UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: 09/29/2005

MEMORANDUM

SUBJECT: *Tau*-fluvalinate: Revised HED Chapter of the Reregistration Eligibility Decision Document (RED). PC Code: 109302, Case #: 2295, DP Barcode: D321911.

Regulatory Action: *Phase 2 Reregistration Action*
Risk Assessment Type: *Single Chemical Aggregate*

FROM: Susan Stanton, Environmental Scientist
Reregistration Branch 3
Health Effects Division (7509C)

AND

John Doherty, Toxicologist
Jose Morales, Chemist
Robert Travaglini, Chemist
Reregistration Branch 3
Health Effects Division (7509C)

THROUGH: Catherine Eiden, Chief
Reregistration Branch 3
Health Effects Division (7509C)

TO: Kylie Rothwell, Chemical Review Manager
Reregistration Branch III
SRRD (7508C)

The attached risk assessment for *tau*-fluvalinate has been revised to correct errors noted in the registrant's 30-day error comments on EPA's preliminary risk assessment, submitted by Wellmark International on May 31, 2005.

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1.0 Executive Summary

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has evaluated the toxicity and exposure data bases for the pesticide active ingredient *tau*-fluvalinate and has conducted a human health risk assessment in support of the Reregistration Eligibility Decision (RED) for this active ingredient.

Use Information

Tau-fluvalinate is an insecticide/miticide in the pyrethroid class of pesticides. It acts as an axonic poison by interfering with the sodium channels of both the peripheral and central nervous systems, stimulating repetitive nervous discharges, leading to paralysis. It is registered for a single food use (beehives/honey) and several non-food uses, including ornamentals (outdoor and container-grown, greenhouse, interior plantscapes, dip for cuttings), building surfaces/perimeters, ant mounds and certain crops (carrots and Brassica/cole crops) grown for seed. *Tau*-fluvalinate has very limited annual domestic usage, with the majority of this usage in commercial greenhouses and on outdoor field- and container-grown ornamentals.

Toxicology

The available toxicity data on *tau*-fluvalinate are adequate to assess the chemical's hazard potential. *Tau*-fluvalinate is a pyrethroid insecticide of the type II class. It is moderately acutely toxic, having been classified in Toxicity Category II by the oral route of exposure and Category III by the dermal route. It is not a primary irritant to either the eye (Toxicity Category III) or skin (Toxicity Category IV) and is not a dermal sensitization agent. The principle systemic effects seen in subchronic and chronic studies include reductions in body weight/body weight gain (dogs and rats), liver weight changes (dogs and rats) and chronic nephritis (mouse).

Tau-fluvalinate is a pyrethroid insecticide that acts on the nervous system in insects. The mammalian studies demonstrate typical clinical signs associated with pyrethroid neurotoxicity, including excessive grooming, bulging eyes, abnormal stance, ruffled fur, hyperactivity, salivation, ataxia, muscle spasms, tremors, gait abnormalities, startle response hyperreaction and more. Some evidence of nerve degeneration was seen at higher doses in the acute neurotoxicity study.

As a type II pyrethroid, *tau*-fluvalinate causes the "pyrethroid reaction", a specific type of dermal irritation following contact. The "pyrethroid reaction" may be one manifestation of the chemical's ability to act on nerve endings. The "pyrethroid reaction" is unlike the primary dermal irritation assessed in acute or subchronic dermal irritation studies. It occurs during animal feeding studies when dermal contact is made with the feed and may result in early termination of such studies for humane reasons due to the severity of skin lesions and subsequent infection. Thus, more definitive subchronic and chronic studies were done by gavage. In humans, the pyrethroid reaction is characterized by tingling sensations and/or itching, often severe, upon contact with the chemical.

The rat developmental toxicity study did not demonstrate developmental toxicity at the highest dose tested. The rabbit developmental toxicity demonstrated some signs of skeletal variations

(curved tibia and fibula) but at the same dose where maternal toxicity was seen. There were no effects of *tau*-fluvalinate on reproductive performance. The offspring were noted to have tremors in one generation and to have slight body weight decrease in another generation, but these effects occurred at a dose that was also toxic to the parents. There is no quantitative or qualitative evidence of increased susceptibility of rat or rabbit fetuses after *in utero* and/or postnatal exposure to *tau*-fluvalinate in the developmental and reproduction studies. Dose-response relationships are well-characterized and clear NOAELs/LOAELs have been identified for the critical effects. Therefore, the special FQPA safety factor can be reduced to 1X, since the degree of concern is low and there are no residual uncertainties for pre- and/or postnatal toxicity.

No evidence of carcinogenicity was seen in mice or rats, and there is no concern for mutagenicity. *Tau*-fluvalinate was negative for mutagenic effects in a battery of tests, including reverse mutation in *Salmonella typhimurium*, sister chromatid exchange in CHO cells, mouse lymphoma mutagenic assay, mammalian cells in culture transformation assay and unscheduled DNA synthesis in rat hepatocytes.

Residue Chemistry

Tau-fluvalinate is registered for a single food use in beehives. The available residue chemistry data are adequate to assess human dietary exposure to *tau*-fluvalinate from the consumption of honey from treated hives. The residue of concern in honey for both tolerance enforcement and risk assessment is *tau*-fluvalinate *per se*. A GC/ECD method is available for the enforcement of tolerances for residues of *tau*-fluvalinate in honey.

Environmental Fate

The available environmental fate data for *tau*-fluvalinate are adequate to assess the residues of concern in drinking water. *Tau*-fluvalinate is highly immobile and practically insoluble in water, indicating a low potential for significant residues in drinking water. None of the major degradates found in environmental fate studies are of toxicological concern. Therefore, the residue of concern in drinking water is *tau*-fluvalinate, *per se*.

Residential Exposure

Although *tau*-fluvalinate is labeled for use in residential areas, a residential exposure assessment was not conducted, since there is little potential for residential exposure from these uses. There are no homeowner applications allowed and, therefore, no potential for residential handler exposure. Also, there are no wide area, broadcast applications of *tau*-fluvalinate in residential areas and, therefore, little potential for post-application residential exposure. The current residential uses (building surfaces/perimeters and ant mounds) are largely spot applications that are not likely to result in significant post-application exposure of adults or children.

Aggregate Risk

Acute and chronic (long-term) aggregate risk assessments were conducted for *tau*-fluvalinate. These assessments considered dietary (food + water) exposure only, since the current uses of *tau*-fluvalinate are not expected to result in significant residential exposure.

Tier 1acute and chronic dietary exposure analyses using both DEEM-FCID™ and Lifeline indicate that aggregate exposure to *tau*-fluvalinate from food and drinking water is well below HED's levels of concern for this pesticide. Estimated chronic exposures are less than 1% of the cPAD for the general U.S. population and all population subgroups. Estimated acute exposures are 5% of the aPAD or less for all population subgroups at the 95th percentile of exposure.

Occupational Exposure

Inhalation exposure of pesticide handlers is likely during the use of *tau*-fluvalinate in a variety of occupational environments. Since no chemical-specific handler exposure data are available for *tau*-fluvalinate, short- and intermediate-term inhalation exposures were assessed using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED data were used with other HED standard values for areas treated per day, body weight and the level of personal protective equipment (PPE) and engineering controls to assess handler exposures to *tau*-fluvalinate. Using these assumptions, the calculated occupational handler exposures for all exposure scenarios at all levels of protection, including baseline (i.e., no respirator), do not exceed HED's level of concern (i.e., MOEs > 100). Estimated inhalation exposures for handlers wearing respirators, as required by current labels, are well below HED's level of concern (MOEs > 900). Post-application inhalation exposure of workers to *tau*-fluvalinate is expected to be minimal, except in greenhouses, where potential inhalation exposure is mitigated by the ventilation requirements of the Worker Protection Standard.

Dermal exposure to *tau*-fluvalinate is expected to be largely self-limiting due to the irritation that occurs on contact with the pesticide as a result of the characteristic "pyrethroid reaction". Therefore, dermal handler and post-application exposures were not assessed. HED believes the issue of dermal exposure can be best addressed by labeling to avoid contact with skin and instructions to wash the affected area immediately following contact. Currently approved end-use product labels include adequate precautionary labeling.

Conclusions

Tau-fluvalinate is an insecticide/miticide with very limited annual domestic usage. Under the conditions of its current use, human health risks to workers handling the pesticide or to the general population, including infants and children, are well below HED's level of concern.

2.0 Ingredient Profile

Tau-fluvalinate is an insecticide/miticide in the pyrethroid class of pesticides. It acts as an axonic poison by interfering with the sodium channels of both the peripheral and central nervous systems, stimulating repetitive nervous discharges, leading to paralysis. It is registered for a single food

use (beehives/honey) and several non-food uses, including ornamentals (outdoor and container-grown, greenhouse, interior plantscapes, dip for cuttings), building surfaces/perimeters, ant mounds and certain crops (carrots and Brassica/cole crops) grown for seed.

Tau-fluvalinate products are registered in the U.S. to Wellmark International. Currently registered end-use formulations include Mavrik Aquaflow (EPA Reg. No. 2724-478), a flowable formulation containing 2 lbs. *tau*-fluvalinate per gallon, and Zoecon RF-318 Apistan Strip (EPA Reg. No. 2724-406), an impregnated plastic formulation containing 10.25% *tau*-fluvalinate by weight. Mavrik is registered for use on ornamentals (outdoor and container-grown, greenhouse, interior plantscapes, dip for cuttings), building perimeters and ant mounds; as well as on carrots and Brassica/cole crops grown for seed under FIFRA §24 (c) Special Local Need registrations in California. The Apistan Strip is registered to control varroa mites in beehives.

2.1 Summary of Registered/Proposed Uses

TABLE 2.1 Summary of Registered Uses of *Tau*-fluvalinate

Use Site	Product	Maximum Application Rate	Application Method	Maximum No. of Applications
Greenhouses (non-food plants), containerized nursery stock	Mavrik Aquaflow 2724-478	10.0 fl. oz. product (0.16 lb. a.i.)/100 gal./20,000 sq. ft.	Broadcast, fogger, bench	4/month
Interior plantscapes	Mavrik Aquaflow 2724-478	10.0 fl. oz. product (0.16 lb. a.i.)/100 gal. 0.5 fl. oz./5 gal./1,000 sq. ft.	Broadcast, fogger, bench	Not Specified (NS)
Woody and herbaceous ornamentals, plantscapes	Mavrik Aquaflow 2724-478	10.0 fl. oz. product (0.16 lb. a.i.)/100 gal./20,000 sq. ft.	Low-pressure fan spray (on base of stem or trunk)	24/year
Flower and foliage cuttings	Mavrik Aquaflow 2724-478	5.0 fl. oz. product (0.08 lb. a.i.)/100 gal.	Dipping	NS
Eugenia and pepper tree	Mavrik Aquaflow 2724-478	10.0 fl. oz. product (0.16 lb. a.i.)/100 gal.	Spray	2 at 14-day intervals
Building perimeters (outdoors)	Mavrik Aquaflow 2724-478	3 tsp. product/5 gal./1,000 sq. ft.	Low-pressure fan spray to edge of structure	4/month
Ant Mound Drench	Mavrik Aquaflow 2724-478	10.0 fl. oz. product (0.16 lb. a.i.)/100 gal.; 1 gal./mound	Drench	NS

TABLE 2.1 Summary of Registered Uses of *Tau*-fluvalinate				
Use Site	**Product**	**Maximum Application Rate**	**Application Method**	**Maximum No. of Applications**
SLN 24(c) CA960010: Carrots grown for seed	Mavrik Aquaflow 2724-478	9.6 fl. oz. product (0.15 lb. a.i.)/Acre	Aerial, ground	NS
SLN 24(c) CA040022: Brassica/cole crops grown for seed	Mavrik Aquaflow 2724-478	9.6 fl. oz. product (0.15 lb. a.i.)/Acre	Aerial, ground	NS
Beehives	Zoecon Apistan Strip RF-318 2724-406	1 strip for each 5 combs of bees or less in each bee chamber	Impregnated strip: Placed in empty hives with gloved hands. Leave strip in hive for 6 to 8 weeks. Treat in the spring and fall.	5 strips/year

2.2 Structure and Nomenclature

Tau-fluvalinate is an enriched isomer pesticide resulting from the partial purification of racemic fluvalinate. Fluvalinate, as initially synthesized, was a mixture of diasterioisomers. These were not cis/trans isomers as is the case with some pyrethroids. The chemical structure of fluvalinate contains two chiral centers with two optical positions possible at each. Thus, racemic fluvalinate is a mixture of four optical isomers, designated as R-2R, R-2S, S-2R and S-2S. Only one of these isomers (S-2R), however, is insecticidally active. In 1980, process changes permitted the synthesis of fluvalinate free of two of the insecticidally inactive isomers, resulting in a compound containing only two of the optical isomers (one insecticidally active and one inactive) and twice the insecticidal activity of racemic fluvalinate. This enriched isomer form was termed "half-resolved" or "(αRS, 2R)-fluvalinate".

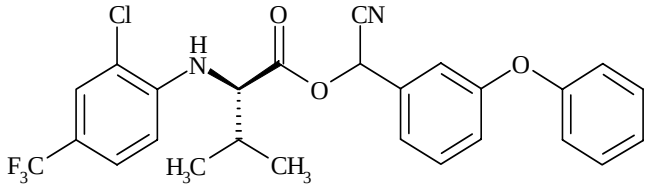
TABLE 2.2. *Tau*-fluvalinate Nomenclature	
Chemical Structure	
Empirical Formula	$C_{26}H_{22}ClF_3N_2O_3$
Common name	*Tau*-fluvalinate
IUPAC name	(*RS*)-α-cyano-3-phenoxybenzyl *N*-(2-chloro-α,α,α-trifluoro-*p*-tolyl)-D-valinate
CAS name	cyano-(3-phenoxyphenyl)methyl *N*-[2-chloro-4-(trifluoromethyl)phenyl]-D-valinate
CAS Registry Number	102851-06-9 (*tau*-fluvalinate) 69409-94-5 (unresolved fluvalinate)

TABLE 2.2. *Tau*-fluvalinate Nomenclature		
Known Impurities of Concern	None	
Chemical Class	Pyrethroid	
End Use Products (EPs):		
2724-478	Flowable formulation containing 2 lbs. *tau*-fluvalinate per gallon	Mavrik Aquaflow
2724-406	Impregnated plastic formulation containing 10.25% *tau*-fluvalinate by weight.	Zoecon Apistan Strip RF-318

2.3 Physical and Chemical Properties

Tau-fluvalinate has low volatility and low water solubility. Based on these characteristics, significant human exposure via the inhalation route or from drinking water would not be expected.

TABLE 2.3. Physicochemical Properties		
Parameter	Value	Reference
Boiling point	164 °C at 0.07 mm Hg	D165590, 3/4/92, F. Toghrol
pH	Not applicable; *tau*-fluvalinate is practically insoluble in water	
Density, bulk density, or specific gravity	1.262 g/mL at 25 °C	D165590, 3/4/92, F. Toghrol
Water solubility	2.4 ppb at 25 °C	D272832 and D273228, 3/21/01, K. Dockter
Solvent solubility at 25 °C	55.31 g/100 mL, methanol 24.05 g/100 mL, octanol Miscible at all levels in isooctane, toluene, acetonitrile, 2-propanol, dimethylformamide, and 1-octanol	D272832 and D273228, 3/21/01, K. Dockter D165590, 3/4/92, F. Toghrol
Vapor pressure	$<1.0 \times 10^{-5}$ Pa ($<10^{-7}$ torr), 25 °C	D272832 and D273228, 3/21/01, K. Dockter
Dissociation constant, pK_a	Not applicable due to the instability of *tau*-fluvalinate under acidic and basic conditions, and its extremely low water solubility.	Phase 4 Review, 1/16/91
Octanol/water partition coefficient	$P_{OW} > 10^6$, 25 °C	D272832 and D273228, 3/21/01, K. Dockter
UV/visible absorption spectrum	Not available	

3.0 Metabolism Assessment

3.1 Comparative Metabolic Profile

Rat/Mouse: There are both rat and mouse metabolism studies that demonstrate that *tau*-fluvalinate is absorbed and excreted.

In the mouse, approximately 59% and 30% of the applied radioactive dose is excreted into the feces and urine, respectively, after 4 days with most excreted within 24 hours. An anilino metabolite was identified in the urine but several other metabolites were not further characterized.

