

PC 109303
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: PP# 4F4329: Conversion of Fenvalerate Tolerances to Esfenvalerate Tolerances; PP#9E6061: Esfenvalerate in/on Brussel Sprouts. PP#7F4859: Esfenvalerate in/on Pistachios. PP#0F6110: Esfenvalerate Post-Harvest uses in/on Almonds, Cocoa Beans, Peanut Kernels and Walnuts. PP#9E5075: Esfenvalerate in/on Canola. PP#0F3852: Esfenvalerate in/on Head Lettuce. PP#0E3912: Esfenvalerate in/on Cardoon. PP#9E3810: Esfenvalerate in/on Chinese Cabbage (bok choy). PP#9E3813: Esfenvalerate in/on Sweet Potato. Reassessed Tolerances for Esfenvalerate under 40 CFR §180.533. **Health Effects Division (HED) Risk Assessment.** PC Code 109303. D274838, D238338, D257618, D259703.

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The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from:

1) the conversion of Section 3 tolerances for fenvalerate established under 40 CFR §180.379 to esfenvalerate established under 40 CFR §180.533; 2) proposed uses of esfenvalerate in/on the following crops: brussel sprouts; pistachios; post-harvest uses in/on almonds, cocoa beans, peanut kernels and walnuts; canola; head lettuce; cardoon; chinese cabbage (bok choy); and sweet potato; and 3) existing tolerances established for esfenvalerate under 40 CFR §180.533 that have been reassessed.

A summary of the findings and an assessment of human risk resulting from the converted uses, proposed uses, and existing uses of esfenvalerate are provided in this document. The risk assessment, the residue chemistry data review, and the dietary risk assessment were provided by José Morales (RRB3), the hazard characterization by John Doherty (RRB3), the occupational/residential exposure assessment by Barry O’Keefe (RAB3), and the drinking water assessment by Ibrahim Abdel-Saheb of the Environmental Fate and Effects Division (EFED).

Recommendation for Tolerances and Registration

Provided that the petitioner submits revised Sections B and F, adequate residue chemistry and toxicological data have been submitted to support the establishment of permanent tolerances for residues of esfenvalerate [(S)-cyano(3-phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl) benzeneacetate] and its non-racemic isomer [(R)-cyano-(3-phenoxyphenyl)methyl-(R)-4-chloro- α -(1-methylethyl) benzeneacetate] and its diastereomers [(S)-cyano(3-phenoxyphenyl)methyl-(R)-4-chloro- α -(1-methylethyl) benzeneacetate and (R)-cyano(3-phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl) benzeneacetate] in/on the following agricultural raw commodities (RACS):

Brussels Sprouts	0.20 ppm
Pistachios	0.10 ppm
Almonds (post-harvest)	50 ppm
Cocoa Beans (post-harvest)	1.0 ppm
Peanut Kernels (post-harvest)	0.20 ppm
Walnuts (post-harvest)	15 ppm
Head Lettuce	5.0 ppm
Cardoon	1.0 ppm
Bok Choy	1.0 ppm
Sweet Potato	0.05 ppm

Note: HED notes that at this juncture it is not possible to make a safety finding under FQPA to support the establishment of new tolerances.

Please find attached the following supporting documents and disciplinary chapters:

Esfenvalerate/Fenvalerate - Report of the Hazard Identification Assessment Review Committee (TXR No. 0051556, 2/10/03, P. Hurley).

Esfenvalerate/Fenvalerate - Toxicology Chapter for the HED Risk Assessment.

Esfenvalerate/Fenvalerate - HED Product Chemistry Chapter.

Esfenvalerate/Fenvalerate - HED Residue Chemistry Chapter of the RED; Summary of Analytical Chemistry and Residue Data.

Esfenvalerate/Fenvalerate - Acute (Probabilistic) and Chronic Dietary Exposure Assessments.

