppm; milkfat at 2.5 ppm (reflecting 0.08 ppm in whole milk); and poultry fat, meat and meat byproducts and eggs at 0.01 ppm. Food and feed additive tolerances of 0.05 ppm have also been established as a result of use of cyfluthrin in food/feed handling establishments and are listed in 40 CFR §185.1250 and §186.1250, respectively.

Product Chemistry

The manufacturing process of technical grade cyfluthrin has been previously described and found to be acceptable (see PP No. 4F3046, 5/18/84 memo of K. Arne). None of the actual or theoretical impurities are expected to cause residue concerns.

Nature of the Residue

The nature of the residue in plants and animals is adequately understood. The HED Metabolism Committee met on August 12, 1996 to discuss cyfluthrin metabolism. It was concluded that cyfluthrin should be regulated in a similar manner as permethrin and cypermethrin. Tolerances would be expressed in terms of the parent cyfluthrin only. The risk assessment will consider residues of cis- and trans-DCVA in addition to the parent compound. Since this time, HED has reconsidered this position and determined that DCVA residues need not be included in the risk assessment (see Attachment XX for detailed discussion

Analytical Methods

Analytical methodology suitable for the enforcement of cyfluthrin tolerances in plant and animal commodities is available.

A GC method with electron capture detection (GC/ECD) is available for the enforcement of tolerances for cyfluthrin residues in/on plant commodities. This method was previously described in Mobay Report 85823 ("A Gas Chromatographic Method for Baythroid® 2 Residues in Crops", MRID 40301501) and has undergone successful petition method validation (PMV; PP#4F3046). This method was forwarded (3/88) to FDA for inclusion in PAM II.

Analytical methodology (Mobay Report 85883: "An Analytical Method for Baythroid® 2 in Bovine and Poultry Tissues, Milk, and Eggs", MRID 40301502) for enforcing cyfluthrin residues in animal commodities is available. This method has also undergone successful PMV (PP#4F3046), and was forwarded (3/88) to FDA for inclusion in PAM II.

Data pertaining to the recovery of cyfluthrin using FDA's multiresidue methods were submitted (Mobay Report 94892; MRID 40355901). These multiresidue screening data were forwarded (PP#4F3046, M. Bradley, 12/4/87) to FDA. The FDA Pestrack Data Base (PAM Vol. I, Appendix, dated 11/6/90) indicates that complete recovery has been obtained for cyfluthrin under FDA multiresidue
method A.

Magnitude of the Residue

MRID # and a report entitled "Revised Chronic and Acute Dietary Exposure Analyses for Cyfluthrin", revised 10/10/97, MRID # not yet available) contains a list of all residue values used in the chronic and acute dietary exposure analyses (including drinking water). The residue values have been verified by HED and are appropriate.

Plants

For purposes of dietary risk assessment, residue data generated from residue field trials conducted at maximum application rates and minimum pre-harvest intervals were used. For chronic dietary exposure analysis, mean anticipated residues values were calculated , substituting half the limit of detection for those samples for which residues were reported as non-detectable. For the acute dietary exposure analysis, field trial residue distributions were used in the Monte Carlo simulations for those foods considered single serving commodities (e.g., carrots, peppers), For those food considered to be blended or processed (e.g., grains and oils), mean field trial residues were calculated, substituting the full limit of detection for those samples for which residues were reported as non-detectable.

All commodities with existing cyfluthrin tolerances, with the exception of hops and radishes, had field trial data available for the analyses. For hops and radishes, the tolerances were used in dietary exposure assessments.

Percent crop treated data, verified by BEAD (see attached memos from D.Brassard), were used in the dietary analyses.

Animals

For chronic dietary analyses, dietary burdens were calculated using mean field trial residues, adjusted for percent of crop treated and applying appropriate processing factors, for all feed items. For the acute analysis, mean field trial residues (no adjustment for percent of crop treated) were used for those fed items that are processed or blended (e.g. grains); while the highest field trial residue value was used for the remaining feed items.

The secondary residues levels in animal tissues were then calculated by multiplying the total dietary burden by the tissue to feed ratio calculated from feeding studies.

Food Handling Establishment Uses

In accordance with Agency guidelines, potential FHE contributions were included in the chronic dietary exposure assessment, but not the acute exposure assessment. A tolerance of 0.05 ppm has been established for residues of cyfluthrin in foods potentially exposed to the insecticide during treatment of food handling establishments. This tolerance level, corrected for percent of FHEs treated with cyfluthrin (value verified by BEAD), was used to estimate exposure for all foods except those having agriculatural uses of cyfluthrin.

Exposure Chracterization

Although dietary exposure estimates were refined, additional refinements could have been performed. Instead of relying exclusively on residue field trial data, monitring data could have been incorporated in the analyses. Aditionally, for the acute dietary analysis, the livestock dietary burdens could have been constructed using Monte Carlo techniques, which would have likely reduced exposure estimates from meat and milk.

Attachment 8

Cyhalothrin

Toxicology and Residue Chemistry Details

Lambda Cyhalothrin

1. Hazard Assessment

a. Acute Toxicity

Acute Toxicity of Lambda Cyhalothrin

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00259805	LD_{50}= 79.0 mg/kg (M) 56.0 mg/kg (F)	II
81-2	Acute Dermal	00259805	LD_{50}=632 mg/kg (M) 696 mg/kg (F)	II
81-3	Acute Inhalation	waived	--	--
81-4	Primary Eye Irritation	00259805	Mild irritant	II
81-5	Primary Skin Irritation	00259805	Non irritant	IV
81-6	Dermal Sensitization	00259805	Non sensitizer	--
81-8	Acute Neurotoxicity	--	--	--

Note: Many of the following studies were conducted with cyhalothrin. Lambda-cyhalothrin is a mixture of 2 of the 4 stereoisomers of cyhalothrin.

b. Subchronic Toxicity

Feeding Studies

In a 90-day feeding study in male and female SPF Alk/AP Wistar-derived rats, 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). Twenty rats/sex/dose level were assigned. 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. Body weight gain and food consumption were significantly reduced for both sexes at 12.5 mg/kg/day. There was also a slight but statistically significant reduction in food efficiency in females at this dose level. The NOEL is 2.5 mg/kg/day and the LEL is 12.5 mg/kg/day based on reduction in bodyweight gain and food consumption in both sexes and food efficiency in females.

In a 90-day feeding study in male and female SPF Alderley Park Wistar-derived rats, 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 (0, 0.5, 2.5, 12.5 mg/kg/day). 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. Body weight gain was significantly reduced in males at 12.5 mg/kg/day. 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 dose levels. The NOEL is 2.5 mg/kg/day and the LEL is 12.5 mg/kg/day based on decreased bodyweight gain.

In a 28-day study in the mouse, **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 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.

Dermal Studies

Review in progress: from study report: groups of 5 male and 5 female rats received repeated dermal applications of lamda-cyhalothrin (96.6%) in olive oil at 1, 10, or 100 mg/kg (reduced to 50 mg/kg after two or three applications, 6 hours/day for 21 consecutive days. No significant signs of skin irritation was observed at any dose level.

Two male rats were found dead after 3 applications of 100 mg/kg. There was no evidence prior to death, at postmortem examination, or from histopathology, of the possible cause of death, but it is thought likely to be due to pyrethroid toxicity. Animals dosed with 50 mg/kg/day displayed clinical signs of slight general toxicity (bizarre behavior, paw flicking, splayed gait, sides pinched in, thin, tip-toe gait, reduced stability, dehydration and reduced splay reflex). Effects on body weight gain and food consumption were also seen in males at this dose level. No toxicologically significant treatment-related effects were observed at any other dose level. The NOEL is 10 mg/kg/day and the LEL is 100/50 mg/kg/day based on death, clinical signs of toxicity and decreased bodyweight gain and food consumption.

Inhalation Studies

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 0.3, 3.3, or 16.7 ug/L. The NOEL was 0.3 ug/L and the LOEL was 3.3 ug/L based on decreased bodyweight gains (high dose males) and food consumption (high dose, both sexes), clinical signs of toxicity (paw flicking, tail erections, tiptoe gait, lachrymation or salivation), punctate foci on cornea (both sexes, mid- and high dose), raised prothrombin time, changes in hematology, clinical chemistry and urinalysis parameters and a slight increase in the incidence of alveolitis in females. The MMAD ranged from 1.47 to 1.91μm and the GSD ranged from 1.02 to 2.24μm. During exposure, salivation and lachrymation were observed in some animals exposed to 3.3 and 16.7 ug/l of the test material, and auditory hypoaesthesia was present in most animals exposed to 16.7 ug/l.

c. Chronic Toxicity/Carcinogenicity

Dogs

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 following parameters were measured: daily clinical pathology, gross necropsy and microscopic examinations. No significant clinical signs were seen 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 NOEL is 0.1 mg/kg/day and the LEL is 0.5 mg/kg/day based on clinical signs of neurotoxicity and other effects.

Rats

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. Female rats fed 50 and 250 ppm cyhalothrin in the diet showed decreased relative adrenal weights. However, the control adrenal weights appeared high when compared to the males. Additional effects at 250 ppm levels included reduced mean body weight (11% for males and 8.5% for females) and decreased food consumption in both sexes. There were no neurological effects noted. The LEL for chronic toxicity in rats is 12.5 mg/kg/day and the NOEL is 2.5 mg/kg/day. There was no indication of oncogenic activity for this chemical.

Mice

Groups of 52/sex CD-1 mice were fed cyhalothrin 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. Under the conditions of the study, cyhalothrin was not oncogenic when fed to mice. There was a significant increase in mammary adenocarcinomas in females receiving 100 and 500 ppm when compared to controls; however, the concurrent control incidence was unusually low and the increased incidence was therefore judged not to be of biological significance. The LOEL for systemic chronic toxicity was 500 ppm, based on decreased weight gain in males during the first 13 weeks of the study and the NOEL was 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 and above in males and females. The number of animals affected were relatively small at 100 ppm (up to 5% males by week 78 versus none in controls), but were significantly more at 500 ppm (up to 30% males at week 52). Thirty-nine percent of the controls had hunched posture by week 104 versus 26, 47 and 32% in the low, mid- and high dose groups. On 2/12/93 and on 6/16/94, the HED RfD/Peer Review Committee concluded that cyhalothrin was not tested at a sufficiently high dose level for carcinogenicity. There was also some concern about incidences of mammary tumors in females (1/52, 0/52, 7/52, 6/52). It was 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. It was also decided by the Toxicology Branch 1 (TB-1) that there is not enough toxicological concern to warrant a requirement for a new carcinogenicity study in the mouse at this time. However, TB-1 is still questioning the adequacy of dosing in this study and may require additional testing in the future. This decision was based on data from the mouse study, the 28-day range finding study in the mouse and the results from mouse and rat carcinogenicity studies conducted with similar pyrethroids.

d. Developmental Toxicity

In a developmental study conducted with NZW rabbits, cyhalothrin (89.25%) was tested at the following dose levels: 0, 3, 10, 30 mg/kg/day during the gestation period (days 6 through 18). The maternal NOEL was 10 mg/kg/day and the maternal LOEL was

132

30 mg/kg/day based on decreased body weight gain (48% of controls) during the dosing period. The developmental NOEL was 30 mg/kg/day (HDT). No effects were observed.