In the rat metabolism study, approximately 75% of the administered dose was recovered in the excreta 24 hours after dosing following a 1 mg/kg dose. A higher dose of 200 mg/kg resulted in only about 45% of the dose being excreted in 24 hours. At the high dose level, the fecal route appeared to be the dominant route of elimination with only about 20% of the dose being recovered in the urine. The parent compound (85%) and an anilino acid (2%) represented the major composition of the feces. For the 1 mg/kg dose group, 30-40% of the administered dose was recovered in the urine with elimination half lives of 12 hours for males and 15 hours for females. Several urinary metabolites were identified, with the major urinary metabolites being 3-(4'-hydroxyphenoxy)benzoic acid and 3-phenoxybenzoic acid (3-PBA). A proposed metabolic pathway reflects the hydrolysis and cleavage of the cyano group at the ester linkage, oxidation of the triflouromethyl group and hydroxylation of the phenoxy ring. Specifically, *tau*-fluvalinate is initially biotransformed to 3-phenoxybenzyl alcohol which is then oxidized to 3-phenoxybenzoic acid (3-PBA) and 3-(4'hydroxyphenoxy)benzoic acid. *Tau*-fluvalinate is also metabolized to anilino acid which may be hydroxylated and converted to the lactone of anilino acid, or may form haloaniline or diacid (Memo from W. B. Greer, 8/26/93, *Fluvalinate - Submission of a Rat Metabolism Study in Compliance with Reregistration Requirements* with attached DER, approved 8/27/93).

Plants: The existing plant metabolism studies indicate that *tau*-fluvalinate is metabolized to decarboxy-fluvalinate (minor pathway) or is cleaved to form anilino acid and phenoxybenzyl alcohol (major pathway), both of which are conjugated to carbohydrates before incorporation into the carbon pool. The major metabolite found in plants was 3-PBA. Other metabolites accounted for less than 10% of the TRR.

Ruminants: In metabolism studies in ruminants most (~80%) of the TRR was found in the GI tract (50%), urine (25%) and feces (4.2%), with minor amounts found in milk, kidney, liver, muscle and fat. *Tau*- fluvalinate, *per se*, comprised 81% and 84% of the TRR in the GI tract and in feces. The major metabolites found in urine were 3-PBA and 3-PBA/glycine conjugate. Minor metabolites found in ruminant matrices included 4'-OH fluvalinate and various PBA conjugates.

Summary: The available metabolism studies indicate that *tau*-fluvalinate is metabolized in a similar way in rodents, plants and ruminants, with unmetabolized parent and 3-PBA (or its conjugates) comprising the majority of the residue in most matrices.

3.2 Nature of the Residue in Foods

The registered use of *tau*-fluvalinate in beehives does not involve the direct application of *tau*-fluvalinate to honey, but rather the possible transfer of secondary residues from tracking by bees who have been in contact with the insecticide strips containing the pesticide. A beehive metabolism (i.e., nature of the residue) study was not required for *tau*-fluvalinate. Generally, HED considers all available metabolism data (e.g., plant, livestock, other arthropods) and environmental fate data (e.g., hydrolysis studies) in determining the residue of concern in honey from pesticide use in beehives (*Residue Data Requirements for Uses in Beehives,* Chem SAC memo, 2/25/99). Based on the available data for *tau*-fluvalinate, the Team has determined that the residue of concern in honey is *tau*-fluvalinate, *per se.* The available data are discussed below.

3.2.1. Description of Primary Crop Metabolism

Currently, there are no registered uses of *tau*-fluvalinate on plant commodities. Previously registered uses on cotton and coffee have been cancelled and the associated tolerances, including tolerances for secondary residues in animal commodities, have been revoked. Metabolism studies on several crops (including cotton, corn, tomatoes, lettuce, cabbage, bean, alfalfa and apples) were submitted by the registrant in connection with previously registered/pending food uses. The studies on cotton, corn, tomatoes, lettuce, cabbage and bean were determined to be unacceptable for various reasons, including inadequate radiolabeling of the test material and/or the need to further elucidate the unknown and unextractable portions of the TRR (G. Herndon memo of 2/6/92). In its review of an IR-4 request to amend the tolerance for coffee, HED concluded that the available plant metabolism studies with alfalfa and apples were adequate to support the registered use of *tau*-fluvalinate on coffee as well as then pending import tolerances for apples, kiwi, and oriental pears (G. Herndon memo of 2/13/92 concerning PP#0F03847). [Note: The coffee use has been cancelled and the import tolerances are no longer being pursued]. The residue of concern was determined to be fluvalinate, *per se*. HED noted that an additional plant metabolism study would be required to support the registration of any other uses of fluvalinate (or *tau*-fluvalinate) on food/feed crops

The available plant metabolism studies indicate that *tau*-fluvalinate is metabolized to decarboxy-fluvalinate (minor pathway) or is cleaved to form anilino acid and phenoxybenzyl alcohol (major pathway), both of which are conjugated to carbohydrates before incorporation into the carbon pool.

3.2.2 Description of Livestock Metabolism

There are currently no registered uses of *tau*-fluvalinate on any livestock feed item. Therefore, data pertaining to the nature of the residue in livestock are not required. However, ruminant and poultry metabolism studies for *tau*-fluvalinate were previously submitted by the registrant in support of the cotton use which has since been cancelled. Based on these studies, HED concluded that the qualitative nature of the residue in animals was adequately understood (R. Cook memo of 12/10/90 concerning PP#0F03347; and W. Cutchin memo of 6/16/95 - *Response to Inquiry. Current Status of Fluvalinate.* DP Barcode: D209130). The residue of concern in livestock commodities was determined to be *tau*-fluvalinate, *per se*.

Tau-fluvalinate is metabolized in ruminant animals the following way: 50 percent in the gastrointestinal tract (81% *tau*-fluvalinate); 25 percent in urine (metabolism of *tau*-fluvalinate to 3-phenoxybenzoic acid (3-PBA) followed by conjugation of 3-PBA with glycine); 4.2 percent in feces (84% *tau*-fluvalinate); 0.18 percent in milk (46% 3-PBA glycine, 33% *tau*-fluvalinate and 6 to 10% 3-PBA glycine bound to unextractable residues); 0.20 percent in kidney (6% *tau*-fluvalinate, 34% 3-PBA, 2% PB alcohol, 18% 3-PBA glycine, 13% 4'OH-3-PBA glycine and 1.3% 3-PBA glucoside); and 0.19 percent in liver (48% *tau*-fluvalinate, 3.7% 4'OH fluvalinate, 7.9% 3-PB Aldehyde, 7.8% 3-PBA glycine and 0.7% 3-PBA glucoside). Of the radiolabeled residue found in fat, 39 percent was identified as *tau*-fluvalinate, 15% 3-PB Aldehyde; in muscle 40 percent was *tau*-fluvalinate, 4% 4'-OH fluvalinate and 12% 3-PB aldehyde.

3.2.3 Description of Rotational Crop Metabolism, including identification of major metabolites and specific routes of biotransformation

Tau-fluvalinate is presently not registered for use on any annual crop; therefore, no residue chemistry data are required under these guideline topics.

3.3 Environmental Degradation

Tau-fluvalinate is highly immobile (K_d values between 853 and 1,708 with corresponding K_{oc} values between 110,000 and 370,000, respectively) and practically insoluble in water (2.4 ppb at 25C), indicating a low potential for significant residues in drinking water. Nevertheless, *tau*-fluvalinate is registered for outdoor, non-food uses (including carrots and Brassica/cole crops grown for seed, ornamentals and building perimeters) that could potentially result in residues in surface or ground water.

The major routes of degradation of *tau*-fluvalinate in laboratory studies are by abiotic processes (photodegradation in water and soil, and pH dependent hydrolysis) and biotic processes under aerobic conditions. *Tau*-fluvalinate is expected to be rapidly degraded in both soil and aquatic environments under aerobic conditions but is expected to be stable under anaerobic conditions. *Tau*-fluvalinate degraded rapidly by aqueous photolysis with a half life of 1 day but was slightly more stable to soil photolysis with a half life of 18 days. *Tau*-fluvalinate degraded in an aerobic soil metabolism study with half lives of 8 and 15 days and had a half life of 63 days in a supplemental terrestrial field dissipation study. In an anaerobic aquatic metabolism study *tau*-fluvalinate degraded with half lives of 255 and 413 days in the whole system.

In water, the major degradates of *tau*-fluvalinate seen in environmental studies were 3-Phenoxy-benzaldehyde (3-PB Aldehyde), 2-(2-Chloro-4-carboxyl)anilino-3-methylbutanoic acid, 2-[4-Carboxyl-2-(chloro)anilino]-3-methylbutanoic acid (Diacid), 2-(2-Chloro-4-trifluoromethyl)-anilino-3-methylbutanoic acid, 2-[2-Chloro-4-(trifluoromethyl)-anilino]-3-methylbutanoic acid (Anilino acid), 2-Chloro-4-trifluoromethylaniline (Haloaniline), and Cyanohydrin. In addition, 4-amino-3-chlorobenzoic acid and carbon dioxide were found as minor degradates in various studies.

3.4 Toxicity Profile of Major Metabolites and Degradates

Toxicology data for the major metabolite of *tau*-fluvalinate, 3-PBA, indicate that this compound and its conjugates are not of toxicological concern. Specific data are not available for other metabolites; however, the major plant and animal metabolites are also metabolites in the rat, and, therefore, their toxicity was assessed when the parent was studied. In addition, none of the major plant or animal metabolites contains the intact ester linkage responsible for the neurotoxicity of *tau*-fluvalinate.

3.5 Summary of Residues for Tolerance Expression and Risk Assessment

3.5.1 Tabular Summary

Table 3.5. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Honey	Parent *Tau*-Fluvalinate	Parent *Tau*-Fluvalinate
	Rotational Crop	N/A	
Livestock	Ruminant		
	Poultry		
Drinking Water		Parent *Tau*-Fluvalinate	Not Applicable

3.5.2 Rationale for Inclusion of Metabolites and Degradates

The risk assessment team concluded that the residue of concern for risk assessment purposes in all commodities and drinking water consists of parent *tau*-fluvalinate only. The team based its decision on the following evidence: (1) The major metabolite in plants and animals, 3-phenoxybenzoic acid (3-PBA), and its conjugates are not of concern based on toxicology data for PBA; (2) the major plant and animal metabolites are also metabolites in the rat, and, therefore, their toxicity was assessed when the parent was studied; and (3) none of the major plant or animal metabolites contains the intact ester linkage responsible for the neurotoxicity of *tau*-fluvalinate.

The team's decision is consistent with HED's earlier determination regarding the toxicological significance of *tau*-fluvalinate metabolites (*PP#6G3401/FAP#6H5501 - Fluvalinate on Various Fruits and Vegetable Crops - Response to Residue Chemistry Branch's Memorandum Dated August 21, 1986 Concerning the Toxicological Significance of Various Animal and Plant Metabolites*; W. Greear; 3/7/87). In the 1987 memo, HED concluded that none of the major plant or animal metabolites of *tau*-fluvalinate were of toxicological concern.

4.0 Hazard Characterization/Assessment

4.1 Hazard Characterization

Tau-fluvalinate is a pyrethroid insecticide of the type II class. *Tau*-fluvalinate is moderately acutely toxic, being classified in Toxicity Category II for oral toxicity and Category III for dermal toxicity. *Tau*-fluvalinate is not a primary irritant to either the eye (Toxicity Category III) or skin (Toxicity Category IV) and is not a dermal sensitization agent.

As a type II pyrethroid, *tau*-fluvalinate causes the "pyrethroid reaction", a specific type of dermal irritation following contact. The "pyrethroid reaction" is unlike the primary dermal irritation assessed in acute or subchronic dermal irritation studies. The "pyrethroid reaction" occurs during feeding studies when dermal contact is made with the feed. The rats or mice develop skin lesions that can potentially become infected to such a degree that the animals need to be sacrificed for humane reasons. The "pyrethroid reaction" can limit the dose levels and duration of exposure to confound subchronic and particularly chronic exposure studies when dosing is by incorporation of the test material into the feed. A study in rats was conducted to establish that the dermal reactions do not come when *tau*-fluvalinate is dosed by gavage and result from dermal contact with either the feed or the feces or emesis (for dogs). Thus, more definitive subchronic and chronic studies were done by gavage.

Subchronic and chronic oral systemic toxicity. In dogs, systemic responses to treatment by gavage were limited to body weight decreases and liver weight increases as well as emesis and salivation. In the rat subchronic study, body weight and liver weight were established as systemic effects of treatment. In the chronic rat study, body weight decrease was the main response to treatment. In the mouse carcinogenicity study, no effects on body weight were noted, but the LOAEL was based on chronic nephritis. Clinical signs of pyrethroid toxicity were noted in the subchronic and chronic studies.

Subchronic dermal toxicity. A 21-day dermal toxicity study in rabbits demonstrated skin lesions at 100 to1000 mg/kg/day that may be related to secondary effects of the "pyrethroid reaction". In addition, there were systemic effects at 500 mg/kg/day and above, including decreased food consumption and body weight effects.

Subchronic inhalation toxicity. There is no study that assesses subchronic inhalation toxicity. *Tau*-fluvalinate may have a special problem with regard to the unknown consequences resulting from the property of this chemical to cause the "pyrethroid reaction" once the respiratory tract is exposed to the chemical. In particular, persons with asthma and emphysema may be especially sensitive. Prevention of possible respiratory hazard associated with the "pyrethroid reaction" should be accomplished by requiring the use of respirators for those product uses where spray mists or other potentially respirable atmospheres containing *tau*-fluvalinate occur.

Developmental and reproductive toxicity. The rat developmental toxicity study did not demonstrate developmental toxicity at the highest dose tested. The rabbit developmental toxicity demonstrated some signs of skeletal variations (curved tibia and fibula) but at the same dose where there was maternal toxicity. There were no effects of *tau*-fluvalinate on reproductive performance. The offspring were noted to have tremors in one generation and to have slight body weight decrease in another generation, but these effects occurred at a dose that was also toxic to the parents.

Neurotoxicity. *Tau*-fluvalinate is a pyrethroid insecticide that acts on the Na conductance channel in both peripheral and central nervous systems. The "pyrethroid reaction" *may be* considered to be one manifestation of the ability of this chemical to act on nerve endings and cause its characteristic tingling sensations. The non-guideline "acute" neurotoxicity study with 7 daily doses in males only resulted in several clinical signs related to nerve stimulation, and there was evidence of nerve fiber degeneration. The subchronic neurotoxicity study did not reveal nerve fiber degeneration but demonstrated excessive grooming and bulging eyes, signs of either nerve stimulation or agitation.

Carcinogenicity. *Tau*-fluvalinate is not considered a likely human carcinogen since neither the rat nor the mouse carcinogenicity studies were determined to demonstrate a positive response for increased tumors.

Mutagenicity. There is no mutagenicity concern. *Tau*-fluvalinate was not shown to be mutagenic or to have genetic toxicity in several studies including the *Salmonella* strains (Ames test), sister chromatid exchange, chromosome aberrations in rats and unscheduled DNA synthesis.

Metabolism. There are both rat and mouse metabolism studies that demonstrate that *tau*-fluvalinate is absorbed and excreted. In the mouse, approximately 59% and 30% of the applied radioactive dose is excreted into the feces and urine, respectively, after 4 days, with most excreted within 24 hours. An anilino metabolite was identified in the urine but several other metabolites were not further characterized. In the rat, approximately 75% of the administered dose was recovered in the excreta 24 hours after dosing at a 1 mg/kg dose. A higher dose of 200 mg/kg resulted in only about 45% of the dose being excreted in 24 hours. At the high dose level, the fecal route appeared to be the dominant route of elimination with only about 20% of the dose being recovered in the urine. The parent compound (85%) and an anilino acid (2%) represented the major composition of the feces. For the 1 mg/kg dose group, 30-40% of the administered dose was recovered in the urine with elimination half lives of 12 hours for males and 15 hours for females. Several urinary metabolites were identified, with the major urinary metabolites being 3-(4'-hydroxyphenoxy)benzoic acid and 3-phenoxybenzoic acid.

Dermal absorption. There is no acceptable guideline study that demonstrates a dermal absorption factor. There is one study (Accession No.: 250142, classified as unacceptable/ guideline, not ungradable) that demonstrated that only 4% of the applied dose was absorbed in a *single* male rat. Comparison of the LOAEL of 125 mg/kg/day (based on "anorexia and general depression") from the rabbit developmental toxicity study with the LOAEL of 500 mg/kg/day (based on systemic response of decreased food consumption) from the 21-day dermal toxicity study would suggest that a dermal absorption factor of 25% (125 mg/kg/day ÷ 500 mg/kg/day x 100) would be appropriate.

Endocrine disruption. There were no indications based on the animal studies submitted for registration purposes that indicate that *tau*-fluvalinate affects either the estrogen, androgen or thyroid or other hormone systems.

Table 4.1a Acute Toxicity Profile - *Tau*-fluvalinate				
Guideline No.	**Study Type**	**MRID(s) (Year)**	**Results**	**Toxicity Category**
870.1100	Acute oral - rat	0094103	LD_{50} = 282 (218-365) mg/kg -males 261 (194-353) mg/kg - females.	II
870.1200	Acute dermal - rabbit	41597301 (1998)	LD_{50} > 2000 mg/kg	III
870.1300	Acute inhalation - rat	--Not applicable (1).--		
870.2400	Acute eye irritation -rabbit	00144622 (1984)	Slight conjunctival discharge observed one hour post instillation. Conjunctival swelling and redness noted for up to three days.	III
870.2500	Acute dermal irritation -rabbit	00144623 (1984)	PII = 0.8	IV
870.2600	Skin sensitization - guinea pig	41889714 (1990)	Not a sensitizer.	Not applicable

(1) - The vapor pressure of technical *tau*-fluvalinate is < 1 x 10^{-7} torr at 25° C (i.e. is a viscous liquid). Refer to B. Greear memo dated 01/10/91.