Esfenvalerate/Fenvalerate - The Occupational and Residential Exposure Assessments.

Drinking Water Assessment for esfenvalerate on christmans trees in Oregon and on cotton in Mississippi (D280680, 2/04/02, I. Abdel-Saheb).

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1.0 EXECUTIVE SUMMARY

Fenvalerate [cyano(3-phenoxyphenyl)methyl-4-chloro- α -(1-methylethyl)benzeneacetate] and esfenvalerate [(S)-cyano(3-phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl)benzeneacetate] are broad spectrum acaricides/insecticides belonging to the pyrethroid class of pesticides.

Fenvalerate is a racemic mixture of four stereoisomers (the S,S; R,S; S,R; and R,R isomers). End-use products containing fenvalerate as the active ingredient were first registered by the basic registrant, E.I. du Pont de Nemours and Company, for use on agricultural crops under the trade name Pydrin®. The basic registrant, DuPont, has cancelled all fenvalerate (Pydrin®) uses on food/feed crops and has replaced its former uses on agricultural crops with esfenvalerate (Asana®). Active uses of fenvalerate in food-handling establishments were supported by other registrants. However, the basic registrants Sumitomo Chemical Company and Bayer Environmental Science have requested voluntary cancellation of the fenvalerate technical grade (Sumitomo communication dated 3/27/03 and Bayer communication dated 4/1/03). There are no registered uses of fenvalerate in the U.S. Therefore, this risk assessment will not deal with any fenvalerate registration or reregistration issues. Because fenvalerate is currently registered for use on some import crops, and because fenvalerate and esfenvalerate are considered toxicologically equivalent, these import crops have been considered in this risk assessment and included in the dietary exposure assessment for esfenvalerate. If the import uses are not supported, the dietary risk assessment can be refined by removing exposures attributed to the uses of fenvalerate on import crops.

Esfenvalerate is the S,S-isomer enriched version of fenvalerate which is sold under the trade name Asana®. DuPont began marketing Asana® in 1992 after the cancellation of Pydrin® uses on agricultural crops. Presently, esfenvalerate is registered to DuPont for use on several food and feed crops. McLaughlin Gormley King Company has also obtained registration for use of esfenvalerate in food-handling establishments. There are registered residential uses for esfenvalerate. When applied on agricultural crops, the typical use rate for esfenvalerate (Asana®) is four times lower than that for fenvalerate (Pydrin®) because the concentration of the S,S-isomer (the most insecticidally active isomer) is about four times higher in Asana® than in Pydrin®. Tolerances for esfenvalerate are listed under 40 CFR§180.533. The registrant has proposed conversion of the existing fenvalerate tolerances to esfenvalerate.

Esfenvalerate is an insecticide used on agricultural crops, residential and commercial lawns, residential gardens, and in and around industrial, commercial, and residential premises. When applied to agricultural crops, the typical use rate for esfenvalerate is four times lower than for fenvalerate because the concentration of the S,S-isomer is higher in esfenvalerate. Applications are made throughout the season with PHI's ranging from 3 to 28 days. Esfenvalerate formulations include liquid concentrates, wettable powders (homeowner-use only) and ready-to-use aerosols and trigger sprayers. Esfenvalerate is not registered for use on agricultural animals. Esfenvalerate can be used by homeowners on lawns, vegetable gardens, and in and around residential premises. Applications to agricultural crops can be made with aircraft, chemigation,

groundboom, airblast, and mechanical aerosol/fogger equipment. Applications at industrial, commercial, and residential sites can be made using handheld equipment such as low-pressure handwand sprayers, backpack sprayers, hose-end sprayers, handgun sprayers, paintbrushes, termiticide injector, in addition to ready-to-use aerosol cans, foggers and pump-trigger sprayers.