In a developmental study conducted with SPF CD rats, **cyhalothrin** (89.25%) was tested at the following dose levels: 0, 5, 10, 15 mg/kg/day during the gestation period (days 6 through 15). The maternal NOEL was 10 mg/kg/day and the maternal LOEL was 15 mg/kg/day based on reduced body weight gain (70% of control) and food consumption (as low as 76%) during the dosing period. The developmental NOEL was greater than 15 mg/kg/day (HDT). No effects were observed.

e. **Reproductive Toxicity**

In the three-generation reproduction study, male and female SPF Wistar-derived rats were fed **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). 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 reproductive and parental NOELs are 1.5 mg/kg/day and the reproductive and parental LOELs are 5.0 mg/kg/day. The developmental NOEL is 5.0 mg/kg/day (highest dose tested)

f. **Mutagenicity**

Mutagenicity Studies With Lambda-Cyhalothrin	
Study	Results
Gene Mutation Assay (Ames Test) MRID/Accession 073981 Report # YV1309 Date: 7/12/84 Acceptable	Not mutagenic under conditions of assay. Tested from 1.6 - 5000 ug/plate with & without metabolic activation. Compound precipitated at 1000 and 5000 ug/plate indicating limit of solubility.
Gene Mutation Assay (Mouse Lymphoma Cells) MRID/Accession 073981 Report # CTL/P/1340 Date: 8/9/85 Acceptable	Tested at dose levels ranging from 125-4000 ug/ml. Chemical precipitated at all dose levels, particularly higher levels. PP321 did not appear to be mutagenic under conditions of study.
Structural Chromosomal Aberration Assay (In vitro cytogenetics in human lymphocytes) MRID/Accession 073981 Report # CTL/P/1333 Date: 7/3/85 Acceptable	Tested at 100, 500 and 1000 ug/ml. Levels based on limit of solubility. Under conditions of bioassay, PP321 was not a clastogen.

133

Mutagenicity Studies With Lambda-Cyhalothrin	
Study	Results
Other Genotoxicity Assays (Mouse Micronucleus) MRID/Accession 073981 Report # CTL/P/1090 Date: 10/31/84 Acceptable	Test animals given a single i.p. dose of either 35 mg/kg or 22 mg/kg. Number per 500 polychromatic erythrocytes containing micronuclei were scored. No increase in number of micronuclei were found when compared to controls.

g. Metabolism

Summary of Metabolism Studies With Lambda-Cyhalothrin (PP321) or Cyhalothrin	
Study	Results
Metabolism - rat MRID/Accession 073217 Report # 1468814 KMR 002/01 Date: 10/08/81 Acceptable in combination with other studies	55% oral absorption. Extensively metabolized when absorbed. After s.c. admin., urinary/fecal excretion ratio 2.5:1.0. Over 50% of dose remained in carcass 7 days after s.c. dose. Metabolism includes cleavage of ester to cyclopropylcarboxylic acid & phenoxybenzyl deriv. Conducted on cyhalothrin.
Metabolism - rat MRID/Accession Report # 1468814 KMR 002/03 Date: 9/13/84 Acceptable in combination with other studies	Distribution patterns & excretion rates in multiple oral dose studies similar to single oral dose studies. Accumulation of unchanged compound in fat upon chronic admin. Otherwise, rapidly metabolized & excreted. Conducted on cyhalothrin.
Metabolism - rat MRID/Accession 073217 Report # MPH 01 Date: 3/23/83 Acceptable in combination with other studies	Cyclopropyl carboxylic acid, 3-phenoxybenzoic acid, glucuronide conjugate 3-4'-hydroxyphenoxy)benzoic acid and sulfate conjugation identified in urine. Conducted on cyhalothrin.
Metabolism - rat MRID/Accession 073981 Report # URO169 Date: 7/31/84 Acceptable in combination with other studies	Cyhalothrin taken up slowly by fat & released slowly. Rapidly released by blood, kidneys, liver. Rate of metabolism of both enantiomer pairs likely identical (i.e. PP321 & PP563).

Summary of Metabolism Studies With Lambda-Cyhalothrin (PP321) or Cyhalothrin	
Study	Results
Metabolism - rat MRID/Accession 073981 Report # URO178 Date: 3/19/85 Acceptable in combination with other studies	Absorption, distribution, metabolism & excretion patterns of PP321 & cyhalothrin following single dose of 1 mg/kg in male rat appear to be identical.
Metabolism - dog MRID/Accession 073217 Report # 146814 KMD 005 Date: 9/17/84 Acceptable	Absorption of C^{14} benzyl label 80% & of C^{14} cyclopropyl label 48%. Metabolite patterns different, indicating extensive cleavage of ester bond. 7 metabolites identified for benzyl (urine) and 12 metabolites identified for isopropyl label. In feces, large proportion radioactivity due to unchanged compound. Excretion in urine & feces rapid (nearly all in 48 hrs.). Cyhalothrin tested.
Metabolism - human MRID not available as yet Report # CTL/P/4208 Study # XH2429 Date: 1/25/94 Review in progress	Oral administration of single 5 mg dose: equal amounts of 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane-1-carboxylic acid (TFMCVA); and 3-phenoxybenzoic acid (3PBA) and 3-(4-hydroxyphenoxy)benzoic acid (4OH3PBA) excreted with peak excretion rates occurring between 2-14 hours after dosing. Estimated mean amount lambda-cyhalothrin (LCH) absorbed: 59% (50-64%). Unabsorbed LCH & TFMCVA detected in feces with exception of 1/6 subjects accounted for < 1.5% of dose. Trace amounts LCH & TFMCVA in plasma. Dermal dose: 20 mg/800 cm^2 in cotton seed oil: concentrations of metabolites extremely low. Estimated mean amount LCH absorbed 0.12% (0.04-0.19%).

h. Neurotoxicity

No neurotoxicity studies are available for either cyhalothrin or lambda-cyhalo

i. Other Toxicological Considerations

No special studies are available for either cyhalothrin or lambda-cyhalothrin.

2. Dose/Response Assessment

a. Reference Dose (RfD)

The RfD is currently based on a NOEL of 0.1 mg/kg/day for clinical signs of neurotoxicity and other effects observed at 0.5 mg/kg/day in a long-term study in dogs using an uncertaintly factor of 100 to account for inter-species extrapolation and intra-species variability. On this basis the RfD is calculated to be 0.001 mg/kg/day. Refer to the attached RfD document for a more detailed discussion.

b. Carcinogenic Classification and Risk Quantification

Lambda cyhalothrin is classified as a category D chemical based on the inadequate dosing in the mouse study. Refer to the mouse oncogenicity summary and the attached RfD documents for a more detailed discussion of this issue.

c. Developmental Concerns

Refer to the attached FQPA document on lambda cyhalothrin written by Susan Makris and David Anderson for a detailed discussion of this issue.

d. Determination of Safety for Infants and Children

Refer to the attached FQPA document on lambdacyhalothrin written by Susan Makris and David Anderson for a detailed discussion of this issue.

e. Dermal Absorption

There is no series 85-2 dermal penetration/absorption study available. A dermal absorption rate of 25% was selected based on the 6-45% dermal absorption observed with the structurally related pyrethroids permethrin (22-45%), deltamethrin (15%) and tralomethrin (6-25%). A range of dermal absorption factors were presented for permethrin and tralomethrin because the studies indicated higher absorption at lower exposure doses but not for deltamethrin. Since no study is available with lambda-cyhalothrin, a value of 25% is assumed.

A metabolism and pharmacokinetics study of lambda-cyhalothrin in male humans has recently been submitted. Agency review of the study is underway, but has not yet been completed. The summary page of the study indicates that dermal absorption in humans is estimated to be between 0.04 to 0.19% with a mean of 0.12%. Preliminary examination of the study indicates that it is likely to be acceptable to the Agency. At

the present time, the default 25% absorption rate will be used. However, when the review of this study is completed, the dermal absorption factor will be recon

f. Other Toxicological Endpoints

i. Acute Dietary

The acute dietary endpoint is provided in the table below. For a complete discussion on the selection of the acute dietary endpoint, refer to the attached TES document for lambda-cyhalothrin.

ii. Short and Intermediate Term Occupational and Residential

The short and intermediate term occupational and residential endpoints are provided in the table below. For a complete discussion on the selection of these endpoints, refer to the attached TES document for lambda-cyhalothrin.

iii. Chronic Occupational and Residential (Non-Cancer)

The chronic occupational and residential endpoints are provided in the table below. For a complete discussion on the selection of these endpoints, refer to the attached TES document for lambda-cyhalathrin.

137

TABLE x. Summary of Toxicological Endpoints for Lambda-Cyhalothrin

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Acute	Dietary	NOEL: 0.5 mg/kg/day (gait abnormalities in dogs on day 2) MOE = 100
Short-Term (1-7 days) Occupational/Residential	Dermal	NOEL: 10.0 mg/kg/day (mortality, clinical signs, decr. body wt. & food consumption in 21-day dermal rat study) MOE = 100
Intermediate-Term (one week to several months) Occupational/Residential	Dermal	NOEL: 10.0 mg/kg/day (mortality, clinical signs, decr. body wt. & food consumption in 21-day dermal rat study) MOE = 100
All time periods	Inhalation	NOEL: 0.3 µg/L (clinical signs of neurotoxicity, changes in clinical chemistry, hematology & urinalysis & alveolitis in 21-day inhalation study in rats) MOE = 100
Cancer	Dietary/Dermal/Inhalation	Classified as Group D:questions on adequacy of dosing in mouse study
Chronic (non-cancer)	Dietary	RfD: 0.001 mg/kg/day based on NOEL 0.1 mg/kg/day (neurotox. clinical signs, ataxia, convulsions in dog study) UF=100

3. Dietary Exposure

Background

Tolerances have been established under 40 CFR 180.438 for residues of lambda-cyhalothrin and its epimer expressed as: a 1:1 mixture of (S)-α-cyano-3-phenoxybenzyl-(Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and (R)-α-cyano-3-phenoxybenzyl-(Z)-(1S,3S)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and its epimer a 1:1 mixture of (S)-α-cyano-3-phenoxybenzyl-(Z)-(1S,3S)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclo-propanecarboxylate and (R)-α-cyano-3-phenoxybenzyl (Z)-(1R,3R)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclo-propanecarboxylate in numerous plant commodities at levels ranging from 0.01 to 6.0 ppm; in the fat of cattle, goats, hogs, horses, and sheep at 3.0 ppm; in the meat and meat byproducts of cattle, goats, hogs, horses, and sheep at 0.2 ppm; milkfat at 5.0 ppm (reflecting 0.2 ppm in whole milk); and poultry fat, meat, meat byproducts, and eggs at 0.01 ppm. Food additive tolerances have been established for residues of lambda-cyhalothrin in all food items (other than those already covered by a higher tolerance as a result of use on growing crops) in food handling establishments (0.01 ppm), dried hops (10.0 ppm), corn grain flour (0.15 ppm), sunflower oil (0.30 ppm), and wheat bran (0.2 ppm). Feed additive tolerances for residues of lambda-cyhalothrin on sunflower hulls (0.50 ppm), tomato pomace (6.0 ppm), and wheat bran (0.2 ppm) have been established under 40 CFR 186.3765.