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - *Tau*-fluvalinate		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100 90-Day oral toxicity - rat. International Research and Development, Study # 322-047, 9/24/81	00094109 (1981) 92069032 (1990) Acceptable/Guideline 0, 0.3, 1, 3, 30 or 50 mg/kg/day. (Technical - "half resolved")	Systemic: NOAEL = 3 mg/kg/day LOAEL = 30 mg/kg/day based on enlarged lymph nodes, deceased Hb, Hct and RBC counts and increased organ and ratio weights. Dermal ("pyrethroid reaction"): NOAEL = 1 mg/kg/day LOAEL = 3 mg/kg/day based on skin lesions.
870.3100 (b) 90-day oral toxicity - mouse. Litton Bionetics, Inc., Study No.: 22088, 11/1/81	00094113 (1981) Supplementary 0, 1, 3, 30, 50 or 100 mg/kg/day. (Technical "half resolved").	NOAEL - could not be established due to the "pyrethroid reaction" - skin lesions, with their sequella (increased WBC counts, enlarged lymph nodes, infected eyes, and splenic changes) in all dosed groups. At higher doses decreased body weight and other blood effects and ovary weight and ovary cysts.

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - *Tau*-fluvalinate		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.3200 21/28-Day dermal toxicity - rabbit Elars BioResearch Lab, Inc, Study No.: 1675-P, October 10, 1981.	00094115 (1981) 92069034 (1990) Acceptable/Guideline	Systemic: NOAEL = 100 mg/kg/day LOAEL = 500 mg/kg/day based on decreased food consumption. Dermal: (site of application) Minimal effects at 100 mg/kg/day. Indications of "pyrethroid reaction at higher doses (biting and scarring).
Non-Guideline 90-Day dermal toxicity - rat. IRDC, Study No.: 322049-322058, Jan 1, 1982.	00126175 (1982). 249604 (1982) "Minimum" (Non-Guideline)	Study summary does not give a NOAEL or LOAEL but discusses mechanism of skin lesion development. States that the dermal exposure, and not oral exposure, results in "pyrethroid reaction". Study is not appropriate for dermal exposure endpoint.
870.3465 90-Day inhalation toxicity	No study available.	
870.3700a Prenatal developmental - rats Argus Research Labs, Study No.: 1819-011, 2/6/98.	44743301 (1998) Acceptable/Guideline. 0, 5, 10 or 15 mg/kg/day.	**Maternal** NOAEL = 5 mg/kg/day LOAEL = 10 mg/kg/day based on decreased body weight and food consumption. **Developmental** NOAEL = ≥ 15 mg/kg/day. No effects seen at highest dose tested.
870.3700b Prenatal developmental - rabbits Hazleton Laboratories, Study No.: 777-137, 12/23/81	0094112 (1981) 92069038 (1990) Acceptable/Guideline 0, 5, 25 or 125 mg/kg/day.	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 125 mg/kg/day based on anorexia and general depression. **Developmental** NOAEL = 25 mg/kg/day LOAEL = 125 mg/kg/day based on skeletal anomalies, curved tibia and fibula.
870.3800 Reproduction and fertility effects - rats Huntingdon Research Center, Study No.; MCI 56/8694, 7/2/86.	44596601 (1986) Acceptable/Guideline 0/0, 0.76/0.84, 1.90/2.08 or 9.53/10.51 mg/kg/day for males/females.	**Parental/Systemic** NOAEL = 1.90/2.08 mg/kg/day LOAEL = 9.53/10.51 mg/kg/day based on clinical signs (skin ulcerations.). **Reproductive**: LOAEL > 9.53/kg/day **Offspring**: NOAEL = 1.90/2.08 mg/kg/day LOAEL = 9.53/10.51 mg/kg/day based on tremors during lactation in both litters, decrease in pup weight in F2 generation (12%, $p < 0.05$) and slightly lower litter size.
870.4100a Chronic toxicity - rat	Refer to 870.4300 combined chronic feeding/carcinogenicity study.	

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - *Tau*-fluvalinate		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.4100b Chronic toxicity (dog) Covance Laboratory, Study No.: 6398-117, 12/17/98.	44743201 (1998) Acceptable/Guideline 0, 3, 12 and 50 mg/kg/day.	NOAEL = 3 mg/kg/day LOAEL = 12 mg/kg/day based on decreased body weight and body weight gain and increased liver weight in females.
870.4200. Carcinogenicity - mouse. International Research and Development, Study No.: 322-048, 1/12/84.	00094889 (1981) 00128336 (1983) 00144628 (1984) 92069036 (1990) Acceptable/Guideline for carcinogenicity, Supplementary (Acceptable/Non-Guideline) for chronic feeding. 0, 2, 10 or 20 mg/kg/day.	Dermal: NOAEL = 2 mg/kg/day LOAEL = 10 mg/kg/day based on dermal lesions. Systemic: NOAEL = 10 mg/kg/day LOAEL = 20 mg/kg/day based on chronic nephritis. No evidence of carcinogenicity.
870.4300. Combined chronic feeding/carcin-ogenicity - rats. International Research and Development, Study No.: 322-053, 8/27/84.	00128334 (1983) 00128335 (1982) 92069048 (1990) Acceptable/Guideline 0, 0.25, 0.5 1, 2.5, 10 and 20 (10 and 20 for 17 weeks only) mg/kg/day.	NOAEL = 0.5 mg/kg/day LOAEL = 1.0 mg/kg/day based on clinical signs of neurotoxicity (abnormal stance, ruffling and transient hyperactivity, followed by hypoactivity in males and females) (see section 4.4) No evidence of carcinogenicity.
Gene Mutation 870.5100. Reverse mutation in *salmonella T.* Litton Bionetics, Study No.: 20988, October 20, 1980.	00094116 (1980) Acceptable. 1 to 10,000 μg/plate.. With or without metabolic activation. (Fluvalinate)	No evidence of mutagenic response.
Cytogenetics 870.5375. Sister chromatid exchange in CHO cells. Microbiological Associates, Study No.: T2258.334001, March 1, 1984.	00144626 (1984) Acceptable. 250 to 2000 nL/mL (Half-resolved)	No evidence of doubling of sister chromatid exchanges or changes in the sister chromatid frequency in presence or absence of metabolic activation.

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - *Tau*-fluvalinate		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
Cytogenetics. 870. 5300. Mouse lymphoma mutagenic assay. Microbiological Associates, Study No.: 2258.701, March 2, 1984.	00144625 (1984) Acceptable. 0.013 to 1 μL/mL without activation and 0.0027 to 0.2 μl/mL with metabolic activation. (Half-resolved)	No evidence of mutagenic activity in presence or absence of metabolic activation.
870.5300. Mammalian cells in culture transformation assay in mouse fibroblast. Litton Bionetics. Study No.: 20992, 11/18/80.	00094117 (1980) 00094118 (1980) Acceptable/Non-guideline.	No evidence of transformation with or without metabolic activation.
Other Effects 870. 5550. Unscheduled DNA synthesis in rat hepatocytes. Microbiological Associates. Study No.: T2258.380, March 2, 1984.	00145614 (1984) Acceptable 0, 5, 10, 50 100 or 500 nl/mL. (Half-resolved).	No indication of induction of unscheduled DNA repair.
870.6200a Acute neurotoxicity screening battery	43433901 (1994) Acceptable/Non-Guideline.* 0, 10 , 60 or 100 mg/kg *Upgraded in RED development	Study does not follow 870.6200 guidelines: Females not included, motor activity not assessed and used multiple (7 day) dosing. NOAEL = 10 mg/kg/day LOAEL = 60 mg/kg/day based on body weight decreases, clinical signs of neurotoxicity and sciatic nerve pathology.
870.6200b Subchronic neuro-toxicity screening battery - rat Ricera, Inc. Study No.: 2504, 6/23/99.	44900601 (1999) Acceptable/Guideline* 0, 2, 8 or 32 mg/kg/day. *Upgraded in RED development	NOAEL = Not established. LOAEL < 2 mg/kg/day based on clinical signs including excessive grooming in both sexes and bulging eyes in females. *A study does not have to demonstrate a NOAEL to be classified as Acceptable/Guideline.
870.6300 Developmental neurotoxicity	No study available.	

Table 4.1b Subchronic, Chronic and Other Toxicity Profile - *Tau*-fluvalinate		
Guideline No./ Study Type	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485 Metabolism and pharmacokinetics-rat Sandoz Agro, Inc. Study No.: 480605, Report No.: 13, 5/20/1992. 870.7485, Metabolism -mice. Zoecon Corp. Study No.: 3760-2-02-84, February 21, 1984.	43214101 (1993) 42322301 (1992) - rat study Acceptable/Guideline. 072918 (1984) - mouse study Acceptable/Non-Guideline.	There are both rat and mouse metabolism studies that demonstrate that *tau*-fluvalinate is absorbed and excreted. In the mouse, approximately 59% and 30% of the applied radioactive dose is excreted into the urine and feces, respectively, after 4 days, with most excreted within 24 hours. An anilino metabolite was identified in the urine but several other metabolites were not further characterized. In the rat, approximately 75% of the administered dose was recovered in the excreta 24 hours after dosing at 1 mg/kg body weight. A higher dose of 200 mg/kg resulted in only about 45% of the dose being excreted in 24 hours. At the high dose level, the fecal route appeared to be the dominant route of elimination with only about 20% of the dose being recovered in the urine. The parent compound (85%) and an anilino acid (2%) represented the major composition of the feces. For the 1 mg/kg dose group, 30-40% of the administered dose was recovered in the urine with elimination half lives of 12 hours for males and 15 hours for females. Several urinary metabolites were identified, with the major urinary metabolites being 3-(4'-hydroxyphenoxy)benzoic acid and 3-phenoxybenzoic acid.
870.7600 Dermal penetration (rat)	MRID No.:00126180 Unacceptable/Guideline Single dose	Approximately 4% of the dose applied to a single male rat was demonstrated to be absorbed with the resulting radioactivity being found in the feces as metabolites.
Special studies		Special 90 day dermal study to investigate mechanism of dermal lesions (see above under MRID No.00126175).

4.2 FQPA Hazard Considerations

4.2.1 Adequacy of the Toxicity Data Base

The toxicology database is adequate for the evaluation of risks to infants and children. Relevant studies include rat and rabbit developmental toxicity studies, a rat multi-generation reproduction study and chronic/carcinogenicity feeding studies in mice and rats. In addition, acceptable short-term (non-guideline) and subchronic (guideline) neurotoxicity studies are adequate to evaluate the neurotoxicity of *tau*-fluvalinate. There is no developmental neurotoxicity study available in the database.

4.2.2 Evidence of Neurotoxicity

Tau-fluvalinate is a pyrethroid insecticide that acts on the nervous system in insects. The mammalian studies demonstrate typical clinical signs associated with pyrethroid neurotoxicity. Some evidence of nerve degeneration was seen at higher doses in the acute neurotoxicity study.

Acute Neurotoxicity Study.

In a non-guideline special "acute" neurotoxicity study (1994, MRID No.: 43433901), 10 male Wistar rats/dose group received 7 daily gavage doses of 0, 10 or 100 mg/kg of *tau*-fluvalinate (87.1% a.i.) in corn oil (10 mL/kg). Due to severe toxicity, the high dose was discontinued and two additional groups of 10 male rats received 7 daily doses if 0 or 60 mg/kg. Functional observational battery tests (FOB) were conducted with clinical examinations pretreatment, on treatment days 1, 2, 4 and 7 and recovery days 7 and 14. Neural tissues were examined microscopically from 5 control and 5 rats treated with 60 mg/kg after 7 days of treatment and from the remaining control and 60 mg/kg animals after 14 days of treatment. Motor activity was not quantitated.

At 10 mg/kg, a single incidence of ruffled fur (days 2 and 3), salivation (day 2) and hyperalgesia (4/10 vs 6/20 controls) were noted. Food consumption was 83% of control on days 1 to 4 of treatment. At 60 mg/kg, significantly decreased food consumption was noted during dosing and recovery (86%, 77%, 74%, 84%, and 90% of controls on days 4 and 7 and on recovery days 1, 8 and 14, respectively). The food consumption was 31% and 26% of controls on days 1-4 and 4-7, respectively. Clinical/behavioral effects seen as early as day 1 in all animals treated with 60 mg/kg but not in controls included salivation, ruffled fur, dyspnea, muscle spasms and sedation. Other observations (observed in 30 to 90% of the animals) included ataxia, coarse exertions tremor, hunched posture, gait abnormalities, serous reddish secretion from the nose, lids half closed, miosis, startle response hyperreaction, reduced grip strength, (maximum 42.2% compared to controls) and reduced rearing count. Also observed were fear, diarrhea, vibrissa reflex hyperreaction and hyperalgesia. The clinical/behavioral signs were transient and were not seen at the end of recovery period. Peripheral nerve fiber degeneration was observed in animals treated with 60 mg/kg. The highest incidence and severity in nerve degeneration was seen in the sciatic nerve (minimal to moderate lesions in 4 animals with minimal lesions in 2 controls). Following recovery, the incidence and severity of the lesions was decreased. **The neurotoxicity LOAEL is 60 mg/kg, based on clinical signs of toxicity (observed as early as day 1) and peripheral nerve degeneration in male rats. The neurotoxicity NOAEL is 10 mg/kg.** Note: The slight decrease in food consumption and incidence of ruffled fur and salivation were not included in the NOAEL. It is unlikely that these occurred following a single dose.

This study is classified as ACCEPTABLE/Non-Guideline but does not satisfy the requirement for a series 870-6200 acute neurotoxicity study in the rat. This study is being reclassified from the original classification as SUPPLEMENTARY. The study is not eligible to be upgraded to an acceptable/guideline 870-6200 study because females were not included, no motor activity assessments were made and the study included multiple daily dosing for 7 daily doses.

Subchronic Neurotoxicity Study.

In a subchronic oral neurotoxicity study (1999, MRID 44900601), groups of Wistar rats (10 rats/sex/group) were administered 0, 2, 8, or 32 mg/kg/day of *Tau*-Fluvalinate (Lot No. 56613870; Batch No. 96026; 88.3% active ingredient) by gavage for 90 days. An additional 5 rats/sex in the control and high-dose groups were maintained without treatment for a 28-day recovery period. Functional observational battery (FOB) and motor activity (MA) testing were

performed prior to administration, during weeks 1, 4, 8, and 13, and after the recovery period. Body weights and food consumption were recorded weekly for each animal. Neuropathologic examinations were performed on 6 animals from each of the control and high-dose groups; brain weights were not obtained.

In the high-dose groups, one male and one female were found dead during weeks 1 and 2, respectively; intestinal lesions were found in both animals. In addition, one male and one female were sacrificed moribund due to self mutilation during weeks 4 and 8, respectively. Clinical signs of toxicity prior to death in these animals were similar to those described below. During the recovery period, one high-dose male was found dead during week 1. Premature sacrifice or death of several other animals was considered incidental to treatment. Ophthalmologic examinations, gross necropsy and neuropathology of surviving animals were unremarkable.
Approximately 4 hours post-dosing, clinical signs reported weekly throughout the study in the high-dose males and females included hunched posture (13 and 14), labored breathing (14 and 13), digging at cage (14 and 14), salivation (15 and 15), anogenital staining (15 and 15), dried material around the nose and/or mouth (15 and 15), colored material around the eyes (13 and 14), lacrimation (13 and 14), and rough coat (15 and 15). Extremely decreased activity was observed in high-dose males and females during the first half of the treatment period, whereas, excessive grooming (11 and 14) and bulging eyes (13 and 14) were more common in the second half of the treatment period. In addition, self mutilation was observed in 5 males and 6 females in the high-dose group. In the mid-dose males and females, clinical signs included hunched posture (2 and 8), digging (4 and 9), salivation (5 and 5) and excessive grooming (6 and 9). Many of these clinical signs in mid- and high-dose males and females were still present the following morning. In the low-dose males and females, excessive grooming was observed in 5 and 6 animals, respectively, and bulging eyes were observed in 6/10 females. None of the control animals showed any of these signs with the exception of bulging eyes in 6/15 control females.