Toxicology

For the purposes of toxicological assessment, fenvalerate and esfenvalerate are considered equivalent toxicologically, and the databases for both chemicals were considered during the endpoint selection process for risk assessment. This risk assessment incorporates the toxicological endpoints of concern as presented in the Report of the Hazard Identification Assessment Review Committee (HIARC), dated February 10, 2003, and in the 2nd Report of the Hazard Identification Assessment Review Committee (HIARC), dated October 22, 2003.

Overall, the studies supporting the toxicity data base for esfenvalerate are considered adequate and there is confidence in the hazard and dose response assessments. Esfenvalerate is a pyrethroid insecticide and is an isomeric enriched technical grade of fenvalerate. There are more recent toxicity studies with esfenvalerate and there are also earlier studies with fenvalerate which have been used to characterize the toxicity of esfenvalerate. Esfenvalerate and fenvalerate belong to the Type II subclass of pyrethroids that usually have a cyano group attached to an *alpha* carbon. The type II pyrethroids produce a characteristic toxicity response in both insects and mammals that is distinct from the type I pyrethroids. The Type I pyrethroids produce responses more closely resembling the fine tremors seen with DDT. The type II pyrethroids produce responses that include choreoathetosis writhing in mammals. It is generally recognized that the sodium conductance channel is the site of action of both type I and type II pyrethroids although the kinetics of the interaction between the type I and type II pyrethroids and the channel are different to produce the differences in responses.

Esfenvalerate is considered moderately toxic via the oral route (Toxicity Category II) but is less toxic by the dermal route (Toxicity Category III). Esfenvalerate is mildly irritating but not a sensitizer. No acute inhalation study with esfenvalerate was available. In the subchronic toxicity study with esfenvalerate in rats decreased body weight and signs of neurotoxicity (jerky leg movements) were evident. The indications of body weight decrease and signs of neurotoxicity (decreased motor activity and hindlimb grip strength) were also apparent in the two subchronic neurotoxicity studies with esfenvalerate. In a chronic feeding study, dogs demonstrated signs of neurotoxicity as indicated by emesis, head shaking, biting extremities as well as the systemic effects including normocytic anemia, increased serum cholesterol, and possible hepatic microgranulomatosis. Mice also show weight loss and anemia, reactive responses in the lymphatic tissue in multiple locations and hepatic microgranuloma and giant cell formation in the liver and spleen.

Esfenvalerate and other type II pyrethroids produce a dermal "pyrethroid reaction" that leads to a specific type of dermal sensation especially in mice possibly resulting from contact with feed. This sensation results in scratching and skin lesions that can become infected and confounding the results of subchronic and chronic studies.

Pyrethroids affect the nervous system and following acute oral administration tremors result. Abnormal gait also results following dermal application in rats. Following feeding administration, neurotoxicity may result at higher doses where other systemic signs such as body weight effects also are seen.

Early in the development of pyrethroids there were concerns that higher doses resulted in a specific degeneration of the peripheral nervous system and extensive studies were conducted to attempt to determine the potential for fenvalerate or esfenvalerate to cause this type of neuropathy. The recently conducted acute and two independent subchronic studies with rats did not indicate neuropathy at the doses tested. The overall current conclusion is that NOAELs have been established for induction of neuropathy (i.e. there was no neuropathy in the recent guideline subchronic neurotoxicity studies and only following higher near lethal doses will a sparse peripheral neuropathy possibly result.)

The rat and rabbit developmental toxicity studies did not indicate that there was developmental toxicity (either quantitative or qualitative) at dose levels at or below maternal toxicity. There was no increased susceptibility in the rat or rabbit developmental toxicity studies at the highest doses tested.

The rat multi-generation reproduction study did not indicate any adverse effects on reproductive performance and parental toxicity consisted of dermal reactions and body weight effects and at higher doses there was abnormal gait in the P1 generation. At the highest dose, the F1 generation could not tolerate the same dose as the P generation and demonstrated in addition to abnormal gait, tremors, ataxia, hyperactivity, vocalization, hypersensitivity and eventual death even after lowering the dose.

