November 14, 1997

MEMORANDUM

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

FROM: Jess Rowland
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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.

This revision addressees the recommendations made by the Risk Assessment Review Committee (RARC). The RARC requested that a clarification be provided concerning the "apparent" use of mortality as an endpoint for *Lambda* Cyhalothrin for Short and Intermediate-Term risk assessments in Sections III and IV, respectively. The RARC also requested that corrections be made on the recommendations made for aggregate risk assessments (Section VII) for Bifenthrin and Esfenvalerate. Section X, Data Call-In Notice has been revised and clarifications are provided in Appendix A.

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
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
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=50	Mortality occurred after 3 dermal applications of a 100 mg/kg dose; dose was reduced to 50 mg/kg/day for the remaining 18 applications in a 21-day dermal study. At 50 mg/kg/day, there was no mortality but there were clinical signs and effects on body weight and food consumption. 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
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=50	Mortality occurred after 3 dermal applications of a 100 mg/kg dose; dose was reduced to 50 mg/kg/day for the remaining 18 applications in a 21-day dermal study. At 50 mg/kg/day, there was no mortality but there were clinical signs and effects on body weight and food consumption. 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 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
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)
lamba-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 (oral and dermal exposure) risk assessment is appropriate since an oral dose (maternal NOEL) based on maternal toxicity in an oral developmental toxicity study was selected for dermal exposure risk assessments. This oral dose should be used in conjunction with a 25% dermal absorption factor. 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.
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 (oral and dermal exposure) risk assessment is appropriate since an oral dose (maternal NOEL) based on neurotoxicity in range-finding developmental toxicity studies was selected for dermal exposure risk assessments.. This oral dose should be used in conjunction with a 25% dermal absorption factor. 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 for most of the pyrethroids. 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)

Additional clarification for the requirements of the neurotoxicity studies is provided in Appendix A of this Attachment.

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 and subchronic neurotoxicity studies for all pyrethroids.

APPENDIX A

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.