No treatment-related effects on body weights, body weight gains, food consumption or neurobehavioral assessment were seen in the low- and mid-dose females or low-dose males. High-dose males had significantly ($p \leq 0.01$) lower body weights and body weight gains compared with the controls throughout the treatment and recovery periods. Absolute body weights of the high-dose males were 80% of the control level for week 1 and declined to 67% of the control level by week 13. The most pronounced effect on body weight gain by the high-dose males occurred as a weight loss for weeks 1 and 2; thereafter body weight gains were 4-36% of the control level. Absolute body weights and body weight gains of the mid-dose males were not statistically different from the controls, however, body weight gains were 86-88% of the control levels for weeks 4-13. Mean absolute body weights of the high-dose females were significantly ($p \leq 0.05$) less than the controls during weeks 1-3 and 5 (90-95% of controls). Body weight gains by the high-dose females were significantly ($p \leq 0.05$ or 0.01) less than the controls for weeks 1 (weight loss) and 3-6 (67-85% of controls). Food consumption by the high-dose males was 49-92% of the control level during weeks 1-10 with statistical significance ($p \leq 0.01$) attained during weeks 1-5, 7, and 10. Food consumption by the high-dose females was significantly ($p \leq 0.01$) less than the controls for weeks 1 and 3 (55% and 84%, respectively, of controls). No dose- or treatment-related effects were noted in any group for fore- and hind-limb grip strength, landing foot splay, home cage observations, or sensorimotor and reflex responses. During handling, the incidence rate of animals with abnormal fur (rough coat and piloerection) was increased in the high-dose

males and females as noted during clinical observations. In the open field, abnormal posture was observed in 7.69-21.43% of high-dose males and in 21.43-38.46% of high-dose females compared with 0.0% of the controls at weeks 4-13. No other dose- or treatment-related abnormalities were observed in any group during open field evaluations. Mean distance traveled was significantly ($p \leq 0.05$ or 0.01) decreased in high-dose males at weeks 1 and 8 to 61% and 73%, respectively, of the control values. For weeks 4 and 13, the distance traveled by the high-dose males was slightly less than the controls: 82% and 90%, respectively. The mean distance traveled by the high-dose females was significantly ($p \leq 0.05$ or 0.01) less than the controls throughout the treatment period (57-78% of control value). Correspondingly, mean resting time was significantly ($p \leq 0.05$ or 0.01) increased in high-dose males and females to 122-129% and 118-135%, respectively, of the control levels. **The LOAEL is 2 mg/kg/day based on clinical signs of toxicity, excessive grooming in males and females, and bulging eyes in females. The NOAEL is less than 2 mg/kg/day.**

This study was previously classified as unacceptable/guideline due to the lack of a NOAEL; however, the lack of a NOAEL does not automatically preclude an acceptable classification, and after reconsideration, the team has upgraded the study to **Acceptable/Guideline**. The study satisfies the guideline requirement for a series 870.6200 subchronic neurotoxicity study in rats. In making its decision to upgrade this study, the team considered the results of the study together with the results of the rat chronic feeding study. The two studies taken together were deemed adequate to establish a NOAEL of 0.5 mg/kg/day for neurotoxic effects. See section 4.4 for more detailed information on the weight-of-the-evidence approach used to select doses and endpoints for *tau*-fluvalinate.

4.2.3 Developmental Toxicity Studies

A. ***Rat Study.***

In a developmental toxicity study (1998, MRID 44743301), *Tau*-Fluvalinate (88.4% a.i., Lot #56613870/96026) was administered by gavage at 0, 5, 10, or 15 mg/kg/day to pregnant Crl:CD®BR VAF/Plus® rats (25/dose) on gestation days (GDs) 6-19. Dams were sacrificed on GD 20. No animals died during the study.

Decreases ($p \leq 0.05$ or 0.01) in body weights and body weight gains were observed in the 10 mg/kg animals as follows: decreased mean body weights (↓5%, GD 20); reduced body weights corrected for gravid uterine weight (↓6%); decreased body weight gains (↓17%, GDs 15-17); reduced body weight gains for the overall treatment interval (↓17%, GDs 6-20) and for the overall study interval (↓13%, GDs 0-20); decreased body weight gains corrected for gravid uterine weight for the overall treatment interval (↓45%, GDs 6-20) and for the overall study interval (↓26%, GDs 0-20). Decreases ($p \leq 0.05$ or 0.01) in absolute (g/day) and relative (g/kg/day) food consumption were noted in the 10 mg/kg animals at GDs 6-9 (↓10-11%), GDs 15-19 (↓11-13%), for the overall treatment interval (↓9-10%, GDs 6-20), and for the overall study interval (↓6-7%, GDs 0-20). At 15 mg/kg, clinical observations were limited to increased incidences of chromorhinorrhea (14/375 possible observations in 8/25 animals, $p \leq 0.01$) and urine-stained abdominal fur (7/375 possible observations in 3/25 animals). When compared to concurrent controls, decreases ($p \leq 0.05$ or 0.01) in body weights and body weight gains were

observed in the 15 mg/kg animals as follows: decreased mean body weights (↓6-8%, GDs 18-20); reduced body weights corrected for gravid uterine weight (↓8%); decreased gravid uterine weights (↓12%, not statistically significant); decreased body weight gains (↓33%, GDs 15-17); reduced body weight gains for the overall treatment interval (↓27%, GDs 6-20) and for the overall study interval (↓22%, GDs 0-20); decreased body weight gains corrected for gravid uterine weight for the overall treatment interval (↓54%, GDs 6-20) and for the overall study interval (↓34%, GDs 0-20). Decreases ($p \leq 0.05$ or 0.01) in absolute (g/day) and relative (g/kg/day) food consumption were noted in the 15 mg/kg animals beginning at GDs 6-9 and continuing throughout treatment (↓8-17%), for the overall treatment interval (↓12-15%, GDs 6-20), and for the overall study interval (↓7-10%, GDs 0-20). No treatment-related gross pathologic findings were noted. The number of corpora lutea, implantations, resorptions, percent males, and pre- and postimplantation losses were similar between control and treated groups. **The maternal LOAEL is 10 mg/kg/day based on decreased body weights, body weight gains, and food consumption. The maternal NOAEL is 5 mg/kg/day.**

There were no treatment-related developmental effects noted at any dose level. **The developmental LOAEL was not observed. The developmental NOAEL is ≥15 mg/kg/day.**

This developmental toxicity study is classified **acceptable (§83-3[a])** and does satisfy the guideline requirement for a developmental toxicity study in the rat.

B. ***Rabbit study.***

In a developmental toxicity study (1981, MRID No. 00094112, and 1990, MRID No.: 92069054) *Tau*-fluvalinate technical (93.1%, Run 23-R, Batch # 0281028) was administered in a corn oil vehicle by gavage at 0, 5, 25, or 125 mg/kg/day to pregnant New Zealand White rabbits (17 females/dose) on gestation days (GDs) 6 through 18. Dams were sacrificed on GD 29. One high-dose female died on Day 16 following signs of labored respiration, cyanosis and depression. The cause of death of this female is not readily apparent but was not considered treatment related. One control animal and one high-dose female were both sacrificed near the end of "term" after discovery of signs indicating abortion. No unusual gross pathology was observed in either animal.

Maternal survival was comparable between the control and treated groups. No treatment-related findings were noted in the low- or mid-dose groups. In the high dose group (125 mg/kg/day), general depression (17/17) was observed at a greater incidence relative to controls (2/14). A transient (statistically significant) mean body weight loss (13-14%) was noted for high-dose females between Days 6-18. The greater incidences of depression and body weight loss in high-dose females are considered compound-related. The number of corpora lutea, implantations, resorptions, percent males, and pre- and post-implantation losses were similar between control and treated groups. **The maternal LOAEL is 125 mg/kg bw/day, based on general depression and a decrease in body weight. The maternal NOAEL is 25 mg/kg bw/day.**

No treatment-related differences in fetal weights and lengths were observed. Accompanying the maternal toxicity in the high dose group were embryo or fetotoxic effects, higher incidence of resorption (40.2% vs. 22.6% in controls), and concurrent lower fetal viability (59.8% vs. 76.7%

in controls). These effects were not statistically significant, but were large and consistent, and are considered to be related to the administration of compound and a secondary effect of maternal toxicity. The number and incidence of visceral anomalies and variants were not statistically different between groups. The incidence of skeletal anomalies were increased in the high dose group as a result of fetuses in one litter having short and spatulate ribs (5 rabbits), short and curved femurs (5 rabbits), and a curved tibia and fibula (4 rabbits). A total of 10 litters and 55 fetuses were examined at the high dose. **The developmental LOAEL is 125 mg/kg/day, based on higher incidence of resorption and concurrent lower fetal viability and evidence of skeletal variants. The developmental NOAEL is 25 mg/kg/day.**

The developmental toxicity study in the rabbit is classified **acceptable/guideline** (83-3[a]) and **satisfies** the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbits.

4.2.4 Reproductive Toxicity Study

In a 2-generation reproduction study (1986, MRID 44596601), *tau*-fluvalinate (93.1% a.i.) was continuously administered in the diet to Sprague-Dawley rats (P generation - 28/sex/dose, 32/sex/dose at the high-dose; F_1 generation - 24/sex/dose) at dose levels of 0, 10, 25 or 125 ppm (equivalent to [M/F]0/0, 0.76/0.84, 1.90/2.08, and 9.53/10.51 mg/kg/day, respectively). Exposure to P animals began at 6 weeks of age and lasted for 10 weeks prior to mating and throughout mating, gestation, and lactation. F_1 pups selected to produce the F_2 generation were exposed to the same dosage as their parents at post-natal day (PND) 21 and continuously throughout the rest of the study. After approximately 12 weeks of treatment, F_1 offspring were paired to produce the F_2 litters that were necropsied at weaning. Mating to produce a second F_{2b} generation was not performed.

Systemic toxicity. There were no differences of toxicological concern in body weight, body weight gain, food consumption, female sexual development, reproductive performance, gross pathologic findings, absolute and body weight-adjusted organ weights, and histological findings. At 125 ppm, treatment-related clinical signs were limited to skin ulceration in P males (3/32 treated vs 0/28 controls), P females (1/32 treated vs 0/28 controls), and F_1 males (2/24 treated vs 0/24 controls). The P female and her litter were severely ulcerated and, therefore, were sacrificed. F_1 dams did not exhibit any treatment-related clinical signs. No observations of toxicological significance were made at the mid- (25 ppm) and low-dose (10 ppm). **The systemic toxicity LOAEL is 125 ppm (9.53/10.51 [M/F] mg/kg/day) based on clinical signs (skin ulceration). The systemic toxicity NOAEL is 25 ppm (1.90/2.08 [M/F] mg/kg/day).**

Offspring toxicity. There were no differences of toxicological concern in litter size, viability, developmental landmarks, gross pathologic findings, absolute and body weight-adjusted organ weights, and histological findings. At 125 ppm, tremors were observed during the lactation period (~LD 14) in the F_1 litters (15/28 treated litters vs 0/28 controls) and F_2 litters (6/20 treated litters vs 1/24 controls). There was a toxicologically significant decrease in F_2 pup weight at PND 21 (↓12%, $p<0.05$). This decrease in pup weight, combined with a slightly lower litter size, caused a significant decrease (↓16%, $p<0.05$) in mean litter weight when compared to controls (286.9 g treated vs 342.1 g controls). No observations of toxicological significance were made

in the 10 or 25 ppm groups. **The offspring toxicity LOAEL is 125 ppm (9.53/10.51 [M/F] mg/kg/day) based on decreased pup body weights and increased incidence of clinical signs (tremors). The reproductive toxicity NOAEL is 25 ppm (1.90/2.08 [M/F] mg/kg/day**).

The reproductive study is determined to be **acceptable/guideline (§83-4)** and does satisfy the guideline requirement for a multi-generational reproductive toxicity study in rats.

4.2.5 Additional Information from Literature Sources

A literature search (PubMed) revealed one paper (J. Steroid Biochem. 35(3-4):409-414 (1990)) suggesting that pyrethroids as a class (including *tau*-fluvalinate) may have endocrine disrupting properties based on inhibition of [3H]methyltrienolone binding with human skin fibroblasts androgen receptors. Not all pyrethroids tested, however, were able to displace [3H]testosterone from sex hormone binding globulin. Although *tau*-fluvalinate is not mentioned specifically, another publication (Sheets et al, Toxicolo. Appl. Pharmacol. 126:186-190 (1994)) discusses the inability of the neonatal rats to detoxify pyrethroids.

4.2.6 Pre-and/or Postnatal Toxicity

4.2.6.1 Determination of Susceptibility

Neither the rat or rabbit developmental toxicity nor the rat multi-generation reproduction studies demonstrated increased toxicity to the fetuses or offspring relative to the dams or parental generation, as indicated by the offspring having LOAELs greater than or equal to the parental LOAELs. In particular, the NOAEL and LOAEL for maternal toxicity in the rat developmental toxicity study were 5 and 10 mg/kg/day, whereas there was no developmental toxicity at 15 mg/kg/day, the highest dose tested. The NOAEL and LOAEL for both the maternal and developmental toxicity for the rabbit developmental toxicity study were 25 and 125 mg/kg/day. However, the developmental effects at 125 mg/kg/day or signs of lower fetal viability and evidence of skeletal variants were considered to accompany the lower body weight seen in the dams. Similarly, the NOAEL and LOAEL for the systemic effects in the parental groups was the same as the NOAEL and LOAEL for the offspring toxicity in the multi-generation reproduction study. The degree of effects in the offspring was not considered severe enough to determine that there is a meaningful concern that the offspring are qualitatively more susceptible than the parents.

Thus, there is no evidence of increased qualitative or quantitative susceptibility of offspring to the toxic effects of *tau*-fluvalinate in the available database.

4.2.6.2 Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility

The team has concluded that there is a low degree of concern for residual uncertainties for pre- and post-natal susceptibility. There is no evidence of increased susceptibility in the guideline developmental or reproductive studies. The team has selected an endpoint for risk assessment that provides a clear NOAEL for the primary effect of interest, neurotoxicity. It is the most conservative (lowest) endpoint in the database and will be protective of other effects seen in the

database, and any potential effects seen in a DNT study. Further, although *tau*-fluvalinate is a neurotoxicant and there is no developmental neurotoxicity study available, the team has determined that the potential for exposure of mothers, their fetuses and neonates to *tau*-fluvalinate is low based on the following:

1) *Tau*-fluvalinate has very limited annual domestic usage, and the majority of this usage is in commercial greenhouses and on outdoor field- and container-grown ornamentals where pregnant women and babies are unlikely to be exposed.

2) Dietary exposures to *tau*-fluvalinate are anticipated to be very low to insignificant, as the only registered food use of *tau*-fluvalinate is in beehives (honey). Honey is not used as an ingredient in infant formulas and is not considered an appropriate food for children less than 2 years old. In addition, the low solubility (2.4 ppb) of *tau*-fluvalinate limits the likelihood of it getting into drinking water in appreciable quantities. The results of acute and chronic dietary exposure analyses conducted using DEEM-FCID and Lifeline software confirm *tau*-fluvalinate's low dietary exposure potential (See section 6.1.2 below).

3) The potential for residential exposure is very low, based on the low annual usage on residential sites and the fact that there are no broadcast applications allowed in residential areas.

Based on *tau*-fluvalinate's limited use and the low probability of exposure, the team has a low degree of concern for pre- and/or post-natal increased sensitivity. Additional information supporting this conclusion, including specific production and usage data, is contained in the Confidential Appendix.

4.3 Recommendation for a Developmental Neurotoxicity Study

The RARC met on 02/09/2005 and considered the factors that both support and do not support requiring a developmental neurotoxicity study as described below. After consideration of these factors as well as the exposure patterns, the RARC agreed that there would not be a sufficient exposure to justify requiring a developmental neurotoxicity study with *tau*-fluvalinate (*Tau*-fluvalinate: Proposed Review and Risk Assessment Strategy Report of the Risk Assessment Review Committee (RARC1), Feb. 9, 2005).

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity study

Tau-Fluvalinate is a pyrethroid insecticide with known effects on the nervous system in insects. In mammals manifestations of neurotoxicity resulting from interaction with the sodium channel (and possibly other nerve membrane phenomena) can result. Since the fetus and neonatal mammals have a lower capacity for detoxifying the intact pyrethroid structure, there is a potential for neurotoxicity to result in fetuses if the intact pyrethroid passes the placenta or if intact pyrethroid can be transported to the newborn mammal via lactation. Although residues of intact pyrethroid in infant formula could result in exposure of newborns, there are currently no food uses of *tau*-fluvalinate likely to result in such residues. Honey, the only food on which *tau*-fluvalinate is used, is not a component of infant formula.

Tau-fluvalinate was shown to cause peripheral nerve histological changes in the non-guideline "acute" neurotoxicity study.

Developmental neurotoxicity studies have been requested for most other pyrethroids.