Esfenvalerate is a pyrethroid insecticide that results in causing tremors following acute oral administration. The evidence of tremors in the acute neurotoxicity study demonstrated the lowest NOAEL (1.75 mg/kg) and LOAEL (1.95 mg/kg) of the available studies regardless of duration and was selected as the RfD to assess risk from acute and chronic dietary exposures as well as from oral incidental and inhalation short-, intermediate- and chronic exposure (no subchronic inhalation study was available). This selection is justified because the lowest combination of NOAEL and LOAEL will protect against toxicity occurring at higher doses and for longer exposures. In the case of esfenvalerate, long term daily exposures are considered as multiple daily exposures with each potentially causing tremors on a daily basis. Current HIARC policy is to use the same endpoint for all oral exposures when the acute NOAEL is lower than the subchronic or chronic NOAEL regardless of gavage or dietary administration unless there is a reasonable basis not to. In the case of esfenvalerate, the potential to cause tremors due to the

interaction of esfenvalerate with the nervous system is considered by HIARC as justification for using the acute neurotoxicity NOAEL for the basis of the chronic RfD. A 100 percent inhalation absorption factor was used to convert all inhalation exposures to an oral equivalent inhalation dose. This endpoint is appropriate for all risk assessments, i.e., short-, intermediate- and long-term exposures, because no cumulative toxicity was seen following repeated doses of esfenvalerate.

The short-, intermediate- and long-term (non-cancer) dermal risk assessments for esfenvalerate are based on a 21-day dermal toxicity study in rats (MRID 45275401). The findings from this dermal toxicity study potentiated a revisit of this active ingredient to the HIARC. Previously, HED elected to use the oral endpoint from the acute neurotoxicity study mentioned above (i.e. 1.75 mg/kg/day). A dermal absorption factor of 25 percent was previously selected, based on dermal absorption data available for structurally-related pyrethroids (HIARC document, February 10, 2003). However, since then this dermal toxicity study has been reviewed. The HIARC met on 8/19/03 to re-evaluate the dermal endpoints, dermal absorption and the database uncertainty factor (UF db) for esfenvalerate. Prior to determining the dermal endpoints, the HIARC discussed the 21-day dermal study and raised the NOAEL/LOAEL in the DER to 25/125 mg/kg/day. With the 21-day dermal study, a revised dermal absorption factor of 2% was then estimated by dividing the LOAEL of 2.5 mg/kg/day from the developmental rat study by the LOAEL of 125 mg/kg/day from the 21-day dermal study. Similar effects had been observed in both studies. This new dermal absorption factor supersedes the previously estimated factor of 25%. The HIARC then determined that all dermal risk assessments (short-, intermediate-, and long-term) should be based on the 21-day dermal rat study with a NOAEL of 25 mg/kg/day, supported by the following rationale: it is a route-specific study; since the effects are not cumulative, it is appropriate for all durations; and, based on the new dermal absorption factor, the HIARC further noted that the oral endpoint from the acute neurotoxicity study of 1.75 mg/kg/day modified by the dermal absorption factor of 2% results in an equivalent dermal dose of 87.5 mg/kg/day which is less conservative than use of the NOAEL of 25 mg/kg/day from the route-specific dermal study for assessing risks from dermal exposures.

Since the toxicological endpoints of concern are based on neurological toxic effects, dermal and inhalation exposures and risks must be aggregated for occupational scenarios and dermal, inhalation, and incidental oral exposures and risks must be aggregated for non-occupational scenarios.

There is no mutagenicity concern for esfenvalerate based on the weight of evidence of the studies submitted. There was no indication of a carcinogenic effect in rats and mice. Fenvalerate/esfenvalerate are currently classified as a Group "E" carcinogen (no evidence of carcinogenicity).