Product Chemistry

The manufacturing process for lambda-cyhalothrin was submitted in support of PP#6F3318 (MRID# 401820-01) and discussed in S. Willett's memo of 9/29/87. There are no toxicological concerns for any of lambda-cyhalothrin impurities. Discussion about structure and isomers appears in M. Flood's memo of 9/19/91 (PP#7F3560/7H5543).

Nature of the Residue in Plants

Data on plant metabolism show that lambda-cyhalothrin is metabolized by cleavage of the ester linkage to form cyclopropane carboxylic acids and the corresponding phenoxybenzoic acid and/or 3-phenoxybenzyl alcohol (M. Flood's memo of 1/22/92, PP#7F3560/7H

HED has decided that the plant metabolites need not appear in the tolerance expression at this time due to lack of toxicological concern and low concentrations found from residue studies (M. Flood's memo of 1/22/92, PP#7F3560/7H5543). The residue to be regulated is lambda-cyhalothrin and its epimer as specified in 40 CFR §180.438.

Nature of the Residue in Animals

Studies of lambda-cyhalothrin metabolism in ruminants and poultry have been reviewed. In addition to the plant metabolites, lambda-cyhalothrin animal metabolites include 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2-hydroxymethyl-2-methylcyclopropane-carboxylic acid (OH-CPA) and 4-hydroxy-3-phenoxybenzoic acid (4'-OH-3-PBAcid) (PP# 1F3992, M. Flood,

Lambda-cyhalothrin is the major component of the residue, except for kidney and liver of ruminants and liver of poultry. In addition to the plant metabolites, 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2-hydroxymethyl-2-methylcyclopropane-carboxylic acid (OH-CPA) and 4-hydroxy-3-phenoxybenzoic acid (4'-OH-3PBAcid) may be present in significant quantities. A residue transfer study in which cows were fed dietary levels of 8, 25 or 80 ppm lambda-cyhalothrin demonstrated that, at $\leq$ 8 ppm, OH-CPA levels in tissue would not exceed 0.01 ppm (See Reference in PP# 2F4109, 2F4114, 7F3560, and 1F3992, M. Flood, 8/31/92). As with plants, the residue to be regulated is lambda-cyhalothrin and its epimer.

HED has determined that animal metabolites do not need to appear in the tolerance expression at this time (PP# 1F3992, M. Flood, 12/26/91 and FAP#OH5599, M. Flood, 8/31/9

Analytical Methods

The analytical methodology used to determine the residues of lambda-cyhalothrin and its epimer in plant matrices is ICI Method 81, with minor modifications, which was first described in MRID# 400540-01. This method has undergone EPA Method Validation for soybeans (PP#6F3318/PP#7F3488, E. Greer memo of 9/30/87).

The petitioner has determined recoveries of cyhalothrin and its metabolites PP890, and 3-PBAcid under FDA's multiresidue protocols (PP#7F3488, S. Willett's memo of 3/15/88; PP#7F3560/7H5543, M. Flood's memo of 9/19/91). As of 11/2/90, results have not been listed in FDA's summary.

Magnitude of the Residue

A report entitled "Reanalysis of Chronic and Acute Exposure and Risk for Lambda-Cyhalothrin Residues" (Report by Leila M. Barraj at Novagen Sciences, Inc., dated 10/10/97, MRID# not yet available) contains revisions to the originally submitted report: "Chronic and Acute Dietary Exposure Analyses and Risk Assessment for Lambda-Cyhalothrin Residues in Food" (Report by Leila M. Barraj at Novagen Sciences, Inc., dated 9/14/97, MRID# 443535-03). The 10/10/97 report contains a list of all residue values used in the chronic and acute dietary exposure analyses (including drinking water). The residue values have been verified by HED and are appropriate.

Plant Commodities

Field Trial Studies

For the purposes of dietary risk assessment, residue data generated from residue field trials conducted at maximum application rates and minimum pre-harvest intervals were used to estimate chronic and acute dietary exposure to potential residues of lambda-cyhalothrin. For chronic dietary exposure analyses, mean anticipated residue values were calculated, substituting one-half the limit of detection for those samples for which residues were reported as non-detectable. For acute dietary exposure analyses, the entire range of field trial residue data which reflected the current labeled maximum rate and minimum PHI for single serving commodities were used (Tier 3 modeling, as outlined in "Final Office Policy for Performing Acute Dietary Exposure Assessment", D. Edwards, 6/13/96). For those foods considered to be blended, mean field trial residues were calculated, substituting the full limit of detection for those samples for which residues were reported as non-detectable (Tier 2 modeling) used residue distributions from field trial studies.

Percent Crop Treated Data

The percent crop treated data that were used in the dietary analyses were verified by BEAD (see attached memos from D. Brassard).

Animal Commodities

For chronic dietary analyses, dietary burdens were calculated using mean field trial residues, adjusted for percent of crop treated and applying appripriate processing factors, for all feed items. For acute dietary analyses for poultry commodities, mean field trial residues (with no adjustment for percent of crop treated) were used for those feed items that are processed or blended, while the highest field trial residue values were used for the remaining f For acute dietary analyses for cattle (beef and dairy), field trial residue data (reflecting the maximum labeled application rates and minimum PHIs) and percent of crop treated data were used in conjunction with Monte Carlo methods to select the feed items comprising the potential cattle diets and associated residues.

The secondary residue levels in animal tissues were then calculated by multiplying the total dietary burden by the tissue-to-feed rario calculated from the lactating ruminant or laying hen feeding studies.

International Tolerances/Maximum Residue Limits

No Codex MRLs for resuides of lambda-cyhalothrin have been established (only cyhalothrin). No Canadian MRLs have been established for residues of lambda-cyhalothrin. Mexico has established tolerances for residues of lambda-cyhalothrin on cottonseed (0.05 ppm) which is in harmony with the U.S. tolerance. Mexico has established tolerances which are below their U.S. counterparts for corn grain (0.01 vs. 0.05 ppm) and sorghum grain (0.1 vs. 0

Exposure Characterization

The dietary exposure estimates calculated in this memo are based on very highly refined residue estimates. Percent of crop treated data were used for all commodities and field trial residue data both with (acute) and without (chronic) Monte Carlo modeling. For acute dietary analyses for cattle (beef and dairy), Monte Carlo methods to select the feed items comprising the potential cattle diets and associated residues. Additional sources of more refined data would include use of monitoring data (if available).

Chemical: **Lambda-Cyhalothrin**
From: Susan Makris
To: Hazard ID SARC
Date: July 17, 1997

The following evaluation of the chemical lambda-cyhalothrin is provided to address FQPA considerations on the sensitivity of infants and children.

FQPA assessment of additional sensitivity for infants and children:

Adequacy of data package: An acceptable three-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits have been submitted to the Agency, meeting basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. There are no data gaps for the assessment of the effect of lambda-cyhalothrin following *in utero* or early postnatal exposure.

Susceptibility issues: The data demonstrated no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to lambda-cyhalothrin.

In both the prenatal developmental toxicity studies in rats and rabbits, there was no evidence of developmental toxicity at the highest doses tested (15 mg/kg/day in rats and 30 mg/kg/day in rabbits). Maternal toxicity (decrease body weight gain and/or food consumption) was observed at these same doses, with a maternal NOEL of 10 mg/kg/day for both species.

In the three-generation reproduction study in rats, offspring toxicity (reduced pup weight) was observed at the dietary level which produced body weight decrements in the parental animals (LOEL = 100 ppm; 5.0 mg/kg/day). The NOELs for parental and offspring toxicity were equivalent at 30 ppm (1.5 mg/kg/day).

Summary/Conclusion:

1. There is no data gap.
2. There is no evidence of additional sensitivity to young rats or rabbits following pre- or postnatal exposure to lambda-cyhalothrin.

Based upon these considerations, the Committee determined that the application of an additional uncertainty factor in the risk assessment of lambda-cyhalothrin under the provisions of the FQPA mandate to ensure the protection of infants and children is not warranted.

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

REVISED 7/28/97

Chemical Name: LAMBDA-CYHALOTHRIIN

PC Code: 128867

Structure:

The Health Effects Division Hazard Identification Assessment Review Committee considered the available toxicology data for Lambda-cyhalothrin at a meeting held on July 24, 1997. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route-to-route extrapolation is necessary, the data to perform this extrapolation are provided.

REPORT PREPARED BY: _____ Date: _____
Jess Rowland, M.S

CHAIRMAN
HAZARD ID COMMITTEE: _____ Date: _____
K. Clark Swentzel, M.S

144

DERMAL ABSORPTION DATA

Dermal absorption study was not available. A dermal absorption rate of 25% was recommended based on the weight-of-the-evidence for structurally-related pyrethroids.

% Absorbed25%

****

ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Guideline No.: Chronic Toxicity - Dog §83-1b

MRID No. 40027902

Summary: In a chronic toxicity study, beagle dogs (6 sex\dose) were given oral administration of gelation capsules containing lambda-cyhalothrin (96.5%) at 0,, 0.1, 0.5 or 3.5 mg/kg/day 7 days/week for 12 month. The following parameters were measure: daily clinical pathology, gross necropsy and microscopic examinations. No clinical signs were seen 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-hour post dosing during week 2 and in the week four time 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, muscle tremors and convulsions. Treatment had no effect on body weights, hematology, clinical chemistry, urinalysis, gross or histopathology. The LOEL was 0.5 mg/kg/day and the NOEL was 0.1 mg/kg/day.

Dose and Endpoint for use in risk assessment: NOEL=0.5 mg/kg/day based on ataxia and convulsions at 3.5. mg/kg/day (LOEL).