4.3.2 Evidence that supports not requiring Developmental Neurotoxicity study

For the reasons described above in section 4.2.6.2 (**Degree of Concern Analysis and Residual Uncertainties for Pre and/or Post-natal Susceptibility)** the team has determined that the potential for exposure of mothers, their fetuses and neonates to *tau*-fluvalinate is low and not significant enough to justify requiring a developmental neurotoxicity study. Total domestic usage is very limited, and most of this use occurs on non-food, non-residential sites where exposure of pregnant women and infants would not be expected. Significant dietary exposure is not expected, based on *tau*-fluvalinate's limited usage, low potential to contaminate drinking water and the fact that honey (the only food use) is not a component of infant formula and not recommended for consumption by children under 2 years of age.

In addition, the conduct of a DNT study with *tau*-fluvalinate would be confounded by the increased sensitivity of the rats to the "pyrethroid reaction". The severity of the dermal irritation that results from this reaction often requires early termination of the study. Such confounding would further affect the assessment of the neonatal pups who may be in dermal contact with the intact test material via proximity to spilled feed. The dams and pups would have to be dosed by gavage in an attempt to circumvent confounding of the study due to the "pyrethroid reaction".

4.3.2.1 Rationale for the UF_{DB} (when a DNT is recommended)

Not applicable. A DNT study is not recommended.

4.4 Hazard Identification and Toxicity Endpoint Selection

Comments about endpoint selection: Based on a weight-of-evidence approach, a conservative NOAEL for neurotoxic effects has been identified for *tau*-fluvalinate. This approach is based on the results of 2 studies: the rat chronic feeding study and the rat subchronic neurotoxicity study. In the chronic study in the rat, clinical signs of neurotoxicity including: excessive salivation, pawing at bottom of the cage, lacrimation, abnormal stance, ruffling, and transient hyperactivity followed by hypoactivity were observed at 1.0 mg/kg/day; these effects were not seen at 0.5 mg/kg/day. In the subchronic study in the rat, excessive grooming and bulging eyes were noted in the animals at 2 mg/kg/day (the lowest dose tested). We evaluated these two studies in parallel because the clinical signs of neurotoxicity in the rat chronic study are transient and mentioned in the report but not well documented. However, the team believes that these early-onset neurotoxic effects are consistent with the typical clinical signs associated with pyrethroids and are most likely the result of preliminary nerve stimulation and/or agitation. At the next highest dose tested in the chronic rat study (2.5 mg/kg/day), the development of tropic (plantar) ulcers could possibly be indicative of amplified and prolonged nervous system stimulation/agitation. Furthermore, the results of the 90-day subchronic neurotoxicity study are consistent with the

results of the rat chronic feeding study, demonstrating marked evidence of neurotoxicity at a similar low dose. The team believes that the results of these 2 studies taken together form the basis for a clear NOAEL of 0.5 mg/kg/day for neurotoxic effects, with minimal effects beginning to be seen at 1.0 mg/kg/day in the chronic study, thus establishing a conservative LOAEL. The selection of this LOAEL is further supported by the increasingly severe neurotoxic effects seen at the higher doses of 2 mg/kg/day and 2.5 mg/kg/day, respectively, in the shorter- term subchronic study and longer-term chronic feeding study. We believe that this conservative determination is protective for all population subgroups.

4.4.1 Acute Reference Dose (aRfD) - General Population

Studies Selected: Rat Chronic Feeding Study & Subchronic Neurtotoxicity Study in the rat (See rationale Section 4.4)

MRID No: 92069048 & 44900601

Executive Summaries:

Rat Chronic Feeding Study: In a combined chronic / carcinogenicity study (1984, MRID 92069048*), tau*-fluvalinate (92.1% a.i, Run 23R, Batch No. 0281028) was administered to Charles Rivers CD rats (85/sex/dose) by gavage at dose levels of 0, 0.25, 0.50, 1.0, or 2.5 mg/kg bw/day for 24 months.

In males and females from groups receiving 1.0 and 2.5 mg/kg/day, transient clinical signs of toxicity included excessive salivation and lacrimation, pawing of the bottom and sides of the cage, abnormal stance, ruffling, and transient hyperactivity followed by hypoactivity. These signs were observed during the first 3 hours after dosing and subsided within 6 hours. No treatment-related effects on hematology, urinalysis, ophthalmology, clinical chemistry or organ weights were observed in male or female rats at any dose. Mean body weights were significantly decreased (13-15%) in females receiving 2.5 mg/kg/day. There were no effects of dosing on food consumption. There was an increase in plantar ulcers in females receiving 2.5 mg/kg/day when compared to controls. No other treatment-related effects on gross or histopathology were observed at any dose. At the doses tested, there were no treatment-related increases in tumor incidences in treated animals when compared with controls. **The LOAEL is 1.0 mg/kg/day, based on abnormal stance, ruffling, and transient hyperactivity followed by hypoactivity in males and females. The NOAEL is 0.50 mg/kg/day .**

This chronic/carcinogenicity study in the rat is classified as **acceptable/guideline** and **satisfies** the guideline requirement for a chronic/carcinogenicity study [OPPTS 870.4300); OECD 453] in the rat.

Subchronic Neurotoxicity Rat Study - See executive summary of this study in Section 4.2.2

Dose and Endpoint for Risk Assessment: NOAEL = 0.5 mg/kg/day based on excessive salivation and lacrimation, pawing of the bottom and sides of the cage, abnormal stance, ruffling, and transient hyperactivity followed by hypoactivity at 1.0 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100. Includes a 10X factor for interspecies extrapolation and a 10X factor for intraspecies variation.

Comments about Study/Endpoint: See explanation above in Section 4.4. On February 9th, 2005, the RARC concurred that the results of the 90-day neurotoxicity study are consistent with the results of the chronic study and that the NOAEL from the rat chronic feeding study should be used for acute, chronic and inhalation endpoints. The acute, short-term, intermediate-term and long-term effects of *tau*-fluvalinate are not cumulative based on the characteristics and nature of typical pyrethroid effects. Furthermore, the RARC concurred that even though *tau*-fluvalinate is a neurotoxicant, the low exposure precludes the need to require a DNT.

Acute RfD = 0.5 mg/kg/day (NOAEL) = **0.005 mg/kg/day**
100 (UF)

4.4.2 Acute Reference Dose (aRfD) - Females age 13-49

The acute RfD for females age 13-49 is the same as for the general population (see above).

4.4.3 Chronic Reference Dose (cRfD)

Studies Selected: Same as for acute dietary (Rat Chronic Feeding Study & Subchronic Neurtotoxicity Studies (See rationale Section 4.4).

MRID No: 92069048 & 44900601

Executive Summaries: See above.

Dose and Endpoint for Risk Assessment: NOAEL = 0.5 mg/kg/day based on excessive salivation and lacrimation, pawing of the bottom and sides of the cage, abnormal stance, ruffling, and transient hyperactivity followed by hypoactivity at 1.0 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100. Includes a 10X factor for interspecies extrapolation and a 10X factor for intraspecies variation.

Comments about Study: See section 4.4.1

Chronic RfD = 0.5 mg/kg/day (NOAEL) = **0.005 mg/kg/day**
100 (UF)

4.4.4 Incidental Oral Exposure (Short and Intermediate Term)

Short-/Intermediate-term oral endpoints are selected when incidental oral exposure could result from residential, recreational, and institutional pesticide use. Based on the limited usage of *tau*-fluvalinate and the nature of the currently registered uses, the potential for incidental oral exposure to *tau*-fluvalinate is very low. *Tau*-fluvalinate is registered for use in residential areas as a perimeter treatment around buildings and as an ant mound drench. Because of the localized nature of these uses, neither would be expected to result in significant incidental oral exposure. There are no broadcast or other wide area uses of *tau*-fluvalinate permitted on residential, recreational or institutional sites. Based on these considerations, the team concluded that an incidental oral exposure endpoint was not required. The RARC concurred with the team's decision (*Tau*-fluvalinate: Proposed Review and Risk Assessment Strategy Report of the Risk Assessment Review Committee (RARC1), Feb. 9, 2005)

4.4.5 Dermal Absorption

There is no acceptable guideline study that demonstrates a dermal absorption factor. There is one study (Accession No.: 250142, classified as unacceptable/ guideline, not ungradable) that demonstrated that only 4% of the applied dose was absorbed in a *single* male rat. Comparison of the LOAEL of 125 mg/kg/day (based on "anorexia and general depression") from the rabbit developmental toxicity study with the LOAEL of 500 mg/kg/day (based on systemic response of decreased food consumption) from the 21-day dermal toxicity study would suggest that a dermal absorption factor of 25% (125 mg/kg/day ÷ 500 mg/kg/day x 100) would be appropriate.

4.4.6 Dermal Exposure (Short, Intermediate and Long Term)

No toxicity endpoint was selected for dermal exposure to products containing *tau*-fluvalinate. Dermal exposure to products containing *tau*-fluvalinate is expected to be largely self-limiting due to the irritation that occurs as a result of the "pyrethroid reaction". The team determined (and the RARC agreed) that the issue of dermal exposure can be best addressed by labeling to avoid contact with skin and instructions to wash the affected area immediately following contact. Currently approved end-use product labels include adequate precautionary labeling.

4.4.7 Inhalation Exposure (Short, Intermediate and Long Term)

Studies Selected: Same as for acute and chronic dietary (Rat Chronic Feeding Study & Subchronic Neurtotoxicity Studies (See rationale Section 4.4).

MRID No: 92069048 & 44900601

Executive Summaries: See above.

Dose and Endpoint for Risk Assessment: NOAEL = 0.5 mg/kg/day based on excessive salivation and lacrimation, pawing of the bottom and sides of the cage, abnormal stance, ruffling, and transient hyperactivity followed by hypoactivity at 1.0 mg/kg/day (LOAEL).

Comments about Study: See section 4.4.1. There is no subchronic inhalation study with *tau*-fluvalinate available for risk assessment. The potential for *tau*-fluvalinate to affect the respiratory system in humans through its ability to cause the "pyrethroid reaction" has not been assessed in animal studies. Even if it were, the most appropriate species for assessing the potential human hazard due to possible respiratory effects may not be the rat, the species commonly used and recommended by the guidelines for subchronic inhalation studies. The potential for *tau*-fluvalinate to affect the respiratory system in humans is an important issue because humans with chronic respiratory conditions such as asthma or emphysema may have incidents triggered by exposure to *tau*-fluvalinate. The RARC recommended that label restrictions be such that applicators and workers wear appropriate respirators when applying products that may result in spray mists or other inhalation hazards. Currently approved product labels require adequate protective clothing, including a NIOSH-approved respirator for both indoor and outdoor applications.

4.4.8 Margins of Exposure

The following margins of exposure (MOEs) represent HED's level of concern for occupational and residential (non-dietary) exposure risk assessments:

Route of Exposure	Occupational MOE (all durations of exposure)	Residential MOE (all durations of exposure)
Dermal	100 (this risk assessment is not required)	100 (this risk assessment is not required)
Incidental Oral	100 (this risk assessment is not required)	100 (this risk assessment is not required)
Inhalation	100	100 (this risk assessment is not required)

For occupational exposure (all durations) risk assessments, an MOE of 100 is required. The MOE is based on 10x for intraspecies variation and 10x for interspecies extrapolation. For residential exposures, an MOE of 100 is required, and is based on 10x for intraspecies variation, 10x for interspecies extrapolation and a 1x special FQPA factor.

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

Exposures resulting from oral and inhalation exposure may be aggregated based on a common toxic endpoint: neurotoxicity. Neither an incidental oral endpoint nor a dermal endpoint was selected for risk assessment, and there is no need to aggregate exposures through these routes with oral (dietary) and inhalation exposures.

4.4.10 Classification of Carcinogenic Potential

Tau-fluvalinate was not demonstrated to be carcinogenic in either the rat or mouse carcinogenicity studies, and none of the mutagenicity/genetic toxicity studies were determined to be positive. Based on lack of carcinogenic effects in the rat and mouse carcinogenicity studies

and lack of a mutagenicity concern, *tau*-fluvalinate can be classified as "not likely to be a human carcinogen".

Table 4.4. Summary of Toxicological Doses and Endpoints for *Tau*-fluvalinate for Use in Human Risk Assessments			
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Special FQPA SF* and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (females 13-49)	No selection. No evidence that there is significant toxicity following a single exposure.		
Acute Dietary (general population)	NOAEL = 0.5 mg/kg/day. UF = 100 aRfD = 0.005 mg/kg/day	1X aPAD = aPAD/FQPA SF aPAD = 0.005/1 = 0.005 mg/kg/day	LOAEL = 1 mg/kg/day. Clinical signs in the rat chronic feeding study coupled with a LOAEL of 2 mg/kg/day based on excessive grooming and bulging eyes in the subchronic neurotoxicity study.
Chronic Dietary (all populations)	NOAEL = 0.5 mg/kg/day UF = 100 cRfD = 0.005 mg/kg/day	1X cPAD = cRfD/FQPA SF cPAD = 0.005/1 = 0.005 mg/kg/day	LOAEL = 1 mg/kg/day. Clinical signs in the rat chronic feeding study coupled with a LOAEL of 2 mg/kg/day based on excessive grooming and bulging eyes in the subchronic neurotoxicity study.
Incidental Oral - all durations.	No selection since there are no residential, recreational or institutional uses likely to result in incidental oral exposure to *tau*-fluvalinate. As per e-mail from K. Rothwell (February 4, 2005) there is no residential turf use.		
Dermal - all intervals	No endpoint selection. Dermal exposure should be self-limiting because of the dermal reactions resulting from contact with product. The issue of dermal exposure can be best addressed by labeling to avoid contact with skin and instructions to wash the affected area immediately following contact.		
Inhalation - all intervals Short-Term (1 - 30 days)	NOAEL = 0.5 mg/kg/day.	1X MOE = 100	LOAEL = 1 mg/kg/day. Clinical signs in the rat chronic feeding study coupled with a LOAEL of 2 mg/kg/day based on excessive grooming and bulging eyes in the subchronic neurotoxicity study.
Cancer (oral, dermal, inhalation)	**Classification:** *tau*-fluvalinate has not been reviewed by CARC or HIARC for carcinogenicity classification. However, since no evidence of carcinogenicity was seen in rat and mouse carcinogenicity studies with *tau*-fluvalinate, and the available mutagenicity/genetic toxicity data base do not indicate a concern, *tau*-fluvalinate may be classified as "not likely to be a human carcinogen".		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable
* Refer to Section 4.5

4.5 Special FQPA Safety Factor

The team evaluated the potential for increased susceptibility of infants and children from exposure to *tau*-fluvalinate as required by the Food Quality Protection Act (FQPA) of 1996 according to

the 2002 OPP 10x Guidance Document. The team concluded that the special FQPA SF can be removed (1X) since there are no/low concerns and no residual uncertainties for pre- and/or postnatal toxicity based on the following evidence:

- In the developmental rat study, maternal toxicity (decreased body weight and food consumption) was observed at 10 mg/kg/day. However, fetal anomalies were not seen at the highest dose tested (15 mg/kg/day) indicating that there is no quantitative or qualitative pre- and/or postnatal toxicity resulting from exposure to *tau*-fluvalinate.

- A clear NOAEL/LOAEL was established for the developmental rabbit study.

- In the 2-generation reproductive study in rats, the fetal anomalies (tremors during lactation in both litters, decrease in pup weight in F2 generation and slightly lower litter size) were seen only at the highest dose tested (9.53/10.51 mg/kg/day for males/females), and they were observed in the presence of maternal toxicity (skin ulcerations). The effects in the offspring, although not also seen in the parents, demonstrated a clear NOAEL and LOAEL and are considered a qualitative increase in susceptibility of low concern.

The *tau*-fluvalinate risk assessment team evaluated the quality of the exposure data; and, based on these data, recommended that the special FQPA SF be reduced to 1X. The recommendation is based on the following:

- The dietary food exposure assessment utilizes tolerance level residues and 100% crop treated information for all commodities. By using these screening-level assumptions, chronic exposures/risks will not be underestimated.

- The dietary drinking water assessment utilizes values generated by models and associated modeling parameters which are designed to provide conservative, health protective, high-end estimates of water concentrations.

4.6 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on *tau*-fluvalinate submitted for registration purposes, there was no estrogen, androgen, and/or thyroid mediated toxicity. When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, *tau*-fluvalinate may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

Reference: *Review of Fluvalinate Incident Reports*, DP Barcode D300199, Jerome Blondell, 03/14/2005

5.1 Incident Reports

Databases for the OPP Incident Data System (IDS), Poison Control Centers, the California Department of Pesticide Regulation, the National Pesticide Telecommunications Network (NPTN) and the National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR) were consulted for incident data involving the insecticidal active ingredient *tau*-fluvalinate.

From the available incident data it is apparent that *tau*-fluvalinate exposure can lead to mild or moderate irritation of eyes and skin. Commonly reported systemic effects include headache, nausea and breathing difficulty. Many of the incidents reported in California were related to the pesticide's use in greenhouses. In addition, beekeepers nationwide have reported dermal or other allergic-type reactions. In a comparison of Poison Control Centers' data for *tau*-fluvalinate and other pesticides, *tau*-fluvalinate was found to be as likely to cause minor symptoms as other pesticides in the database but much less likely to cause serious effects requiring hospitalization or critical care.