FQPA Considerations

Esfenvalerate did not result in developmental toxicity in either rats or rabbits or in reproductive effects in the multi-generation reproduction study. There was no indication of increased offspring susceptibility in these studies. Therefore, the HIARC determined that the hazard based special FQPA Safety Factor can be removed (reduced to 1X) because there is no evidence of quantitative or qualitative susceptibility following *in utero* exposure to rats or rabbits or pre/postnatal exposure to rats and there are no residual uncertainties for pre/postnatal toxicity. The residue chemistry database is substantially complete. Residue chemistry data gaps associated with esfenvalerate field trials do not affect exposure estimates, and use of the residue chemistry data is not expected to underestimate dietary exposure to esfenvalerate. For exposure via drinking water, the Environmental Fate and Effects Division (EFED) has used PRZM/EXAMS and SCIGROW for estimating residues in water. Due to the conservative, health-protective nature of the models and the input parameters, HED believes exposure via drinking water will not be underestimated. Therefore, the current hazard and exposure data support reducing the Special FQPA Safety Factor to account for increased sensitivity of infants and children to 1X.

A special developmental neurotoxicity study in rats is required for esfenvalerate. The HIARC recommended that the DNT study for esfenvalerate be modified to assess potential latent behavioral effects that have been attributed to exposure of rodents to pyrethroids during development (Eriksson and Fredriksson, 1991). This would entail retaining the offspring on study for approximately 4-6 months past cessation of treatment (that is, until at least 90 days of age, instead of 60-70 days of age); and conducting behavioral testing (i.e., motor activity, auditory startle, and cognitive function) and neuropathology assessments at that time. Other assessments that could be considered for addition to the protocol include: a) receptor density of muscarinic and nicotinic cholinergic receptors (mAChR and nAChR) coupled to biochemical measurements of the activity and b) effects on axonal/dendritic growth.

Although the HIARC determined that although the FQPA Special Safety Factor could be reduced to 1X, the UF_{db} for the lack of a developmental neurotoxicity study (DNT) will remain a 10X for all endpoints except for dermal exposure (see rationale provided below). An estimation of the doses that may be used in the DNT were based on the acute neurotoxicity study, which is a gavage study. The requested DNT study will also be a gavage study. If it is assumed that the NOAEL in the acute neurotoxicity study becomes a LOAEL for pups in the DNT study, then the estimated NOAEL for pups will be 1.75/10 or 0.175 mg/kg/day using an uncertainty factor of 10 for a lack of a NOAEL. This value is 10 times lower than the current oral and inhalation endpoints. Therefore, the UF_{db} factor of 10 will remain for the oral and inhalation risk assessments. HIARC determined that the UF_{db} could be reduced from a 10X to a 3X for dermal risk assessments based on the following rationale: assuming that the estimated NOAEL for pups in the DNT study will be 0.175 mg/kg/day, then a dermal equivalent dose would be estimated by dividing the NOAEL of 0.175 mg/kg/day by 2%, which results in an equivalent dermal dose of ~ 10 mg/kg/day. Since use of the dermal endpoint of 25 mg/kg/day is 2.5X > (less protective) than 10 mg/kg/day, an additional UF_{DB} of 3X applied to the dermal endpoint of 25 mg/kg/day should

be adequate to protect infants and young against dermal exposures until the results of the DNT study are submitted and reviewed.

To derive both the acute and chronic reference doses, a total uncertainty factor (UF) of 1000 was applied to the dose selected for risk assessment (1.75 mg/kg) to account for both interspecies extrapolation (10x) and intra-species variability (10x), and an additional database uncertainty factor of 10x was applied until the data from the special DNT study are received and evaluated. Since the special FQPA SF has been reduced to 1x, the acute and chronic population adjusted doses (aPAD and cPAD) are equal to the aRfD (0.0018 mg/kg) and cRfD (0.0018 mg/kg), respectively.