Comments about study and/or endpoint: Ataxia were also seen in dogs receiving other structurally-related pyrethroids (e.g., bifenthrin, lambda cyhalothrin, fenpropathrin, telfluthrin and tralometh

This risk assessment is required.

****

SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

Study Selected - Guideline No.: 21-Day Dermal Toxicity §82-2

MRID No:: None (Summary page of the study report was sent by Fax to the Agency)

Summary: Groups of 5 male and 5 female rats received repeated dermal applications of lamda-cyhalothrin in olive oil at 1, 10, or 1000 mg/kg (reduced to 50 mg/kg after two or three applications for 21 consecutive days. The summary page stated no significant signs of skin irritation were observed at any dose level. Two male rats were found dead after 3 applications of 100 mg/kg. There was no evidence prior to death, at postmortem examination, or from histopathology, of the possible cause of death, but it is thought likely to be due to pyrethroid toxicity. Animals dosed with 50 mg/kg/ displayed clinical signs of slight general toxicity. Effects on body weight gain and food consumption were also seen in males at this dose

Dose and Endpoint for use in risk assessment: NOEL = 10 mg/kg/day based on systemic toxicity at 50 mg/kg/day (LOEL).

Comments about study and/or endpoint: Only a summary of the study results were provided to the Agency by Fax on 7/24/97. No details were available on the types of toxicity observed in this stu

This risk assessment is required.

****

INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

Study Selected - Guideline No.: 21-Day Dermal Toxiicty - Rat §82-2

MRID No: None

Summary: See Short-Term

Dose and Endpoint for use in risk assessment: NOEL = 10 mg/kg/day based on systemic toxicity at 50 mg/kg/day (LOEL).

Comments about study and/or endpoint: Only a summary of the study results were provided to the Agency by Fax on 7/24/97. No detail were available on the types of toxicity observed in this stu

This risk assessment is required.

****

CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

Study Selected - Guideline No.: Chronic Toxicity - Dog Chronic Toxicity - Dog §83-1b

MRID No.: 40027902

146

Summary: See Acute Dietary

Dose and Endpoint for use in risk assessment: NOEL= 0.1 mg/kg/day based on ataxia and convulsions in all dogs at 0.5 mg/kg/day (LOEL).

Comments about study and/or endpoint: This study/dose was used to derive the RfD. Since the dose (NOEL) selected is from an oral study, a dermal absorption rate of 25% should be used in risk as

This risk assessment is required.

****

INHALATION EXPOSURE (ANY TIME PERIOD)

Study Selected - Guideline No.: 21-Day Inhalation Toxicity-Rat §None

MRID No.: 4137702

Summary: In a 21-day in alation study, rats were exposed to lambda-cyhalothrin at 0.3,3.3, or 16/7ug/L. The NOEL was 0.3 ug/L and the LOEL was 3.3 ug/L based on decreased body weight gains, clinical signs, of toxicity (paw flicking, tail erections and tiptoe gait), punctate foci on cornea, raised prothrombin time, changes in hematology, clinical chemistry and urinalysis parameters and a slight increase in the incidence of alveolitis in females.

Dose and Endpoint for use in risk assessment: NOEL= 0.3 ug/L based on clinical signs indicative of neurotoxicity (paw flicking, tail erections and tiptoe gait) at 3.3 ug/L.

Comments about study and/or endpoint: Since this was the only inhalation study available, this dose should be used for short-, intermediate and chronic inhalation risk assessments.

This risk assessment is required.

**********C

CANCER CLASSIFICATION AND BASIS: No evidence of carcinogenicity was demonstrated in studies conducted with mice or rats.

Q_1* = Not Applicable

****

RfD AND BASIS:

RfD = 0.001 mg/kg/day

NOEL for critical study: 0.1 mg/kg/day

UF: 100 1

Study Type - Guideline No.: Chronic Toxicity/Carcinogenicy stud[illegible] -

MRID 40027902

****

148

ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Lambda Cyhalothrin

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00259805	LD_{50}= 79.0 mg/kg (M) 56.0 mg/kg (F)	II
81-2	Acute Dermal	00259805	LD_{50}=632 mg/kg (M) 696 mg/kg (F)	II
81-3	Acute Inhalation	waived	--	--
81-4	Primary Eye Irritation	00259805	Mild irritant	II
81-5	Primary Skin Irritation	00259805	Non irritant	IV
81-6	Dermal Sensitization	00259805	Non sensitizer	--
81-8	Acute Neurotoxicity	--	--	--

Memorandum 23 Aug 1993

SUBJECT: RfD/Peer Review Report of Cyhalothrin/ Karate

This document is not available electronically

Attachment 9

Cypermethrin

Toxicology and Residue Chemistry Details

Cypermethrin

1. Hazard Assessment

a. Acute Toxicity

81-1. Acute oral toxicity-rats.

Study #1. Nine groups of 5/sex of fasted Alderley Park strain rats were dosed as either 100, 150, 200, 250, 320, 400, 500, 640 or 800 mg/kg of cypermethrin (91.5%, 53:47 cis:trans) in maize (corn) oil (10 ml/kg) and reactions to treatment were noted. MRID No.: 00056800.
The following LD_{50}s were determined.

LD_{50} = 247 (187-329) mg/kg in males
= 309 (150-500) mg/kg in females

Deaths occurred at 150 mg/kg and above. All of the rats dosed with 500 mg/kg and above died. Deaths were usually in the first day. The symptoms noted included subdued behavior, excessive salivation, urinary and fecal incontinence, dehydration, ataxia, unsteady gait and piloerection. Some of these symptoms were said to persist for 14 days.

Study #2. Four groups of 5/sex Alderley Park strain rats were dosed with 105, 144, 333, 478 or 618 mg/kg cypermethrin 70% technical in corn oil (10 ml/kg) by gavage. The rats were observed for reactions to treatment for 15 days. MRID No.: 40377701.

The following LD_{50s} were determined.

LD_{50} = 263 (151-428) mg/kg in males
= 446 (303-622) mg/kg in females.

Deaths occurred at 144 mg/kg and above for males and at 333 mg/kg and above for females. All rats dosed with 618 mg/kg died. Deaths were usually in day 1 or 2 but occasionally on day 3. The symptoms induced decreased activity, ataxia, salivation, dehydration, piloerection, urinary incontinence and upward curvature of the spine. Signs were apparent within 48 hours but regressed by day 7. No macroscopic effects were evident. Initial body weight loss was recovered.

Study #3. The acute oral toxicity was assessed in fasted female Alderley Park strain rats using an "aqueous suspension" and a corn oil solution following gavage administration. For the aqueous suspension, dose levels of 3200, 4000, 5000 or 6400 mg/kg were administered. For the corn oil solution, dose levels of 1000, 1260, 1600, 2000 or 4000 mg/kg were used. The volumes of the aqueous suspension or the corn oil suspension were not stated. The cypermethrin used for the aqueous suspension was 93% purity and 33:67 cis:trans. The cypermethrin used for the corn oil solution was 92% pure and 44:56 cis:trans. The rats were observed for 14 days. MRID No.: 241597.
The following LD_{50}s were determined.

LD_{50} = 4123 (3946-4864) mg/kg in aqueous suspension.

LD_{50} = 1741 (1502-2019) mg/kg in corn oil solution.

152

The signs of toxicity in the rats dosed with the aqueous suspension were said to occur after one hour and last for up to 5 days and included coma, subdued behavior, ataxia of hind limbs, irritability/hypersensitivity, tremors and weight loss. The signs of toxicity in the rats dosed with the corn oil solution occurred after 1 to 3 hours and lasted up to six days and included the same signs as with the aqueous suspension. Overall, the lower values for cypermethrin in corn oil (refer to study #1) are considered best to define the acute oral toxicity of cypermethrin. Study 3 used an aqueous suspension and the medium to help suspend this water insoluble compound was not stated. In study 3, the volume of the corn oil administered was not provided. The series 81-8 acute neurotoxicity study described how the volume of corn oil affects the toxicity. In this study, the content of the cis isomer was much less than the content in the cis isomer in study #1. The cis isomer may govern the acute toxicity in mammals. Therefore, study #1 is considered to best describe the acute oral toxicity to cypermethrin.

81-2. Acute dermal toxicity

A-rats. A single groups of 5/sex Alderley Park strain rats were dosed with 4 ml (4920 mg)/kg of cypermethrin (91.5%, 53:47 cis:trans, undiluted) and observed for 14 days. MRID No.: 00056800. One male rat died three days after application. Thus the acute dermal toxicity to rats is > 4920 mg/kg/day. Signs of toxicity included subdued behavior, unsteady/defective gait, urinary incontinence, ungroomed appearance and piloerection. They were said to come 24 hours after application and persist (in some) for the 14 day observation period.

B-Rabbits. A single group of 5/sex New Zealand White rabbits were dosed with 2 ml/kg (2460 mg/kg) of cypermethrin (91.5%, 53:47 cis:trans, undiluted) on an abraded area of their skin and observed for 14 days. MRID No.: 00056800. No rabbits died and the LD_{50} was determined to be > 2460 mg/kg. The symptoms reported were in three males only and included lacrimation (one male), discharge from the eye and "nervous and shaking".

81-3. Acute inhalation toxicity-rats.

One group of 5/sex Sprague-Dawley strain rats were exposed to an atmosphere of 1.32 mg/L and two additional groups of 5 females were exposed to 2.19 or 3.48 mg/L for four hours. The MMAD of the particles ranged from 2.22 to 2.62 Um. MRID No.: 42395702. An LC_{50} of 2.5 (1.6-3.4) mg/L for females for a four hour exposure was determined. The LC_{50} for males was not calculated but is presumed to be a higher level than for females. The symptoms noted included ataxia, decreased locomotion, dyspnea, hypersensitivity to touch and sound, prostration, tremors, tonic convulsions and "walking on toes". Other more general symptoms included anogenital staining, abdominal gripping, biting cage, chromadacryorrhea, cyanosis, lacrimation, oral and nasal discharge and wet material on fur. The hypersensitivity to sound and/or touch and possibly some other neurological symptoms developed at day 3 and lasted till day 6. Some initial weight loss was noted.

81-4. Primary eye irritation.

In a primary eye irritation study (MRID No.: 00056800) 0.1 ml of cypermethrin (91.5%, 53:47 cis:trans, undiluted) was instilled into the conjunctival sac of the left eye of three male and six female New Zealand White rabbits. The eyes were irrigated for one minute with water, 20-30 seconds after instillation. No corneal opacity or iritis were noted. Slight redness of the conjunctivae with slight chemosis and some discharge were noted that persisted to day 7 in at least two rabbits. All redness of the conjunctivae regressed after 4 days in the washed eyes. Cypermethrin is not considered an irritant in the eye. Toxicity Category III.

81-5. Primary dermal irritation.