5.2 Other

Tau-fluvalinate is not included in the Agricultural Health Survey (AHS) Applicator questionnaire and is not on the current National Health and Nutrition Examination Survey (NHANES) list.

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

6.1.1 Residue Profile

Reference: *Tau-Fluvalinate. RED - Reregistration Eligibility Decision Document. Residue Chemistry Considerations. Case No. 2295*; D300204; J. Morales; 02/22/05

A tolerance is established at 40 CFR §180.427 (a) under the name "Fluvalinate" for "residues of (alpha *RS* , 2R)-fluvalinate [(*RS*)-alpha-cyano-3-phenoxybenzyl (*R)*-2-[2-chloro-4-(trifluoromethyl)anilino]-3-methylbutanoate" in/on honey at 0.05 ppm. "Fluvalinate" is the common name for the racemic mixture of the 4 isomers of cyano-(3-phenoxyphenyl)methyl N-[2-

chloro-4-(trifluoromethyl)phenyl]-valinate (CAS name). "*Tau*-fluvalinate" is the term for the half resolved mixture (2 of the 4 isomers). The tolerance expression should be revised to reflect the correct common name and the CAS name as follows: "Tolerances are established for residues of the insecticide *tau*-fluvalinate [cyano-(3-phenoxyphenyl)methyl N-[2-chloro-4-(trifluoromethyl)phenyl]-D-valinate] ...".

The nature of the residue in honey is adequately understood. Currently tolerances are expressed in terms of *tau*-fluvalinate, *per se*. The current tolerance expression is adequate. Adequate data are available to reassess the established tolerance for honey at the same level. However, based on the available data, the established tolerance may be reduced from 0.05 ppm to 0.02 ppm.

A GC/ECD method is available for the enforcement of tolerances for residues of *tau*-fluvalinate in honey; this method has been forwarded to FDA for publication in PAM Vol. II. This method has a limit of detection of 0.01 ppm.

Acceptable methods are available for enforcement and data collection purposes for both plant and animal commodities. The Pesticide Analytical Manual (PAM) Volume II lists Method I, a GC method with electron capture detection (ECD), for the enforcement of tolerances for *tau*-fluvalinate residues of concern in/on plant and animal commodities. The stated limits of quantitation are 0.01 ppm for plant commodities (except oil) and animal commodities, and 0.02 ppm for oil. These methods are not currently required to support reregistration of *tau*-fluvalinate, as there are no registered uses on any plant or animal commodities.

The FDA PESTDATA database dated 11/01 (PAM Volume I, Appendix I) indicates that *tau*-fluvalinate is completely recovered (average recovery >80%) using multiresidue methods Sections 302 (Luke method; Protocol D) and 303 (Mills, Onley, Gaither method; Protocol E, nonfatty). Recovery using Section 304 (Mills Method; Protocol F, fatty food) was variable (47-96%).

The reregistration requirements for magnitude of the residue in/on honey have been satisfied. Residues of *tau*-fluvalinate were below the limit of detection (<0.01 ppm) in all samples of honey from the brood and super layers, except one, taken 0, 28, 42, and 70 days following placement of 10% Impr strips in beehives; the strips were removed after 42 days, and the honey supers were not removed during treatment. One honey sample from the brood layer bore detectable residues at 0.015 ppm. Residues were also found to be <0.01 ppm in honey from hives treated at exaggerated rates (2-4x) with longer exposure times.

The above data actually represent an exaggerated rate since honey supers remained in place during treatment (current registration specifies that honey supers be removed during treatment); however, these were the data used to establish the current honey tolerance.

All previously registered uses of *tau*-fluvalinate (or *tau*-fluvalinate) on food/feed crops have been canceled.

6.1.2 Acute and Chronic Dietary Exposure and Risk

Reference: *Tau-fluvalinate Acute and Chronic Dietary Exposure Assessments for the Reregistration Eligibility Decision*; S. Stanton; 03/11/2005; DP Barcode D300203.

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™),Version 2.00/2.02, and the Lifeline Model Version 2.0, which use food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998.

Acute Dietary Exposure Results and Characterization

The Tier 1 acute analysis assumed 100% crop treated and reassessed tolerance-level residues of 0.02 ppm in honey. Drinking water was incorporated directly in the dietary assessment using the 1 in 10 year annual peak concentration for surface water generated by the PRZM-EXAMS model (See Section 6.2, "Water Exposure/Risk Pathway" for information on the drinking water estimates used in the analysis).

The resulting acute dietary exposure estimates using the DEEM-FCID model were less than 6% of the aPAD for the U.S. population and all population subgroups. *Tau*-fluvalinate acute dietary exposure (food + water) at the 95th percentile was estimated at 0.000069 mg/kg/day for the U.S. population (1.4% of the aPAD) and 0.000257 mg/kg/day (5.1% of the aPAD) for the most highly exposed population subgroup (All Infants). Estimated acute exposures at the 95th percentile using the Lifeline model were consistent with the DEEM-FCID results (1.2% of the aPAD for the U.S. population and 3.9% of the aPAD for infants).

Nearly all of the estimated acute dietary exposure to *tau*-fluvalinate is from drinking water. Estimated acute dietary exposure to *tau*-fluvalinate from honey represents between <0.01% and 0.06% (children, 1-2 yrs. old) of the total estimated exposure.

Chronic Dietary Exposure Results and Characterization

The Tier 1 chronic analysis assumed 100% crop treated and reassessed tolerance-level residues of 0.02 ppm in honey. Drinking water was incorporated directly in the dietary assessment using the 1 in 10 year annual mean concentration for surface water generated by the PRZM-EXAMS model (See Section 6.2, "Water Exposure/Risk Pathway" for information on the drinking water estimates used in the analysis).

The resulting chronic dietary exposure estimates using the DEEM-FCID model were less than 1% of the cPAD for the U.S. population and all population subgroups. *Tau*-fluvalinate chronic dietary exposure (food + water) was estimated at 0.000014 mg/kg/day for the U.S. population (0.3% of the cPAD) and 0.000045 mg/kg/day (0.9% of the cPAD) for the most highly exposed population subgroup (All Infants). Estimated chronic exposures using the Lifeline model were consistent with the DEEM-FCID results (0.2% of the cPAD for the U.S. population and 0.8% of the cPAD for infants).

Nearly all of the estimated chronic dietary exposure to *tau*-fluvalinate is from drinking water. Estimated chronic dietary exposure to *tau*-fluvalinate from honey represents <0.01% of the total estimated exposure for the U.S. population and all population subgroups.

Table 6.1. Summary of Dietary Exposure and Risk for *Tau*-fluvalinate

Population Subgroup	Acute Dietary (95th Percentile)[1]				Chronic Dietary			
	DEEM-FCID™		Lifeline		DEEM-FCID™		Lifeline	
	Dietary Exposure (mg/kg)	% aPAD	Dietary Exposure (mg/kg)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.000069	1.4	0.000060	1.2	0.000014	<1	0.000010	<1
All Infants (< 1 year old)	0.000257	5.1	0.000197	3.9	0.000045	<1	0.000038	<1
Children 1-2 years old	0.000109	2.2	0.000126	2.5	0.000021	<1	0.000020	<1
Children 3-5 years old	0.000098	2.0	0.000103	2.0	0.000020	<1	0.000017	<1
Children 6-12 years old	0.000068	1.4	0.000062	1.2	0.000013	<1	0.000010	<1
Youth 13-19 years old	0.000056	1.1	0.000046	<1.0	0.000010	<1	0.000007	<1
Adults 20-49 years old	0.000064	1.3	0.000051	1.0	0.000013	<1	0.000008	<1
Adults 50+ years old	0.000058	1.2	0.000051	1.0	0.000014	<1	0.000009	<1
Females 13-49 years old	0.000064	1.3	0.000056	1.1	0.000013	<1	0.000009	<1

[1]Acute exposure is reported at the 95th percentile since it was a Tier 1 dietary assessment. Estimated exposures at the 99th and 99.9th percentiles were also well below HED's level of concern, with the highest estimated exposure at the 99.9th percentile (infants using the DEEM-FCID software) representing only 13% of the aPAD.

6.2 Water Exposure/Risk Pathway

Reference: *Tier II Estimated Environmental Concentration for the Use of Tau-Fluvalinate for Apiary Uses, Carrots for Seed (24-C SLNs), Building Perimeters, Nurseries, Ornamentals, Indoor Landscapes and Honey for the Human Health Drinking Water Risk Assessment*; Mark Corbin; D304067; 02/03/2005.

Tau-fluvalinate is highly immobile (K_d values between 853 and 1,708 with corresponding K_{oc} values between 110,000 and 370,000, respectively) and practically insoluble in water (2.4 ppb at 25C), indicating a low potential for significant residues in drinking water. Nevertheless, *tau*-

fluvalinate is registered for outdoor, non-food uses (including carrots and Brassica/cole crops grown for seed, ornamentals and building perimeters) that could potentially result in residues in surface or ground water.

The estimated drinking water concentrations from surface water sources were calculated using PRZM (Pesticide Root Zone Model) and EXAMS (Exposure Analysis Modeling System). Based on the modeling results, the 1 in 10 year annual mean (chronic, non-cancer) concentration in surface water is estimated to be 0.65 ppb. The 1 in 10 year annual peak (acute) concentration is estimated to be 1.31 ppb. The estimated ground water concentrations were calculated using the Tier I SCI-GROW (Screening Concentration In Ground Water) model. The estimated acute and chronic drinking water concentration from ground water sources is 0.0025 ppb. The higher PRZM-EXAMS estimated drinking water concentrations for surface water were used for the acute and chronic dietary analyses. The modeling results are summarized below:

Table 6.2. Summary of Estimated Surface and Ground Water Concentrations for *Tau*-fluvalinate.

Exposure Duration	***Tau*-fluvalinate**	
	Surface Water Conc., ppb [a]	**Ground Water Conc., ppb [b]**
Acute	1.31	0.0025
Chronic (non-cancer)	0.65	0.0025

[a] From the Tier II PRZM-EXAMS - Index Reservoir model. Input parameters are based on multiple (12) applications to woody ornamentals in Oregon at the maximum application rate of 0.34 lb. a.i./A, the upper 90th percentile aerobic soil metabolic half-life of 22.2 days, a photolysis half-life of 1 day and the average K_{oc} value of 244,000.

[b] From the SCI-GROW model assuming 12 applications to woody ornamentals at the maximum use rate of 0.34 lb. ai/A, the median K_{oc} of 270,000, and the average aerobic soil metabolic half-life of 11.5 days.

6.3 Residential (Non-Occupational) Exposure/Risk Pathway

Although *tau*-fluvalinate is labeled for use in residential areas, a residential exposure assessment was not conducted, since there is little potential for exposure from these uses. *Tau*-fluvalinate may be applied in residential areas to building surfaces/perimeters and ant mounds by commercial applicators only (i.e., no homeowner applications are permitted).

- Building surfaces and perimeters: Perimeter applications are made to a band of soil and/or vegetation 6 to 10 feet wide around and adjacent to the structure. Sites may include vegetation areas, soil, trunks of woody ornamentals and fence lines adjacent to or around the structure. Surface applications are made as crack and crevice treatments to structures such as porches, window and door frames, eaves and foundations.

- Ant mounds: *Tau*-fluvalinate is applied as a drench to individual ant mounds.

6.3.1 Residential Handler Exposure/Risk

A residential handler exposure assessment was not conducted, since there are no homeowner uses of *tau*-fluvalinate and, therefore, no potential for such exposure. All applications in residential areas are made by commercial applicators.

6.3.2 Residential Post-Application Exposure/Risk

The residential uses of *tau*-fluvalinate are largely spot applications. There are no wide area treatments, such as broadcast applications on home lawns, that would result in significant post-application exposure of adults or children. Therefore, a residential post-application exposure assessment is not required.

6.3.3 Other (Spray Drift, etc.)

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for *tau*-fluvalinate. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

For most pesticide active ingredients, water monitoring data are considered inadequate to determine surface and ground water drinking water exposure estimates, so model estimates have been used to estimate residues in drinking water (EDWCs). In order to determine if aggregate risks are of concern, HED has historically calculated drinking water levels of comparison, or DWLOCs. The DWLOC is the maximum amount of a pesticide in drinking water that would be acceptable in light of combined exposure from food and residential pathways. The calculated DWLOCs were then compared to the EDWCs provided by EFED to determine if a potential concern existed for dietary exposure to residues in drinking water.

In order to fully implement the requirements of FQPA, HED and EFED have been working toward refining the screening-level DWLOC approach to conducting aggregate risk assessments that combine exposures across all pathways. As part of this process, EFED and HED have agreed that EDWCs can be used directly in dietary exposure assessments to calculate aggregate dietary (food + water) risk. This is done by using the relevant model value as a residue for drinking water (all sources) in the dietary exposure assessment. The principal advantage of this approach is that the actual individual body weight and water consumption data from the CSFII are used, rather than assumed weights and consumption for broad age groups. This refinement has been used in estimating the dietary exposure component in the *tau*-fluvalinate aggregate risk assessments.

7.1 Acute Aggregate Risk

The acute aggregate risk assessment considered exposures from food and water only, because there are no residential uses expected to contribute to acute exposures for this chemical. Since water exposure was incorporated directly into the DEEM-FCID and Lifeline dietary exposure analyses, the acute dietary risk estimates reported in section 6.1.2 represent the total acute aggregate risk for *tau*-fluvalinate. The acute aggregate risk estimates for the U.S. population and all subgroups are <6% of the aPAD and, therefore, below HED's level of concern.

7.2 Short-Term Aggregate Risk

There are no residential uses expected to contribute to short-term exposures for this chemical, based on its current use patterns. Therefore, a short-term aggregate assessment is not required.

7.3 Intermediate-Term Aggregate Risk

There are no residential uses expected to contribute to intermediate-term exposures for this chemical, based on its current use patterns. Therefore, an intermediate-term aggregate assessment is not required.

7.4 Long-Term Aggregate Risk

The long-term (chronic) aggregate risk assessment considered exposures from food and water only, because there are no residential uses expected to contribute to chronic exposures for this chemical. Since water exposure was incorporated directly into the DEEM-FCID and Lifeline dietary exposure analyses, the chronic dietary risk estimates reported in section 6.1.2 represent the total chronic aggregate risk for *tau*-fluvalinate. The chronic aggregate risk estimates for the U.S. population and all subgroups are < 1% of the cPAD and, therefore, below HED's level of concern.

7.5 Cancer Risk

A cancer aggregate risk assessment is not required, since there was no evidence of carcinogenicity in the toxicology studies submitted for *tau*-fluvalinate.

8.0 Cumulative Risk Characterization/Assessment

Tau-fluvalinate is a member of the pyrethroid class of pesticides. Although all pyrethroids alter nerve function by modifying the normal biochemistry and physiology of nerve membrane sodium channels, EPA is not currently following a cumulative risk approach based on a common mechanism of toxicity for the pyrethroids. Although all pyrethroids interact with sodium channels, there are multiple types of sodium channels, and it is currently unknown whether they have similar effects on all channels. In addition, we do not have a clear understanding of effects on key downstream neuronal function, e.g., nerve excitability, nor do we understand how these key events interact to produce their compound-specific patterns of neurotoxicity. There is ongoing research by both the EPA's Office of Research and Development and the pyrethroid registrants to evaluate the differential biochemical and physiological actions of pyrethroids in mammals. This research is expected to be completed by 2007. When the results of this research are available, the Agency will make a determination of common mechanism of toxicity as a basis for assessing cumulative risk. For information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism of toxicity, see EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Pathway

Reference: *Tau-Fluvalinate. Occupational and Residential Exposure Chapter of the Reregistration Eligibility Decision Document (RED);* DP Barcode: D300202; R. Travaglini; 03/24/05

9.1 Short/Intermediate/Long-Term Handler Risk

Occupational handlers may be exposed through the following routes during mixing, loading and application of *tau*-fluvalinate using aerial, groundboom, high/low pressure handwand or fogging equipment and during flagging operations for spray applications:

- *Dermal*: Although dermal exposure is expected, no toxicity endpoint for dermal exposure to *tau*-fluvalinate has been selected. Dermal exposure to *tau*-fluvalinate is expected to be largely self-limiting due to the irritation that occurs on contact with the pesticide as a result of the characteristic "pyrethroid reaction"; and HED believes the issue of dermal exposure can be best addressed by labeling to avoid contact with skin and instructions to wash the affected area immediately following contact. Currently approved end-use product labels include adequate precautionary labeling and protective equipment requirements (long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks and a NIOSH-approved respirator) to mitigate risk from dermal exposure. Therefore, a full dermal exposure assessment was not conducted. However, a screening level assessment was conducted, based on the systemic NOAEL of 100 mg/kg/day from the 21/28-day dermal toxicity study in rabbits. In this study, minimal irritation effects were seen at the 100 mg/kg/day dose with indications of the "pyrethroid reaction" only at the higher doses (500 and 2000 mg/kg/day). Margins of Exposure (MOEs) based on this endpoint exceeded 100 for all handler scenarios at the baseline level of protection (long-

sleeved shirts and long pants, but no gloves or respirator) and are, therefore, not of concern.