The HED's level of concern for noncancer risks (i.e., target level for MOEs or Margins of Exposure) is defined by the uncertainty factors that are applied to the assessment. The HED applies a factor of 100 to account for inter-species extrapolation to humans from the animal test species and to account for intra-species sensitivity. Based on the requirements of the 1996 Food Quality Protection Act (FQPA), the Agency must also consider sensitive populations in its non-occupational risk assessments. As mentioned above, the HED is applying a database uncertainty factor (UF_{db}) of 10x for non-occupational inhalation and oral exposures, and 3x for non-occupational dermal exposures to esfenvalerate due to the lack of a developmental neurotoxicity study with a special protocol for pyrethroids. The FQPA special safety factor (SF) was reduced to 1X. The total uncertainty factors that have been applied to noncancer risk assessments is 100 for occupational scenarios, 1000 for nonoccupational inhalation and oral exposure scenarios, and 300 for dermal exposure scenarios. Therefore, occupational risk estimates, expressed as Margins of Exposure (MOEs) that are ≥ 100 are not of concern. Non-occupational risk estimates (MOEs) ≥ 1000 are not of concern for non-occupational inhalation and oral exposures. And, non-occupational risk estimates (MOEs) ≥ 300 are not of concern for non-occupational dermal exposures.

Since the toxicological endpoints of concern are based on the similar adverse effects, dermal and inhalation exposures and risks must be aggregated for occupational scenarios and dermal, inhalation, and incidental oral exposures and risks must be aggregated for nonoccupational scenarios. For non-occupational scenarios, aggregate risks will be estimated using the Aggregate Risk Index (ARI). ARIs >1 are not of concern.

Residue Chemistry

The nature of the residue of esfenvalerate in livestock and plants has been adequately delineated. The residues to be regulated are esfenvalerate [(S)-cyano(3-phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl) benzeneacetate] and its non-racemic isomer [(R)-cyano-(3-phenoxyphenyl)methyl-(R)-4-chloro- α -(1-methylethyl) benzeneacetate] and its diastereomers [(S)-cyano(3-phenoxyphenyl)methyl-(R)-4-chloro- α -(1-methylethyl) benzeneacetate and (R)-cyano(3-phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl) benzeneacetate]. The tolerances were

reassessed and established based on field trial residue data performed at maximum label rates and minimum PHIs.

Dietary Exposure and Risk Estimates

A highly refined probabilistic dietary exposure and risk assessment was conducted for fenvalerate and esfenvalerate. Chronic and acute exposure estimates were based on data from (1) field trial studies for esfenvalerate, (2) USDA's Pesticide Data Program (PDP) monitoring data for fenvalerate and esfenvalerate (for the years 1998 to 2001), (3) estimates of percent crop treated for esfenvalerate, and (4) the USDA Continuing Survey of Food Intake by Individuals (CSFII) conducted from 1994 through 1996 and 1998. PDP data for esfenvalerate and fenvalerate are available for the following commodities: apples, green beans, canned sweet peas, broccoli, carrots, cherries, canned sweet corn, cucumbers, cantaloupe melons, head lettuce, nectarines, peaches, peanut butter, pears, peppers, potatoes, winter squash, strawberries, and tomatoes.

Estimates of chronic and acute dietary exposure were calculated using Novigen's Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.33). For the chronic analysis, mean anticipated residues calculated from PDP data were used. For the acute analysis, the distribution of the residues in PDP (substituting half the limit of detection for non-detectable values and adjusted for percent crop treated data) were used to create RDFs. Conservative assumptions were made in the calculation of anticipated residues (i.e. PDP data reported as total fenvalerate (the sum of fenvalerate and esfenvalerate residues for PDP commodities, thus leading to an overestimation of the residue values), use of esfenvalerate field trials on several commodities, use of tolerance level residues for the food handling establishments using esfenvalerate data only). Since the PDP data used was reported as total fenvalerate, this dietary assessment is overly conservative. Further refinement can be conducted if the imported uses on fenvalerate are cancelled (i.e. esfenvalerate PDP only may be used, therefore the residue levels would be lower for PDP commodities).