A single groups of six New Zealand White rabbits were with prepared by clipping and abrading and a dose of 0.5 ml of cypermethrin (91.5%, 53:47 cis:trans, undiluted) was applied in four places (twice on each flank) and kept in place for 24 hours. (MRID No.: 00056800).
Slight to mild erythema developed on the intact and abraded skin which generally regressed at 48 hours. The overall primary irritation index was determined to be 0.71. Toxicity Category IV.

81-6. Dermal sensitization-guinea pigs.

Cypermethrin should be regarded as a dermal sensitizer since two studies with the guinea pig Maximization test are positive and other studies with end-use products are also positive.

Study #1. Cypermethrin (91.5%, 53:47 cis:trans) was assessed for sensitization potential using the Buehler method using two groups of 10 Dunkin-Hartley strain guinea pigs. The induction phase consisted of topical applications of 0.3 ml of undiluted test material/animal applied in a patch to the shorn skin in the scapular region and held in place by bandages for six hours. This induction was repeated on alternate days for a total of 10 times over a period of 21 days. The guinea pigs were left untreated for a period of 14 days before challenge. The control animals were treated with water. The challenge phase consisted of application of 0.3 ml of a 5% (w/w) solution in corn oil/animal applied to the right flank and held in place for six hours. Assessments for sensitization were made at 24 and 48 hours after removal of the challenge application. MRID No.: 00056800. No signs of reaction were reported following the challenge application. Thus, cypermethrin was not a sensitizer in this study.

Study #2. In this study the maximization test of Magnusson and Kligman was used to assess for sensitization. The test consisted of a two phase induction (intradermal and topical) and a challenge phase using Dunkin-Hartley strain guinea pigs. In the induction phase, the scapular region was prepared and a row of three intradermal injections of 0.1 ml each were made for adjuvant, the test material (5%) in corn oil and the test material (5%) in corn oil plus adjuvant. One week later, the same scapular region was treated again and 0.25 ml of test material (neat) applied on a filter paper and kept in place for 48 hours. The challenge phase was initiated two weeks after the topical induction and consisted of application of 0.1 ml of a 50% solution of cypermethrin (71.6% technical) on filter paper and kept in place for 24 hours. There were 20 guinea pigs in the group treated with cypermethrin at induction and 10 controls. MRID No.: 40377701. Twelve of 20 guinea pigs induced by cypermethrin had "mild to moderate erythema at 24 or 48 hours after the challenge application. Rechallenge with 5%, 20% and 50% verified the initial positive response. Thus, cypermethrin was considered a moderate sensitizer in the guinea pig Maximization test.

Study 3. This study also utilized the maximization test of Magnusson and Kligman. The details were similar to above but a 96.7% sample of 46.1:53.9 cis:trans ratio was used. MRID No.: 00241597. Four test guinea pigs died of unknown causes. Of the remaining 16, 10 guinea pigs were considered to demonstrate a positive response and cypermethrin was considered to be a sensitizer in the guinea pig maximization test.

Table 1. Summary of acute toxicity of technical cypermethrin

Study	Results	Toxicity Category

154

81-1. Acute Oral-rats. 91.5%, 53:47 cis:trans) MRID No.: 00056800 Acute Oral-rats 71.6% MRID No.: 40377701 Acute Oral-rats 95%, 33:67 cis:trans MRID No.: 00241597	LD_{50} = 247 (187-329) mg/kg in males = 309 (150-500) mg/kg in females Vehicle: corn oil See series below for symptoms and duration. LD_{50} = 263 (151-428) mg/kg in males = 446 (303-622) mg/kg in females Vehicle: corn oil LD_{50} = 4123 (3496-4864) mg/kg in females. Vehicle: aqueous suspension	II
81-2. Acute Dermal -rabbits. MRID No.: 00056800 Acute Dermal- rats. MRID No.: 00056800.	LD_{50} > 2460 mg/kg - rabbits Transient symptoms included: lacrimation, shaking and in at least one rabbit. LD_{50} >4920 mg/kg - rats Transient signs included subdued behavior, unsteady gait, urinary incontinence, ungroomed appearance, piloerection.	III
81-3. Acute Inhalation - rats. MRID No.: 42395702	LC_{50} = 2.5 (1.6-3.4) mg/L for females; males > 2.5 mg/L. Symptoms: ataxia, decreased locomotion, hypersensitivity to sound and touch, staggered gait, tonic-clonic convulsions, tremors and "walking on toes"). Some symptoms persist for a few days.	III
81-4. Primary Ocular Irritation - rabbits. MRID No.: 00056800	No corneal involvement. Slight redness of the conjunctivae with chemosis that persisted to day 7 in at least two females.	IV
81-5. Primary Dermal Irritation - rabbits. MRID No.: 00056800	PIS = 0.71	IV
81-6. Dermal Sen-sitization - guinea pigs. MRID No.s: 00056800 Buehler) and MRID No.: 40377701 (maximization).	Not a sensitizer in the Buehler assay. Moderate sensitizer in two studies with Magnusson Kligman Maximization method. Some products are sensitizers. Cypermethrin should be regarded as a dermal sensitizer.	–

b. Subchronic Toxicity

Adequacy of data base for subchronic toxicity (series 82). The data base for subchronic toxicity is considered to be complete except for a series 82-4 subchronic inhalation toxicity study of 90-days duration. This study is required if inhalation exposure is for periods greater than 21-days.

Subchronic oral study in the rat

In a subchronic toxicity study (MRID 00056802 and 92027034 cypermethrin (92% purity) was administered to four groups of 20 SPF Alderley Park strain rats/sex at dose levels of 0, 75, 150 or 1500 ppm (corresponding to 0, 3.75, 7.5 or 75 mg/kg/day) for 90 days. Groups of 4/sex/dose were allowed 28 days for recovery. The male rats dosed with 7.5 mg/kg/day had increases (260%) in hepatic aminopyrine demethylase. This was increased to 539% in the 75 mg/kg/day dose group. Females (466%) were increased in the 75 mg/kg/day dose group only. Recovery was evident after 28 days. Body weight was decreased in the 75 mg/kg/day dose groups for both males (i.e. 17% at week 9) and females (i.e. 8% at wee 9). The LOEL is 1500 ppm (75 mg/kg/day) based on body weight. The NOEL is 150 ppm (7.5 mg/kg/day). The increase in hepatic aminopyrine demethylase is considered a physiological rather than toxicological response but its presence is indicated. This subchronic toxicity study is classified supplementary and does not satisfy the guideline requirement for a subchronic oral study (82-1) in rats. The study does not require upgrading because an acceptable chronic feeding study with rats is available.

155

Subchronic oral study in the dog

In a subchronic toxicity study (MRID 00112929) cypermethrin (98% purity) was administered to four groups of 4 beagle dogs/sex at dose levels of 0, 5, 50, 500 or 1500 ppm (corresponding to 0..125, 1.25, 12.5 and 37.5 mg/kg/day) for 13 weeks. Responses to treatment were noted at 37.5 mg/kg/day in both sexes and consisted of whole body tremors, exaggerated gait, ataxia, incoordination, hyperaesthesia, licking and chewing of paws as well as diarrhea and anorexia and decreased body weight. The LOEL is 1500 ppm (37.5 mg/kg/day, based on clinical signs indicating neurotoxicity. The NOEL is 500 ppm (12.5 mg/kg/day). This subchronic toxicity study is classified supplementary and does not satisfy the guideline requirement for a subchronic oral study (82-1) in dogs. The limiting factors include no data tables for clinical signs to determine their onset and duration, there is no discussion of the body weight effect at 1500 ppm and the copy available is unreadable in most places.

21-Day dermal study in the rabbit

In a 21-day dermal toxicity study (MRID No.: 00090035) with rabbits, 10/sex/dose group, cypermethrin was applied at dose levels of control, 2, 20 or 200 mg/kg/day applied in 20% (w/w) PEG 300 with daily applications for three weeks for a total of 15 applications. 5/sex/group were abraded prior to application of the test material. At 200 mg/kg/day, liver necrosis was noted in 4 of 5 females and 3 of 5 males with abraded skin. Two of 5 females but no males with unabraded skin were also affected. There was also a possibility of an effect on the testis since there was a decrease in absolute (19%, $p < 0.05$) and relative (15%, not significant) weight that was not accompanied by pathological changes. 200 mg/kg/day was considered a threshold level for clinical signs (i.e. flaccid body, salivation). There was local site of application irritation noted in all dose groups. The LOEL is 200 mg/kg/day based on liver effects. The NOEL is 20 mg/kg/day. This subchronic dermal toxicity study is classified ACCEPTABLE and satisfies the guideline requirement for a subchronic dermal study (82-2) in rabbit.

21-Day inhalation study in the rat

In a 21-day subchronic inhalation toxicity study (MRID 43507101) cypermethrin (87.1% purity, 1:1 cis:trans) was ad-ministered to 5/sex rats (Alpk:Apfsd, Wistar Derived)/sex/dose group by nose only exposure at concentrations of 0, 0.01, 0.05 or 0.25 mg/L for six hours per day, 5 days per week for a total of 15 exposures. Additional satellite groups of 5/sex were included for recovery assessment and analysis of cypermethrin in the brain. The MMAD was determined to be 2.63 to 2.86 uM. At 0.05 mg/L/day there was slight but consistently statistically significant (< 5% body, $p < 0.05$) body weight loss also reflected as a 16% decrease in body weight gain. All males and 4 females had occasional salivation. At 0.25 mg/L clinical signs were evident from day 10 on (particularly including decreased activity, salivation, lachrymation, tail erection, head and/or paw flicking and tip toe gait and others, see results). Changes in RBC parameters were slight and equivocal. Cypermethrin was not detected in the brain at day 10 or 22. The LOEL is 0.05 mg/L based mainly on body weight decrease. The NOEL is 0.01 mg/L. Classification: This study is classified as acceptable. It should be noted that since the study was for 21 days only, an additional study of 90 days duration may be required if it is justified by the exposure patterns to cypermethrin. Histo-pathology was assessed for only 5 rats/sex and 10 rats/sex should have been assessed. Future studies should assess 10/sex/group.

c. Chronic Toxicity/Carcinogenicity

Chronic oral study in the dog

In a chronic toxicity study (MRID 00112909, 42068503, 92027037) cypermethrin (90.6%) dissolved in corn oil was administered to 4 groups of 6/sex beagle dogs in gelatin capsules at dose levels of 0, 1, 5 or 15

158

mg/kg/day for 52 weeks. The males (4.75 fold) and females (10 fold) dosed with 5 mg/kg/day had increased incidence of passage of liquid stools starting in the first week of dosing and the incidence of this condition greatly increased to 31 fold at the 15 mg/kg/day dose level compared to controls. At 15 mg/kg/day, body tremors, gait abnormalities, uncoordination, disorientation and hyper-sensitivity to noise were evident in the first week in addition to body weight decrease. The LOEL is 5 mg/kg/day based on gastrointestinal effects. The NOEL is 1 mg/kg/day. This chronic toxicity study is classified acceptable and satisfies the guideline requirement for a chronic oral study (82-1) in the dog.