- *Inhalation:* Even though the volatility of this chemical is low, both short- and intermediate-term inhalation exposure may occur based on the use patterns for *tau*-fluvalinate. Long-term inhalation exposure is not anticipated. An endpoint for short- and intermediate-term inhalation exposure has been selected, based on the NOAEL of 0.5 mg/kg/day from the rat chronic feeding study. Excessive salivation and lacrimation, pawing of the bottom and sides of the cage, abnormal stance, ruffling, and transient hyperactivity followed by hypoactivity were seen at the LOAEL of 1.0 mg/kg/day in this study.

***Tau*-fluvalinate Handler Exposure Scenarios:** Pesticide handlers may be exposed to *tau*-fluvalinate in a variety of occupational settings based on its currently registered use patterns. These use patterns are summarized below, along with assumptions regarding the daily area or acreage treated by handlers:

Table 9.1a Summary of *Tau*-fluvalinate Use Patterns

Crop or Treated Area	Max. Application Rate (lbs ai/acre; lbs./gallon)	Application Method	Application Formulation	Daily Area or Acreage Treated[1]
bee hives	10.25 % a.i./strip	placement	impregnated	5 combs
carrots/brassica	0.15	aerial/ground-boom	liquid	350/80 acres
outdoor/indoor ornamentals	0.0016 lbs ai/gal.	low pressure handwand	liquid	40 gal./day
outdoor perimeter treatments (structures, buildings, etc)	0.0016 lbs ai/gal	high pressure handwand	liquid	1000 gal./day
greenhouses	0.0016 lbs ai/gal	high pressure handwand	liquid	1000 gal./day
greenhouse fog treatment	0.0016 lbs ai/gal	fogger	liquid	1000 gal./day
cut flowers/cuttings	0.0008	dip	liquid	1000 gal./day
ant mounds	0.0016 lbs ai/gal	low pressure handwand	liquid	40 gal./day

[1] The daily areas treated were defined for each handler scenario (in appropriate units) by determining the amount that can be reasonably treated in a single day (e.g., acres, # or combs or gallons per day). When possible, the assumptions for daily areas treated were taken from the Health Effects Division Science Advisory Committee on Exposure SOP #9: Standard Values for Daily Acres Treated in Agriculture, completed on July 5, 2000.

HED evaluated occupational inhalation exposures for uses on carrots/brassica, outdoor/indoor ornamentals, outdoor perimeter treatments (structures, buildings, etc), greenhouses and ant mounds. HED did not evaluate the remaining uses (beehives, greenhouse fog treatment and cut flowers/cuttings), as explained below:

- In the case of the treated strips used in beehives, an outdoor use, HED believes that exposure to the *tau*-fluvalinate impregnated in the strips will be minimal due to its low vapor pressure (10^{-7} Torr).

- In the case of cut flowers/cuttings, HED feels that the high pressure handwand greenhouse scenario would be a comparable, protective estimate of exposure to *tau*-fluvalinate through this use.

- In the case of greenhouse fog treatments, HED does not have data with which to estimate possible *tau*-fluvalinate exposures through this use. To address these potential exposures, HED is requiring the registrant to submit occupational exposure data for greenhouse exposure scenarios (OPPTS Guideline 875.2500).

HED identified 8 specific occupational handler exposure scenarios for the selected uses and evaluated each of these for short- and intermediate-term inhalation exposures to *tau*-fluvalinate:

13. Mix/load: Liquids to Support Aerial Application on carrots/brassica,
14. Application: Aerial Spray Application on carrots/brassica,
15. Application: Groundboom Spray Application on carrots/brassica,
16. Flagger: To Support Aerial Application on carrots/brassica,
17. Mix/load/application on non-agricultural outdoor areas, structures, buildings etc. (high pressure handwand),
18. Mix/load/application for greenhouses (high pressure handwand),
19. Mix/load/application for outdoor ornamentals (low pressure handwand), and
20. Mix/load/application for ant mounds (low pressure handwand).

Data and Assumptions For Handler Exposure Scenarios:

Because no chemical specific data and/or studies were submitted for this chemical, PHED V1.1 has been used to assess the exposure scenarios for *tau*-fluvalinate. PHED was designed by a Task Force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation and member companies of the Crop Life America (formerly the American Crop Protection Association). PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates).

The assumptions used in calculating handler exposures and risks are listed below:

- *Application Rates:* The application rates are the maximum allowable rates that were identified on the registered product labels for each use assessed in this document.

- *Acreage Treated*: The daily acres treated are HED standard values (Health Effects Division Science Advisory Committee on Exposure SOP #9: Standard Values for Daily Acres Treated in Agriculture, completed on July 5, 2000).

- *Unit Exposures:* The unit exposure values calculated by PHED generally range from the geometric mean to the median of the selected data set. To add consistency and quality control to the values produced from this system, the PHED Task Force has evaluated all data within the system and has developed a set of grading criteria to characterize the quality of the original study data. The assessment of data quality is based on the number of observations and the available quality control data. While data from PHED provides the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases.

- *Amount Handled:* Based on the daily acres treated.

- *Personal Protective Equipment (PPE):* HED calculated Margins of Exposure (MOEs) for the baseline, minimum PPE, PPE1, PPE2 and engineering controls for each occupational exposure scenario under the following assumptions:

  All Scenarios: All occupational handlers are wearing footwear (socks plus shoes or boots). Footwear is assumed to provide 100 percent exposure protection.

  Baseline Attire: All handlers are wearing long-sleeved shirts and long pants, but no gloves or respirator.

  Minimum PPE (PPE 1): All handlers are wearing long-sleeved shirts, long pants and gloves, but no respirator.

  PPE 2: All handlers are wearing long-sleeved shirts, long pants, gloves and a PF5 respirator (dust/mist respirator with a protection factor of 5). **Note: Current labels require this level of protection.**

  Engineering Controls: Indicates the use of an appropriate engineering control such as a closed tractor cab or closed loading system for granulars or liquids.

Occupational Handler Exposure and Risk Estimates:

Summaries of the short- and intermediate-term inhalation risks at each level of protection (baseline , PPE1, PPE2 and Engineering Controls) are presented below in Tables 9.1b through 9.1d. The short-and intermediate-term MOEs are the same because the toxicological endpoints for both exposure durations are the same for *tau*-fluvalinate.

*Note: Baseline Attire and Minimum PPE (PPE1) differ only in the use of gloves, which would not affect inhalation exposure. Therefore, the estimated inhalation exposures and risks for these levels of protection would be the same and are presented together in Table 9.1b.

Table 9.1b Short- and Intermediate-Term Inhalation Exposures and Risks Assuming Baseline PPE or PPE1

Exposure Scenario (Scenario #)	Inhalation Unit Exposure (Ug/lb ai)[1]	Crop[2]	Application Rate[3]	Daily Area Treated[4]	Inhalation Dose (mg/kg/day)[5]	Inhalation MOE[6]
Mixer/Loader						
Mixing/Loading Liquids for Aerial application (1)	1.2	Carrots & brassica crop group grown for seed	0.15 lb ai per acre	350 Acres per day	0.0009	560
Applicator						
Sprays for Aerial application (2)	Not Applicable (see engineering controls)	carrots & brassica crop group grown for seed	0.15 lb ai per acre	350 Acres per day	Not Applicable (see engineering controls)	Not Applicable (see engineering controls)
Sprays for Groundboom Application (3)	0.74	carrots & brassica crop group grown for seed	0.15 lb ai per acre	80 acres per day	0.00013	3900
Flagger						
Flagging for Sprays application (4)	0.35	Carrots & brassica crop group grown for seed	0.15 lb ai per acre	350 Acres per day	0.00026	1900
Mixer/Loader/App						
Mixing/Loading/Applying Liquids for High-Pressure HandWand application (5)	120	non-agricultural areas; non-residential/industrial outdoor areas; buildings, structures.	0.0016 lb ai per gallon	1000 Gallons per day	0.0027	180
Mixing/Loading/Applying Liquids for High-Pressure HandWand application (6)	120	greenhouses	0.0016 lb ai per gallon	1000 Gallons per day	0.0027	180
Mixing/Loading/Applying Liquids for Low Pressure Handwand application (7)	30	outdoor ornamentals	0.0016 lb ai per gallon	40 Gallons per day	0.000027	18000
Mixing/Loading/Applying Liquids for Low Pressure Handwand application (8)	30	ant mounds	0.0016 lb ai per gallon	40 Gallons per day	0.000027	18000

[1]Baseline and PPE1 inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2]Crops and use patterns are from product labeling & LUIS Report.
[3]Application rates are based on maximum values found in various sources including LUIS and various labels. In most scenarios, a range of maximum application rates is used to represent the range of rates for different crops/sites/uses. Most application rates upon which the analysis is based are

presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon).
[4]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[5] Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ ug unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[6]Inhalation MOE = 0.5 mg/kg/day (oral NOAEL) / Daily Inhalation Dose. Target Inhalation MOE is 100.

Table 9.1c Short- and Intermediate-Term Inhalation Exposures and Risks Assuming PPE2

Exposure Scenario (Scenario #)	Inhalation Unit Exposure (Ug/lb ai)[1]	Crop[2]	Application Rate[3]	Daily Area Treated[4]	Inhalation Dose (mg/kg/day)[5]	Inhalation MOE[6]
Mixer/Loader						
Mixing/Loading Liquids for Aerial application (1)	0.24	Carrots & brassica crop group grown for seed	0.15 lb ai per acre	350 Acres per day	0.00018	2800
Applicator						
Sprays for Aerial application (2)	Not Applicable (see engineering controls)	carrots & brassica crop group grown for seed	0.15 lb ai per acre	350 Acres per day	Not Applicable (see engineering controls)	Not Applicable (see engineering controls)
Sprays for Groundboom Application (3)	0.15	carrots & brassica crop group grown for seed	0.15 lb ai per acre	80 Acres per day	0.000026	19000
Flagger						
Flagging for Sprays application (4)	0.07	Carrots & brassica crop group grown for seed	0.15 lb ai per acre	350 Acres per day	0.000053	9500
Mixer/Loader/App						
Mixing/Loading/Applying Liquids for High-Pressure HandWand application (5)	24	non-agricultural areas; non-residential/industrial outdoor areas; buildings, structures.	0.0016 lb ai per gallon	1000 Gallons per day	0.00055	910
Mixing/Loading/Applying Liquids for High-Pressure HandWand application (6)	24	greenhouses	0.0016 lb ai per gallon	1000 Gallons per day	0.00055	910
Mixing/Loading/Applying Liquids for Low Pressure Handwand application (7)	6	outdoor ornamentals	0.0016 lb ai per gallon	40 Gallons per day	0.0000055	91000
Mixing/Loading/Applying Liquids for Low Pressure Handwand application (8)	6	ant mounds	0.0016 lb ai per gallon	40 Gallons per day	0.0000055	91000

[1]PPE2 inhalation unit exposures represent a dust/mist respirator with a protection factor of 5. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2]Crops and use patterns are from product labeling & LUIS Report.

[3]Application rates are based on maximum values found in various sources including LUIS and various labels. In most scenarios, a range of maximum application rates is used to represent the range of rates for different crops/sites/uses. Most application rates upon which the analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon).
[4]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[5] Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ ug unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[6]Inhalation MOE = 0.5 mg/kg/day (oral NOAEL) / Daily Inhalation Dose. Target Inhalation MOE is 100.

Table 9.1d Short- and Intermediate-Term Inhalation Exposures and Risks Assuming Use of Engineering Controls

Exposure Scenario (Scenario #)	Inhalation Unit Exposure (Ug/lb ai)[1]	Crop[2]	Application Rate[3]	Daily Area Treated[4]	Inhalation Dose (mg/kg/day)[5]	Inhalation MOE[6]
Mixer/Loader						
Mixing/Loading Liquids for Aerial application (1)	0.083	carrots & brassica crop group grown for seed	0.15 lb ai per acre	350 Acres per day	0.000062	8000
Applicator						
Sprays for Aerial application (2)	0.068	carrots & brassica crop group grown for seed	0.15 lb ai per acre	350 Acres per day	0.000051	9800
Sprays for Groundboom Application (3)	0.43	carrots & brassica crop group grown for seed	0.15 lb ai per acre	80 Acres per day	0.0000074	68000
Flagger						
Flagging for Sprays application (4)	0.07	carrots & brassica crop group grown for seed	0.15 lb ai per acre	350 Acres per day	0.0000053	95000
Mixer/Loader/App						
Mixing/Loading/Applying Liquids for High-Pressure HandWand (5)	Not Applicable (NA)	non-agricultural areas; non-residential/industrial outdoor areas; buildings, structures	0.0016 lb ai per gallon	1000 Gallons per day	Data not available	Data not available
Mixing/Loading/Applying Liquids for High-Pressure HandWand application (6)	NA	greenhouses	0.0016 lb ai per gallon	1000 Gallons per day	Data not available	Data not available
Mixing/Loading/Applying Liquids for High-Pressure HandWand application (7)	NA	outdoor ornamentals	0.0016 lb ai per gallon	40 Gallons per day	Data not available	Data not available
Mixing/Loading/Applying Liquids for Low Pressure Handwand application (8)	NA	ant mounds	0.0016 lb ai per gallon	40 Gallons per day	Data not available	Data not available

[1]Engineering controls inhalation unit exposures represent no respirator. Values are reported in the PHED Surrogate Exposure Guide dated August 1998 or are from data submitted by the Outdoor Residential Exposure Task Force dated May 2000.
[2]Crops and use patterns are from product labeling & LUIS Report.

[3]Application rates are based on maximum values found in various sources including LUIS and various labels. In most scenarios, a range of maximum application rates is used to represent the range of rates for different crops/sites/uses. Most application rates upon which the analysis is based are presented as lb ai/A. In some cases, the application rate is based on applying a solution at concentrations specified by the label (i.e., presented as lb ai/gallon).
[4]Amount treated is based on the area or gallons that can be reasonably applied in a single day for each exposure scenario of concern based on the application method and formulation/packaging type. (Standard EPA/OPP/HED values).
[5] Inhalation dose (mg/kg/day) = [unit exposure (ug/lb ai) * 0.001 mg/ g unit conversion * Inhalation absorption (100%) * Application rate (lb ai/acre or lb ai/gallon) * Daily area treated (acres or gallons)] / Body weight (70 kg).
[6]Inhalation MOE = 0.5 mg/kg/day (oral NOAEL) / Daily Inhalation Dose. Target Inhalation MOE is 100.

HED believes that the risk values presented in this occupational assessment represent the best quality results that could be produced given the exposure, use and toxicology data that are available. HED also believes that the risks represent reasonable worse-case estimates of handler exposure, because maximum application rates are coupled with medium- to high-end estimates of area treated daily to define risk estimates that likely fall in the upper percentiles of the actual exposure distributions. Using these worst-case assumptions, estimated occupational handler MOEs for all exposure scenarios at all protection levels are greater than 100 and are, therefore, not of concern.

Estimated inhalation exposures at the baseline and PPE1 levels of protection are particularly conservative, since they assume respirators are not being used by handlers. In fact, current labels require handlers to wear NIOSH approved respirators (in addition to long-sleeved shirt, long pants, chemical-resistant gloves, shoes and socks) for both indoor and outdoor applications.

9.2 Short/Intermediate/Long-Term Postapplication Risk

Post-application dermal exposure to *tau*-fluvalinate is expected to be largely self-limiting due to the irritation that occurs on contact with the pesticide as a result of the characteristic "pyrethroid reaction" (see sec. 9.1). Therefore, post-application dermal exposure and risk were not assessed.

With the exception of the greenhouse uses, post-application inhalation exposure to *tau*-fluvalinate is expected to be minimal. Potential post-application inhalation exposure in greenhouses is likely mitigated by the ventilation requirements of the Worker Protection Standard (WPS). For these reasons, a post-application inhalation exposure assessment was not deemed necessary for *tau*-fluvalinate. However, to confirm that the established re-entry interval (REI) of 12 hours is adequate, HED is requiring the registrant to conduct an inhalation post-application exposure study (OPPTS Guideline 875.2500). The study should be conducted in exact accordance with the use directions on the product label, including ventilation criteria. The study should be designed in such a way that it will be of sufficient duration for the pesticidal residue levels to dissipate to zero (0) or to the level of detection in two separate, distinct parts of the treated area. The registrant should submit a study protocol developed under the aforementioned guidelines for Agency review prior to conducting the study.

10.0 Data Needs and Label Requirements

10.1 Toxicology

- 90-Day Inhalation Study (OPPTS Guideline 870.3465) - This study requirement is reserved pending outcome of the airborne residue dissipation study for greenhouses (see below).

10.2 Residue Chemistry - None

10.3 Occupational and Residential Exposure

- Post-application occupational exposure data for greenhouse exposure scenarios (OPPTS Guideline 875.2500)

References:

Tau-Fluvalinate. RED - Reregistration Eligibility Decision Document. Residue Chemistry Considerations. Case No. 2295; D300204; J. Morales; 02/22/05

Tau-Fluvalinate RED - Reregistration Eligibility Decision. Product Chemistry Considerations. Case No. 2295; D311824; J. Morales; 02/22/05

Tau-fluvalinate Acute and Chronic Dietary Exposure Assessments for the Reregistration Eligibility Decision; D300203; S. Stanton; 03/11/05

Tier II Estimated Environmental Concentration for the Use of Tau-Fluvalinate for Apiary Uses, Carrots for Seed (24-C SLNs), Building Perimeters, Nurseries, Ornamentals, Indoor Landscapes and Honey for the Human Health Drinking Water Risk Assessment; D304067; Mark Corbin; 02/03/2005

Revised, Corrected Tau-Fluvalinate. Occupational and Residential Exposure Chapter of the Reregistration Eligibility Decision Document (RED); D319595; R. Travaglini; 06/26/05

Review of Fluvalinate Incident Reports, D300199, Jerome Blondell, 03/14/2005

Appendices

1.0 TOXICOLOGY DATA REQUIREMENTS

The toxicology data requirements (40 CFR 158.340) for *tau-fluvalinate* are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	no	no
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes (1)
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	–
870.3465 90-Day Inhalation	reserved (2)	--
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotox. Screening Battery (rat)	yes	Partial (3)
870.6200b 90 Day Neuro. Screening Battery (rat)	yes	yes
870.6300 Develop. Neuro	no	--
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	--
Special Studies for Ocular Effects		
Acute Oral (rat)	no	–
Subchronic Oral (rat)	no	–
Six-month Oral (dog)	no	--

(1) - Satisfied by the chronic dog study. (2) - Reserved pending outcome of the greenhouse fogger/mist study (i.e., airborne residue dissipation study). (3) - A non-guideline study is available for partial fulfillment of this requirement; an additional study is not required.

2.0 NON-CRITICAL TOXICOLOGY STUDIES

1. **(82-1a)** 13-Week Feeding Study in Rats. Zoecon Corporation. 1981. MRID No. 00094109, 92069032. HED Doc. No. 002256.

In a 90-day subchronic feeding study in rats (1981, MRID 00094109), groups of 20 male and 20 female 21 day old Charles River COBS CD rats were administered 0.3, 1.0, 3.0, 30.0 or 50.0 mg/kg b.w./day *tau*-fluvalinate (88.2-93.1.%, Lot #455-95, 468-27, Run 23) in the diet which was adjusted weekly for concentration.

Salivation and abnormal gait were observed in the 50.0 mg/kg/day group. Skin lesions were observed in males at 3.0 mg/kg/day and higher dose levels. Skin lesions were observed in females beginning at 30.0 mg/kg/day. Body weights were 15.8 and 25.3% less than controls in males in the 30.0 and 50.0 mg/kg/day groups, respectively. Body weights were 6.3 and 11.9% less than controls in females in the 30.0 and 50.0 mg/kg/day groups, respectively. The hematocyte, hemoglobin levels and erythrocyte counts were decreased at 30.0 and 50.0 mg/kg/day. The BUN was increased somewhat in the 30.0 and 50.0 mg/kg/day groups. Albumin and total bilirubin were decreased at 30.0 and 50.0 mg/kg/day. On histological examination of the tissues, there was significant damage to the skin characterized by focal ulceration and inflammation extending to the muscularis. **The Systemic LOEL was 3.0 mg/kg/day based on the occurrence of skin lesions (due to systemic neurotoxicity). The Systemic NOEL was 1.0 mg/kg/day.**

The study is **acceptable** and **satisfies** the requirement for a guideline series 82-1(a) 90-day subchronic feeding study in rats.

2. **(82-1a)** 13-Week Feeding Study in Mice. Zoecon Corporation. 1981. MRID No. 00094113. HED Doc. No. 004705.

In a 13-week subchronic feeding study in mice (1981, MRID 00094113), groups of 10 male and 10 female 41-day old CD-1 mice were administered 0, 1, 3, 30, 50 or 100 mg/kg b.w./day of *tau*-fluvalinate (89.9-93.1%, Anal 10801-91, Anal 0281037, Run 23R) in the diet. Compound-related effects noted included infected skin lesions, related effects, and their sequelae (increased WBC counts, enlarged lymph nodes, infected eyes, and splenic changes in all dosage groups). Male body weights were significantly decreased in groups receiving 30 mg/kg/day or more. Female HCT, HGB, RBC and reticulocytes were significantly decreased in the 100 mg/kg/day group. The ovaries in the 100 mg/kg/day group were significantly decreased and had ovarian cysts. Histological examinations of the ovaries were not performed in the other groups. **The NOEL and LOEL were not determined.**

The study is **supplementary** and **does not satisfy** the requirement for a guideline series 82-1(a) 90-day subchronic feeding study in rodents.

3. **(82-1a)** 14-Day Range Finding Study in Mice. Zoecon Corporation. 1981. MRID No. 00094105. HED Doc No. 002256. (also racemic mixture)

In a 14-day rangefinding toxicity study in mice (1981, MRID 00094105), groups of 5 male and 5 female CD-1 mice were administered 0, 0.2, 0.7, 2.0, 7.0, 20.0, 70.0. 200.0 or 700.0 (doses approximately 0, 0.03, 0.10, 0.30, 1.00, 3.00, 10.00, 30.00 or 100.00 mg/kg/day) of *tau*-fluvalinate (89.9%, #1080-91) in the diet. Another group of 5 male and 5 female mice per group were administered 0, 20.0, 70.0, 200.0 or 700.0 ppm (doses approximately 0, 3.0, 10.0, 30.0 or 100.0 mg/kg/day) of fluvalinate (racemic) (93.8%, Anal 0979-069, Run #7) in the diet.

Tau-fluvalinate - Hair loss, local crusting and skin ulceration were note at 10 (F) and 30 mg/kg/day (M and F) and above. Excessive salivation, ataxia, reduced motor activity, skin paleness and death occurred at 100 mg/kg/day. Body weight was reduced at 100 mg/kg/day.

Fluvalinate (racemic) - Hair loss, local crusting and skin ulceration were observed in females at 10 mg/kg/day and in males at 100 mg/kg/day.

Tau-fluvalinate is more toxic on a mg/kg basis than the racemic technical. Females appear to be more sensitive than males. Quantitative differences in observations can be attributed to compound potency. There do not appear to be any qualitative differences between the two mixtures.

The study is **supplementary** (by design - rangefinding) and **does not satisfy** the requirement for a guideline series 82-1(a) 90-day subchronic feeding study in mice.

4. **(82-2)** 21-Day Dermal Toxicity Study in Rabbits. Zoecon Corporation. 1981. MRID No. 00094115. HED Doc. No. 002256

In a 3-week dermal toxicity study (1981, MRID 00094115), groups of 10 male and 10 female young adult New Zealand White rabbits were administered 0, 100, 500 or 2000 mg/kg/day of *tau*-fluvalinate (93.1%, Lot 23R, #0281037, ZTS-0029). The skin on the backs of one-half of the animals was abraded.

A well defined erythema was observed in all treated animals. A barely perceptible edema was noted in all treated males and females. Skin sores were noted at dose levels of 100 mg/kg/day and above. Males in the 2000 mg/kg/day group had decreased body weights. Food consumption was decreased in males in the 500 and 2000 mg/kg/day groups and in females in the 2000 mg/kg/day group. Histological lesions including acanthosis, hyperkeratosis, acute and chronic dermal inflammation and epidermal ulceration were observed in all treated animals. **The NOEL is less than 100 mg/kg/day. The LOEL is 100 mg/kg/day based on skin irritation (possibly a systemic neurologic effect as well). The systemic NOEL is 100 mg/kg/day and the LOEL is 500 mg/kg/day based on decreased food intake**.

The study is **acceptable** and **satisfies** the requirement for a guideline series 82-2 21-day dermal study in rabbits.

5. **(83-3)** Chronic dosing study in dogs. Covance Laboratories Inc., 9200 Leesburg Pike, Vienna, VA 22182-1699. Covance 6398-117, December 17, 1998. MRID 44743201. Unpublished.

In a chronic toxicity study (1998, MRID 44743201), *tau*-fluvalinate (88.4% purity) was administered to 4 beagle dogs/sex/dose in capsules at dose levels of 0, 3, 12, and 50 mg/kg/day for 52 weeks.

There was no effect on mortality in either sex of dogs. Clinical signs with a possible relationship to test substance exposure included salivation in 3/4 males and females and a marked increase in the frequency of emesis (observed in all dogs), mainly postdose, in the high dose male and female groups, signs consistent with CNS toxicity. The body weights of the high-dose males were significantly reduced reaching 85% of controls at week 40; those of the mid and high-dose females were consistently less than controls with effects biologically although not statistically significant, 89 and 93% at 52 weeks, respectively. The overall body weight gains of the high-dose males (40% of controls, $p<0.05$) and mid- and high-dose females (47 and 63%, N.S., respectively) were also reduced by exposure to *Tau*-Fluvalinate for 52 weeks. There were no compound-related effects on food consumption, hematology, clinical chemistry, or gross and histologic pathology. Liver weights, absolute and relative to body and brain weight, were significantly increased by exposure to the test compound in the high dose male (120, 138, and 121%, respectively, all $p<0.05$)and females (124, 129, and 127%, respectively, $p<0.05$ for relative body weight) and possibly in the mid-dose female group (110,110, and 104%, respectively, all N.S.). **The *Tau*-fluvalinate LOAEL for female dogs is 12 mg/kg/day based on decreased body weight and body weight gain and increased liver weight. The NOAEL for female dogs is 3 mg/kg/day. The *Tau*-fluvalinate LOAEL for male dogs is 50 mg/kg/day, based on decreased body weight and body weight gain, increased liver weight, and increased emesis and salivation. The NOAEL for males is 12 mg/kg/day.**

This chronic study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic oral study [OPPTS 870l4100, OECD 452] in the dog.

6. **(83-5)** 2-Year Dosing/Carcinogenicity Study in Mice. Zoecon Corporation. 1984. MRID No. 00094889, 00128336, 00144628, 92069036. HED Doc. No. 004705.

In a 24-month combined chronic/carcinogenicity study (1984, MRID 00094889, 00128336, 00144628, 92069036), groups of 60 49-day old Charles River CD-1 mice (except for a second control group containing 50 animals/sex/dose) were administered 0, 2, 10 or 20 mg/kg b.w./day of *tau*-fluvalinate (92.1%. Run 23, Anal #0281028) in the diet which was frequently adjusted to achieve the appropriate concentrations. Ten animals/sex/dose were sacrificed from the 2 control groups and the 10 and 20 mg/kg/day groups at week 52.

Skin lesions were noted in the 10 and 20 mg/kg/day groups. Chronic nephritis was increased in males in the 20 mg/kg/day group. There was no indication that *tau*-fluvalinate was carcinogenic in mice.

The NOEL is 2 mg/kg/day. The LOEL is 10 mg/kg/day based on dermal lesions (due to systemic neurotoxicity). *Tau*-fluvalinate is not carcinogenic in mice.

The study is **acceptable** and **satisfies** the requirement for a guideline series 83-2 carcinogenic study in mice. The study is **supplementary** and **does not satisfy** the requirement for a guideline series 83-1 chronic feeding study in mice.

7. **(85-1)**. Metabolism study in mice. Zoecon Corporation, Palo Alto, CA; No. 3760-2-02-84; dated February 21, 1984. Accession No. 072918. Unpublished.

In a metabolism study (1984, MRID No. 072918) [trifluoromethy-^{14}C-] *tau*-fluvalinate and non-labeled *tau*-fluvalinate, were administered in feed to male and female mice (ICR strain, Simonsens Laboratories, Gilroy, CA). Treatment groups consisted of 3 rats/sex given at doses of approximately 26 mg/kg/day for six days.

Tau-fluvalinate was rapidly absorbed, metabolized, distributed and excreted following oral administration and most material was recovered in the urine and feces in both male and female mice pre-fed unlabelled *tau*-fluvalinate at approximately 26 mg/kg/day. Approximately 59 percent and 30 percent of the applied dose was excreted in the feces and urine, respectively, during the 4-day experiment, with most of the radioactivity eliminated during the first day. The major products identified in the urine included 2-[2-chloro-4-(trifluoromethyl)anilino]-3-methyl-butanoic acid (anilino acid) and the taurine conjugate of the anilino acid, which accounted for 8.2-12.0 and 1.7-3.2 percent of day 1 radioactivity in urine, respectively. In addition, 7 urinary metabolites were found but not identified. Parent *tau*-fluvalinate represented 15-23% of the radioactivity in the day 1 fecal extracts, and the anilino acid represented approximately 11 percent of fecal radioactivity. In addition, five fecal metabolites were found but not identified. Little radioactivity was found in any of the tissues or carcasses and no major sex differences were observed. This metabolism study in the mice is classified **acceptable/non-guideline and does not satisfy** the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in mice. The limiting factor is the study used only 3 mice/sex whereas the Guidelines require 4 mice/sex.

8. **(85-1).** Metabolism study in rats. Sandoz, Study No. 480605-13, May 20, 1992.

In this study (1992, MRID No.: 42322301), a single oral dose of 14C-fluvalinate at 1 mg/kg (Group A), 200 mg/kg (Group C), or unlabelled *tau*-fluvalinate at 1 mg/kg/day for 14 days followed by a single dose of 14C-fluvalinate at 1 mg/kg (Group B) were administered to CD rats. The rats were sacrificed 96 hours later following. For groups A and B, approximately 75% of the dose was detected in the excreta by 24 hours after dosing. For the high dose rats (Group C), however, elimination of the radioactivity was only 45% of the dose at 24 hours. By 96 hours after administration, approximately 90% of the dose in all groups was eliminated. Over the 4-day test period, fecal excretion was the dominant elimination pathway accounting for approximately 60 to 80% of the administered *tau*-fluvalinate dose. The relative amounts of parent compound and the major fecal metabolite, anilino acid varied with dose. For groups A and B, the parent compound and anilino acid represented about 55 and 10% respectively, of the fecal radioactivity. For the high dose group (200 mg/kg) the parent compound and anilino acid represented about 85% and 2% respectively, of the fecal radioactivity. Additional fecal metabolites, although less significant were haloaniline, 3-phenoxybenzoic acid, and 3-(4"-hydroxyphenoxy)benzoic acid. With respect to urinary excretion, the low dose groups (A and B), followed first order kinetics and urinary radioactivity accounted for 30-40% of the administered dose. The elimination half-

life was estimated as 12 hours for male rats and 15 hours for females rats. For the high dose group, the urinary radio activity represented less than 20% of the administered dose, suggesting saturation of absorption or elimination processes. Urinary metabolites included haloaniline, 3-phenoxybenzoic acid A, lactone of anilino A, 3-phenoxybenzyl alcohol, diacid and 3-(4"-hydroxyphenoxy)benzoic acid A. The major urinary metabolites were 3-(4"-hydroxyphenoxy)benzoic acid A, and 3-phenoxybenzoic acid A. Residues in various tissues and the carcass at 96 hours after dosing, accounted for only 2-8% of the administered dose. Although sex related differences in the metabolism of *tau*-fluvalinate were detected, none were considered significant. Pretreatment with the chemical (Group B) did not significantly affect the metabolism and disposition of *tau*-fluvalinate.

This study is classified as **Acceptable/Guideline** and satisfies the requirement for a series 85-1 general metabolism study in rats.

3.0 Tolerance Reassessment Summary; Codex/International Harmonization

Tolerance Reassessment Summary for *Tau*-Fluvalinate.				
Commodity	Current Tolerance (ppm)	Range of Residues (ppm)	Tolerance Reassessment (ppm)	Comment/*[Correct Commodity Definition]*
Tolerance Listed Under 40 CFR §180.427 (a):				
Honey	0.05	<0.01-0.015	0.02	

No Codex MRLs have been established for *tau*-fluvalinate; therefore, issues of compatibility between Codex MRLs and U.S. tolerances do not exist. A Mexican MRL of 0.1 mg/kg has been established for cottonseed. No Canadian MRLs have been established for fluvalinate or *tau*-fluvalinate. We note that *tau*-fluvalinate is registered for use in Canada in honey bee chambers; this use presumably falls under the PMRA General MRL of 0.1 mg/kg. [Regulation B.15.002(1) of the Canadian Food and Drugs Regulations (FDR) establishes 0.1 ppm as the "General Maximum Residue Limit." This regulation states that a food is adulterated if it contains residues of a pesticide at a level greater than 0.1 ppm unless a specific MRL has been established in Table II, Division 15 of the FDR.]

Confidential Appendix

This appendix has been removed to a separate file so that it can be stored on the RAD database.