Carcinogenicity study in the mouse

In a carcinogenicity study (MRID 00112911 and 92027038) cypermethrin (53-54% cis and 46-47% trans) was administered to groups of 70/sex Swiss derived Alderley Park strain SPF mice at dose levels of control-1, control-2, 100, 400 and 1600 ppm (corresponding to 0, 0, 14, 57 or 229 mg/kg/day) for 97 weeks for males and 101 weeks for females. Liver weight was increased at 57 mg/kg/day (20% absolute weight) and above in males and for females at the high dose only (15% for relative weight) at the interim sacrifice but not at the terminal. Other systemic effects were noted at 229 mg/kg/day included reduction in RBC parameters (hemoglobin, hematocrit and RBC count in males, mean cell volume and hemoglobin) and platelet counts (for males at interim but not terminal sacrifice) and neutrophils and body weight gain (i.e. about 9% at week 6 for males and 12% for females at week 11). The LOEL is 400 ppm (57 mg/kg/day) based on liver weight. The NOEL is 100 ppm (14 mg/kg/day). This study was determined to be positive for induction of benign alveologenic neoplasms. Adequacy of dosing for carcinogenicity is based upon typically 9% decreases in males and 12% in females in the first months of the study. This carcinogenicity study is classified acceptable and satisfies the guideline requirement for a carcinogenicity study (83-2) in mice.

Chronic feeding/oncogenicity study in the rat

In a chronic toxicity/carcinogenicity study (MRID 00112910) cypermethrin (88-93% purity, 55% cis and 45% trans) was administered to 5 groups of 52/sex Wistar derived Alderley Park SPF strain rats at dose levels of control-1, control-2, 20, 150 or 1500 ppm (corresponding to 0, 0, 1, 7.5 or 75 mg/kg/day) for 2 years. Satellite groups of 12/sex were sacrificed after one year of dosing. Definite signs of toxicity were evident at 75 mg/kg/day and these consisted of body weight gain decrease throughout the study (i.e. about 10% for males and 13% for females at week 13), *slight* effects on several hematological parameters (both red and white cells), *slight* effects on clinical chemistry parameters (decreased cholesterol and triglycerides and glucose and increased urea. Decreases in urine volume, pH and an increase in specific gravity were noted. Liver weight was increased in females. The LOEL is 1500 ppm (75 mg/kg/day) based on body weight. The NOEL is 150 ppm (7.5 mg/kg/day). Cypermethrin was not considered to be oncogenic in this study. A possible association with increased testicular interstitial tumors was not considered definite. This chronic toxicity/carcinogenicity study is classified as acceptable and satisfies the guideline requirement for a chronic oral feeding/carcinogenicity study (83-5) in rats.

d. Developmental Toxicity

Developmental toxicity study in the rat

In a developmental toxicity study (MRID 00056804, 92027039 or 92027061, cypermethrin (98.2% purity) in corn oil was administered by gavage to four groups of 25 mated CD strain Charles River rats at dose levels of 0, 17.5, 35, or 70 mg/kg/day on days 6-15 of gestation. The rats were sacrificed at day 21 of gestation. Dose levels of 35 (12%) and 70 (28%) mg/kg/day resulted in decreased body weight gain. The dams dosed with 70 mg/kg/day displayed neurological signs such as splayed limbs, spasms, and hypersensitivity to noise and convulsions. The maternal LOEL is 35 mg/kg/day, based on body weight. The maternal NOEL is 17.5 mg/kg/day. No effects on either skeletal or visceral structures were reported.

159

The developmental LOEL is > 70 mg/kg/day. The developmental NOEL is > 70 mg/kg/day. The developmental toxicity study in the rat is classified acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3 (a) in the rat.

Developmental toxicity study in the rabbit

In a developmental toxicity study (MRID 00056805), cypermethrin (98.5% purity) in corn oil was administered to banded Dutch rabbits by gelatin capsule at dose levels of 0 (empty capsule), 0 (capsule plus corn oil), 3, 10 or 30 mg/kg/day on days 6 to 18 inclusive of gestation. There were no effects on the does of any kind reported. The maternal LOEL is > 30 mg/kg/day. The maternal NOEL is > 30 mg/kg/day. There were no treatment related effects on either the skeletal or visceral structures reported. The developmental LOEL is > 30 mg/kg/day. The developmental NOEL is > 30 mg/kg/day. The developmental toxicity study in the rabbit is classified supplementary and does not satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3b in the rabbit. The study is not considered upgradeable because the dose levels selected are too low.

Developmental toxicity study in the rabbit

In a developmental toxicity study (MRID No.: 43776302) cypermethrin (94-96% pure, cis/trans ration approximately 1:1) was administered to 20 New Zealand White rabbits per dose group by gavage at dose levels of 0, 100, 450 or 700 mg/kg/day from days 7 through 19 of gestation. The does were sacrificed on day 29 of gestation. Cypermethrin was administered as a 50% w/v solution in corn oil at varying volumes and corn oil was administered to the control group. Body weight gain was decreased during dosing at 450 (25%) and 700 (30%) mg/kg/day and this was followed by compensatory increases. Exacerbation of some clinical signs such as anorexia, abdominogenital staining and decreased feces and red or pink material in the pan also resulted in the 700 mg/kg/day dose group and in a few does in the 450 mg/kg/day group. The maternal LOEL is 450 mg/kg/day, based on body weight gain. The maternal NOEL is 100 mg/kg/day. There were no indications of developmental toxicity. The NOEL and LOEL for developmental toxicity is > 700 mg/kg/day. classification: This developmental toxicity study in the rabbit is classified acceptable and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b).

e. Reproductive Toxicity

In a 3 generation reproduction study (MRID 00112912, 42068504, 92027040) cypermethrin (90.6 to 93.1%) was administered to four groups of 15 male and 30 female Wistar derived SPF strain rats at dose levels of 0, 50, 150 or 1000/750 ppm (reduced to 750 ppm after 12 weeks because of severe neurological symptoms). These dose levels correspond to 2.5, 7.5 or 50/37.5 mg/kg/day. Three successive generations were produced, each consisting of 2 separate breedings to produce six sets of litters. At 150 ppm (7.5 mg/kg/day), parental weight gain was decreased in males (i.e. about 7% for F_2 at week 5) and females (i.e. about 4.5% for F_0 at week 8 and about 10% for F_2 week 8). At 1000/750 ppm (50/37.5 mg/kg/day) parental body weight gain was typically 10% decreased for both males and females and there was decreased mean litter weight gain during lactation (i.e. 12% to 21% for F_1B and 12 to 17% for F_1B females for days 10 to 28). At 1000 ppm (50 mg/kg/day) there were obvious clinical signs of neurotoxicity (i.e. ataxia etc). The LOEL is 150 ppm (7.5 mg/kg/day) based on consistent decreased body weight gain in both sexes. The NOEL is 50 ppm (2.5 mg/kg/day). The reproductive study in the rat is classified acceptable and satisfies the guideline requirement for a 3-generation reproductive study (OPPTS 870.3800, §83-4) in the rat.

f. Mutagenicity

Adequacy of data base for mutagenicity (Series 84): The data base for mutagenicity is considered to be adequate. Based on the available mutagenicity studies (summarized below), there are no concerns for mutagenicity at this time.

Study Identification Type	Results
Mutagenicity:	
S. typhimurium (Ames test). MRID No.: 00090037 and 92027042 and 92027062 also 00090036 and 00126834	No evidence of bacterial mutations in *S. typhimurium* strains TA-1535, TA-1537, TA-1538, TA-98 or TA-100 with and without metabolic activation (S-9) at dose levels of 4, 20, 100, 500 or 2500 ug/plate. Strains of yeast (*s. cerevisiae*) also assessed and negative.
Mouse Lymphoma mutagenicity assay. MRID No.: 41551101	No evidence of mutagenicity in the mouse lymphoma assay (L5178Y) at dose levels of 12.5, 25, 50 or 150 ug/ml with and without metabolic activation with S-9 fraction.
CHO/HGPRT assay. MRID No.: 41968206	In an in vitro gene mutation assay, Chinese hamster ovary cells (CHO-K1-BH_4 subclone D1) were exposed to dose levels of 0, 1, 10, 25, 50 100, 400, 700 or 1000 ug/ml in the presence or absence of S9 activation medium. No evidence of increased forward mutation rate at the HGPRT locus was observed at any dose tested under the conditions of these assays. The solubility limit of cypermethrin-s in the culture media was about 100 ug/ml.
Chromosome aberrations:	
Chinese hamster bone marrow cells. MRID No.: 00090038 and 92027043	No evidence of increased chromosome aberrations in chinese hamster bone marrow cells following gavage dosing with 0, 20 or 40 mg/kg.
Other mechanism of mutagenicity/ toxicity:	
Dominant lethal assay - male mice. MRID No.: 00090039	No evidence of dominant lethal activity in CD-1 strain mice at dos levels of control, 2.5, 5, 7.5 or 10 mg/kg/day for five consecutive days. An initial observation of a possible effect in a preliminary experiment with animals dosed at 2.5 or 5 mg/kg for 5 days was not repeated at higher doses.
Unscheduled DNA synthesis -rat primary hepatocytes in vivo. MRID No.: 41599801	No evidence of induction of unscheduled DNA synthesis in vivo at dose levels of 100 and 200 mg/kg by gavage in corn oil) in Alpk:APfSD strain rats (males only) assessed 4 and 12 hours post dosing. The 200 mg/kg dose was considered near the MTD and displayed toxic behavioral reactions.

g. Metabolism

Adequacy of data base for metabolism (Series 85-1). The data base for metabolism is considered to be complete. No additional studies are required at this time.

Several studies with both rats, dogs and mice are available to support the requirement for metabolism in mammals. Some of these studies assess individual cis and trans radiolabelled isomers and other studies assess the metabolism of cypermethrin with the label in either the cyclopropyl of the phenoxybenzyl ring. In general the following has been demonstrated from these studies:

Cypermethrin is readily absorbed from the gastrointestinal tract and extensively metabolized. It mostly excreted in the urine that contains several characterized metabolites derived from conjugation of the hydrolysis products of the parent compound following cleavage of the esteratic linkage site. The following three Executive Summaries describe the metabolism of cypermethrin in rats.

First Study. First group. Six/sex rats Wistar strain rats were dosed with a single dose 0.61 mg/animal of labelled cis-cypermethrin isomers in 0.5 ml of corn oil. The rats were individually housed in metabolism cages and their urine and fecal matter collected daily until sacrifice. Two rats of each sex were sacrificed after 24 and 72 hours and after eight days. Samples of the blood and selected tissues were assessed for radioactivity content. Second group. Three/sex rats were dosed with 0.615 mg/animal of labelled trans cypermethrin in 0.8 ml of corn oil. In addition to the urine and fecal collections, expired air was also collected from one male and one female. MRID NO.: 41551102. Total recovery was from 97.2 to 100.5%. About 70% of cis and 80% of trans cypermethrin was excreted in 24 hours. Essentially all was excreted in 8 days. Most of the label was excreted in the urine (>53%) with less in the feces and (< 20%) for the trans (males and females) and cis (males only) groups and < 1% in the air for all groups. A sex difference with respect to excretion in the urine from the cis isomer was noted for females since about equal amounts (35%) were found in both the urine and feces. Several urinary and fecal metabolites were tentatively characterized.

Second Study. One group of three/sex Wistar strain rats was dosed with a single oral dose (approximately 1.3 mg/kg) of ^{14}C-cyclopropyl labelled cypermethrin in corn oil (0.8 ml). The rats were then placed in glass metabolism cages and their urine and feces were collected. Special metabolism cages for trapping any radioactivity expired through their respiratory system were used for one male and female rat. The rats were sacrificed after three days and their blood and selected tissues were assessed for radioactivity. MRID NO.: 41551103. 85.5% for males and 97.2% for females of ^{14}C was excreted in 72 hours. The urine (55.8% for males and 69.4% for females) was the major route of excretion with the feces containing the balance. The air contained only 0.1% or less. Tissue retention was highest in the skin (1.2%) and liver (0.74% for males but only 0.18% for females) and fat (0.57 to 0.66%).

Third Study. In a series of nine different studies, labelled cypermethrin (1 mg/kg or less) in corn oil or separated cis or trans cypermethrin isomers were given by gavage to single or groups of two or three Wistar strain rats. Their urine and in some cases fecal matter were collected at various intervals such as 18 hours to 3 days. In another set of experiments, labelled cypermethrin was administered to rats that were fitted with bile duct cannalulas and their bile collected for 4-5 hours while the rat was under anesthesia. MRID NO.: 41551104. cis and trans ^{14}C-cyclopropyl labelled cypermethrin was demonstrated to form glucuronide conjugations of cis and trans acids and hydroxyacids. Only 1.6% or less of the total dose is excreted in the bile. Most of the cypermethrin in the feces was unmetabolized. The glucuronide conjugates in the urine were found to be unstable and subject to hydrolysis.

In addition to the above studies, other data on the metabolism of cypermethrin in rats can be found in MRID Nos.: 00056806, 00056807, 00056809, 00056810 and 00056812 and in 00089002, 00089003 and 00089004 that supports the observations reported above. Also other studies demonstrate the metabolism and pharmacokinetics in mice is similar to that of the rat (MRID Nos.: 00089007, 00089008 and 00089009) and dogs (00089010, 00089011, 00089012 and 00089013).

h. Neurotoxicity

81-7. Acute delayed type neurotoxicity-hens.

Cypermethrin is not an organophosphate insecticide and this study is not required, however, cypermethrin was tested in the hen following a protocol similar to the series 81-7 guideline. The dose levels tested were 0, 2500, 5000 and 10000 mg/kg but there was no indication of the delayed type neurotoxicity noted. MRID No.: 00070564.

81-8. Acute neurotoxicity screen-rats.

There are two acute neurotoxicity studies with cypermethrin.

First Study. This study was sponsored by the Agency.

A total of eight groups of 8/sex Long-Evans strain rats were dosed with cypermethrin (97% a.i.) at dose levels of 0, 20, 60 or 120/100 mg/kg) in 1 ml/kg of corn oil (McDaniel and Moser in Neurotoxicology and Teratology 15:71-83 (1993)). Separate groups were treated for FOB and motor activity assessments. FOB assessments were made at 1.5 and 3 hours after dosing and motor activity was assessed 3 hours after dosing. Assessments for FOB and motor activity were also made at pretest and at 24 and 48 hours after dosing. The rats displayed gait, muscle effects and choreoathetosis. Motor activity was decreased for all dose groups for males (estimated 45%, 66% and 85% for the 20, 60 and 100 mg/kg dose group respectively) and gait abnormalities were present in the low dose group. Body temperature was increased about one °C in the low dose male group but decreased for the higher groups. Some ten other parameters were affected at 60 mg/kg and/or above. These included: salivation, urination, arousal, abnormal motor movement, forelimb or hindlimb grip strength, landing foot splay, touch response and tail pinch response. The LOEL and NOELs for neurotoxicity are < 20 mg/kg. At 20 mg/kg decreased motor activity and gait abnormalities resulted.

Second Study. The second study was submitted by the registrant:

Four groups of Sprague-Dawley strain rats (10/sex) were dosed with cypermethrin in corn oil as control, 30, 100 or 200 mg/kg. The rats were assessed at pretest, four hours after treatment and on days 7 and 14 for FOB and motor activity. After day 14, 5/sex were prepared for neurohistopathology. MRID No.: 43152001. At 100 mg/kg, ataxia (2 males and 2 females) and related conditions (staggered or impaired gait, decreased activity, splayed hindlimbs and limp condition) and decreased motor activity (49%, $p < 0.001$ for males and 33%, $p < 0.01$ for females) resulted. In addition some females had salivation, lacrimation and/or soiled fur. At 200 mg/kg: deaths resulted (one male and two females) as well as several other parameters being affected. The LEL is 100 mg/kg based primarily on ataxia and related conditions. The NOEL is 30 mg/kg.

161

The first study above is considered to define the neurotoxicity to cypermethrin because responses were noted at lower dose levels. The second study used a variable and large dose of corn oil and a different strain of rat.

82-5. Subchronic neurotoxicity in hens.

No study. Cypermethrin is not an organophosphate and a subchronic neurotoxicity study in hens is not required.

82-7. Subchronic neurotoxicity screen in rats.

Four groups of 10/sex Sprague-Dawley strain rats were dosed as control, 500, 1300 or 1700 ppm (31, 77 or 102 for males and 37, 95 or 121 for females mg/kg/day) for 90 days in a subchronic neurotoxicity study. MRID No.: 41352002. At 1300 ppm, females displayed ataxia (1/10), splayed hindlimbs (5/16), impaired gait (4/10) and decreased feces (4/10) as well as decreased body weight gain (~41%). Males had only decreased body weight gain (~27%) and increased landing foot splay. At 1700 ppm, males showed ataxia (8/10) and additional related symptoms and females had decreased motor activity (~27%). The LEL is 1300 ppm (77 mg/kg/day) based on several effects. The NOEL is 500 ppm (31 mg/kg/day).

i. Other Toxicological Considerations

2. Dose/Response Assessment

a. Reference Dose (RfD)

The RfD has been determined to be 0.01 mg/kg/day based on a NOEL of 1.0 mg/kg/day from a chronic oral study in the dog with an uncertainty factor of 100 (RfD memorandum dated 10/29/96). In the study, dogs were administered cypermethrin in gelatin capsules at dose levels of 0, 1, 5 or 15 mg/kg/day for 52 weeks. The LOEL was 5 mg/kg/day based on increased incidence of passage of liquid stools at 5 mg/kg/day and above and body tremors, gait abnormalities, uncoordination, disorientation and hyper-sensitivity to noise at 15 mg/kg/day. For cypermethrin, the dog appears to be the most sensitive species via the oral route.

b. Carcinogenic Classification and Risk Quantification

Cypermethrin is classified as a weak C carcinogen with no Q_1^* based on the increased incidence in lung adenomas in female CD-1 mice (Cancer Peer Review report, dated 2/17/88). An RfD approach was recommended for human risk assessment purposes.

c. Developmental Concerns

There are no developmental concerns for cypermethrin. In the prenatal developmental toxicity studies in rats and rabbits, there was no evidence of developmental toxicity at the highest doses tested (70 mg/kg/day in rats and 700 mg/kg/day in rabbits). Decreased body weight gain was observed at the maternal LOEL in each study; the maternal NOEL was established at 17.5 mg/kg/day in rats and 100 mg/kg/day in rabbits. In the three-generation reproduction study in rats, offspring toxicity (reduced mean litter weight gain) was observed only at the highest dietary level tested (700/1000 ppm; 50/37.5 mg/kg/day), while toxicity

in the parental animals was observed at the lower treatment levels. The parental systemic NOEL was 50 ppm (2.5 mg/kg/day) and the parental systemic LOEL was 150 ppm (7.5 mg/kg/day).

d. Determination of Safety for Infants and Children

An acceptable three-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits have been submitted to the Agency. There are no data gaps for the assessment of the effect of cypermethrin following *in utero* or early postnatal exposure. The data demonstrated no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to cypermethrin. Based on these considerations, the Hazard ID Committee (7/17/97) determined that the 10x factor to account for enchanced sensitivity of infants and children (as required by FQPA) should be removed.

e. Dermal Absorption

There is no series 85-2 dermal penetration/absorption study available. A dermal absorption rate of 25% was selected based on the 6-45% dermal absorption observed with the structurally related pyrethroids permethrin (22-45%), deltamethrin (15%) and tralomethrin (6-25%). A range of dermal absorption factors were presented for permethrin and tralomethrin because the studies indicated higher absorption at lower exposure doses but not for deltamethrin. Since no study is available with cypermethrin, a value of 25% is assumed.

f. Other Toxicological Endpoints

i. Acute Dietary

The Toxicology Endpoint Selection Committee (TES, 8/27/96) selected an acute dietary endpoint NOEL of 1.0 mg/kg/day based on increased incidence of passage of liquid stools at 5 mg/kg/day and above starting the first week of dosing in a chronic oral toxicity study in the dog. The committee concluded that these signs may also occur following a single dose. The dogs received cypermethrin in gelatin capsules at dose levels of 0, 1, 5 or 15 mg/kg/day for 52 weeks. At 15 mg/kg/day, body tremors, gait abnormalities, uncoordination, disorientation and hypersensitivity to noise were evident in the first week in addition to body weight decrease. A 100 fold MOE is recommended.

ii. Short and Intermediate Term Occupational and Residential

For the short and intermediate term dermal endpoints, the TES Committee again recommended using the chronic oral study in the dog as the study of choice. However, this time the NOEL of 5 mg/kg/day is to be used with a dermal absorption factor of 25%. Although the NOEL for the chronic oral dog study is 1 mg/kg/day and the LOEL is 5 mg/kg/day, this is based on gastrointestinal disturbances (increased "passage of liquid stools") associated with the oral route of exposure. However, for dermal exposure risk assessments the Committee determined that the NOEL should be 5 mg/kg/day and the LOEL 15 mg/kg/day based on neurotoxic signs at this dose level. The Committee made this distinction in the NOELs/LOELs because the signs noted at the study LOEL (5 mg/kg/day) are gastrointestinal effects (oral) effects and thus are not relevant for dermal exposure whereas neurotoxic signs are relevant for this exposure scenario since neurotoxic signs (decreased motor activity and gait abnormalities etc) were also observed in rats at the lowest dose tested (20 mg/kg/day) in an acute neurotoxicity study. An MOE of 100 is recommended.

The data base for cypermethrin includes a 21-day dermal toxicity study with rabbits (MRID No.: 00090035). This study, however, was not used because the rat is a more sensitive species based on the comparison of the maternal toxicity in developmental studies in rats and rabbits. The maternal NOEL was 17.5 mg/kg/day and the LOEL is 35 mg/kg/day in rats and the NOEL and LOEL are 100 and 450 mg/kg/day in rabbits and both are based on bodyweight changes. The chronic feeding study with dogs with a NOEL and LOEL for neurotoxicity of 5 and 15 mg/kg/day demonstrates that the dog is more sensitive than either the rat or rabbit.

For inhalation endpoints, the Committee recommended using the NOEL of 0.01 mg/L from a 21-day inhalation study in rats. In a 21-day subchronic inhalation toxicity study cypermethrin was administered to 5/sex rats/sex/dose group by nose only exposure at concentrations of 0, 0.01, 0.05 or 0.25 mg/L for six hours per day, 5 days per week for a total of 15 exposures. At 0.05 mg/L/day there was slight but consistently statistically significant body weight loss also reflected as a 16% decrease in body weight gain. All males and 4 females had occasional salivation. At 0.25 mg/L clinical signs were evident from day 10 on (particularly including decreased activity, salivation, lachrymation, tail erection, head and/or paw flicking and tip toe gait and others, see results). Changes in RBC parameters were slight and equivocal. Cypermethrin was not detected in the brain at day 10 or 22. The LOEL is 0.05 mg/L based mainly on body weight decrease. The NOEL is 0.01 mg/L. An MOE of 100 is recommended.

iii. Chronic Occupational and Residential (Non-Cancer)

For the chronic dermal endpoint, the TES Committee again recommended using the chronic oral study in the dog as the study of choice. As with the short and intermediate term endpoints, the NOEL of 5 mg/kg/day is to be used with a dermal absorption factor of 25% (see short and intermediate term section for full explanation). The recommended MOE is 100.

TABLE 1. Summary of Toxicological Endpoints for Cypermethrin

Exposure Duration	Exposure Route	Endpoint and Toxicological Effect
Acute	Dietary	NOEL: 1.0 mg/kg/day (gastrointestinal disturbances in dogs seen during first week of study) MOE = 100
Short-Term (1-7 days) Occupational/Residential	Dermal [Inhalation]	NOEL: 5.0 mg/kg/day (neurotoxic signs in dogs starting at week 1). Dermal absorption rate: 25%. MOE = 100
Intermediate-Term (one week to several months) Occupational/Residential	Dermal [Inhalation]	NOEL: 5.0 mg/kg/day (neurotoxic signs in dogs starting at week 1). Dermal absorption rate: 25%. MOE = 100
[All time periods]	[Inhalation]	NOEL: 10.0 µg/L (decrease in body wt. gains in 21-day inhalation study in rats) MOE = 100
Cancer	Dietary/Dermal/Inhalation	weak C no Q* (lung tumors). RfD approach for assessment of risk.
Chronic (non-cancer)	Dietary	RfD: 0.01 mg/kg/day based on NOEL of 1.0 mg/kg/day (gastrointestinal disturbances in dogs) UF=100

Cypermethrin

Dietary Exposure and Risk Assessment/Characterization

2. Dietary Exposure

Tolerances have been established (40 CFR 180.418) for the residues of cypermethrin, in or on a variety of raw agricultural commodities at levels ranging from 0.05 ppm in animal commodities to 10 ppm in head lettuce. Registered uses include cotton, onions, pecans, head letuce, and brassica vegetables.

Nature of the Residue

The HED Metaboism Committee discussed cypermethrin plant and animal metabolism data and crop field trial information as outlined in the 5/24/95 J. Morales memorandum. The metabolites found in plants and livestock also are formed in the rat. It was concluded that 3-phenoxybenzoic acid (PBA) and its conjugates are not of concern based on toxicology data for PBA. In the absence of toxicology data, the cis and trans isomers of DCVA (3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acid) are considered to be of comparable toxicity to the parent. In light of Codex Maximum Residue Limits including only the parent compound, the parent being recoverable by the FDA multiresidue methods I and II, and DCVA not likely to be measured by these methods, it was concluded that tolerances should be set in terms of cypermethrin only. However, risk assessment should continue to include cis and trans-DCVA. Crop field trials should continue to include analyses for residues of cis and trans-DCVA. If monitoring data are to be used in the future to estimate "anticipated residues" for refined risk assessment, residues of DCVA isomers will be estimated from the ratio of parent compound to these metabolites in each crop

Analytical Enforcement Methodology

Adequate enforcement methodology (GC/ECD) is available in PAM II as Method I to enforce the tolerance expression.

Magnitude of the Residue

Residue data from field trials and the FDA monitoring program (1992-1995) and hte PDP monitoring program (1994) were used to estimate chronic dietary exposure. For the chronic analyses, mean residues from FDA monitoring were used for lettuce and onions (dry bulb). Residue field trial data were used for mustard greens, broccoli cabbage, cotton, green onions, and pecans.

For acute dietary exposure analysis, field trial residue data, along with percent of crop treated data, were used in the Monte Carlo anlaysis.

167

Attachment 10

Zeta-Cypermethrin

Toxicology and Residue Chemistry Details

Zeta-cypermethrin

1. Hazard Assessment

a. Acute Toxicity

Acute Toxicity of z-Cypermethrin

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral Acceptable	41776115	LD_{50} (M): 134.4 mg/kg (F): 86.0 mg/kg Clinical signs of neurotoxicity observed.	II
81-2	Acute dermal		Not available; bridged from cypermethrin	III
81-3	Acute inhalation		Not available	
81-4	Primary Eye Irritation		Not available; bridged from cypermethrin	IV
81-5	Primary Dermal Irritation		Not available; bridged from cypermethrin	IV
81-6	Dermal Sensitization		Not available; bridged from cypermethrin: 18.9% formulation moderate sensitizer	N/A

b. Subchronic Toxicity

z-Cypermethrin (88.2% a.i.) was tested in a 90-day feeding study in groups of 10 male and 10 female Fisher 344 (CDF) rats at the following dose levels: 0, 10, 50, 150, 250, 500 or 900 ppm (0, 0.6, 2.7, 8.4, 13.8, 28.2 or 55.7 mg/kg/day for males and 0, 0.6, 3.3, 9.6, 16.3, 32.2 or 65.2 mg/kg/day for females) (MRID 41776101). At 500 ppm, females had significantly decreased glucose levels. Clinical chemistries were not obtained for females at 900 ppm due to high mortality. This was attributed to decreased food consumption. At 500 and 900 ppm, both sexes had significantly decreased body weights (12 and 38%, respectively in males, 9 and 35%, respectively in females), body weight gains (15 and 63%, respectively in males and 21% in females at 500 ppm) and food consumption when compared to controls. At 900 ppm, 70 and 100 percent of the males and females, respectively died. The deaths were attributed to "inanition". Food efficiency was also significantly decreased (48% in males and 65% in females). These animals exhibited abdominal-genital staining, ataxia, clonic convulsions, chromodacryorrhea, chromorhinorrhea, decreased feces, decreased locomotion, dehydration, hypersensitivity to touch and sound, splayed hindlimbs and unthriftiness. Females also exhibited abdominal recumbency and walking on toes. Males had significant

decreases in erythrocyte and leukocyte counts when compared to controls. Hemoglobin and hematocrit were also decreased in males as well as increases in BUN. The NOEL is 250 ppm (13.9 mg/kg/day) and the LOEL is 500 ppm (28.2 mg/kg/day) based on decreases in body weight and body weight gains and food consumption at 28.2 mg/kg/day and above and deaths; clinical signs of neurotoxicity; decreases in erythrocyte and leukocyte counts, hemoglobin and hematocrit and increases in BUN at 55.7 mg/kg/day. The study is acceptable.

The 21-day dermal, subchronic oral study in the dog and the 21-day inhalation studies are bridged from cypermethrin.

Subchronic oral study in the dog

In a subchronic toxicity study (MRID 00112929) **cypermethrin** (98% purity) was administered to four groups of 4 beagle dogs/sex at dose levels of 0, 5, 50, 500 or 1500 ppm (corresponding to 0..125, 1.25, 12.5 and 37.5 mg/kg/day) for 13 weeks. Responses to treatment were noted at 37.5 mg/kg/day in both sexes and consisted of whole body tremors, exaggerated gait, ataxia, incoordination, hyperaesthesia, licking and chewing of paws as well as diarrhea and anorexia and decreased body weight. The LOEL is 1500 ppm (37.5 mg/kg/day, based on clinical signs indicating neurotoxicity. The NOEL is 500 ppm (12.5 mg/kg/day). This subchronic toxicity study is classified supplementary and does not satisfy the guideline requirement for a subchronic oral study (82-1) in dogs. The limiting factors include no data tables for clinical signs to determine their onset and duration, there is no discussion of the body weight effect at 1500 ppm and the copy available is unreadable in most places.

21-Day dermal study in the rabbit

In a 21-day dermal toxicity study (MRID No.: 00090035) with rabbits, 10/sex/dose group, **cypermethrin** was applied at dose levels of control, 2, 20 or 200 mg/kg/day applied in 20% (w/w) PEG 300 with daily applications for three weeks for a total of 15 applications. 5/sex/group were abraded prior to application of the test material. At 200 mg/kg/day, liver necrosis was noted in 4 of 5 females and 3 of 5 males with abraded skin. Two of 5 females but no males with unabraded skin were also affected. There was also a possibility of an effect on the testis since there was a decrease in absolute (19%, $p < 0.05$) and relative (15%, not significant) weight that was not accompanied by pathological changes. 200 mg/kg/day was considered a threshold level for clinical signs (i.e. flaccid body, salivation). There was local site of application irritation noted in all dose groups. The LOEL is 200 mg/kg/day based on liver effects. The NOEL is 20 mg/kg/day. This subchronic dermal toxicity study is classified ACCEPTABLE and satisfies the guideline requirement for a subchronic dermal study (82-2) in rabbit.

21-Day inhalation study in the rat

In a 21-day subchronic inhalation toxicity study (MRID 43507101) **cypermethrin** (87.1% purity, 1:1 cis:trans)

170