HED SOP 99.6 was used for the classification of food forms with respect to level of blending (8/20/99). The appropriate use of these data in the DEEM™ software depends in part on the classification of each commodity as "blended-B", "partially blended-PB", or "not blended-NB". Monitoring data were translated to similar crops when possible, generally according to the HED SOP 99.3 "Translation of Monitoring Data", and adjusted for percent crop treated for the crop for which translation is being conducted.

A cancer dietary risk assessment was not required since esfenvalerate is currently classified as a Group E carcinogen.

Chronic dietary exposure analyses were conducted for the overall U.S. population and 25 population subgroups, including infants and children. Probabilistic acute dietary exposure was estimated for the overall U.S. population and various population subgroups.

The **acute** dietary risk estimates are below the Agency's level of concern (<100% aPAD) at the 99.9th exposure percentile for the general U.S. population (37% aPAD) and all other population subgroups. The most highly exposed population subgroup was children 1-2 years at 67% of the aPAD. For all included commodities, the **chronic** risk estimates are below the Agency's level of concern (<100% cPAD) for the general U.S. population (33% cPAD) and all population subgroups. The most highly exposed population subgroup was children 1-2 years at 66% of the cPAD.

Residential (non-occupational) Exposure and Risk Estimates.

For residential handlers, MOEs are of concern (i.e. MOEs < 1000) for a few scenarios: these include low-pressure handwand sprayer applications to building perimeters and outdoor surfaces, ready-to-use fogger applications to indoor spaces, pump sprayer applications using the wettable powder formulation with to building perimeters, outdoor surfaces, residential lawns, and applications of ready-to-use (RTU) formulations with pump sprayers to indoor surfaces and outdoor perimeters. Note: EPA has no data in PHED to directly assess exposures from trigger-pump sprayers and has used PHED data for aerosol can applications as a reasonable worse-case surrogate.

The residential handler scenarios that are **not** of concern (i.e., MOE \geq 1000) include low-pressure handwand applications to indoor surfaces and residential turf and gardens; backpack sprayer and hose-end sprayer applications to building perimeters, outdoor surfaces, and residential turf and gardens; watering can applications to building perimeters and outdoor surfaces; aerosol can applications to indoor and outdoor surfaces; and pump-trigger applications of wp formulations to indoor surfaces and ready-to-use (RTU) formulations to residential gardens.

The HED considered a number of residential postapplication exposure scenarios covering different segments of the population, including toddlers, youth-aged children, and adults. MOEs are of concern for several scenarios, because they exceed the HED's level of concern (i.e., Oral MOE < 1000; Dermal MOE < 300) for non-cancer risk assessments in non-occupational settings. These scenarios include applications to lawns using the wettable powder formulation and applications indoors from space, surface and crack and crevice broadcast sprays. Exposures of concern include:

- dermal exposures to adults and children from activities on treated indoor surfaces from applications by broadcast sprays (MOEs of 97 for adults and 68 for toddlers) or crack and crevice sprays (MOEs of 200 for adults and 140 for toddlers),
- oral exposures to toddlers (MOE of 620) from transfer of pesticide from lawns to hand to mouth following wettable powder applications,
- oral exposures to toddlers from transfer of pesticide from indoor surfaces to hand to mouth from broadcast spray (MOE of 140) and crack and crevice spray (MOE of 280) applications.

The residential postapplication scenarios where risks are not of concern (i.e., Oral and Inhalation MOEs \geq 1000; Dermal MOEs \geq 300) include:

- dermal exposures to adults and children from high contact activities on treated lawns following liquid concentrate applications,
- dermal exposures to adults and children from high contact activities on treated lawns following wettable powder applications,
- dermal exposures to adults from mowing lawns,
- dermal exposures to adults and youth from gardening,
- oral exposures to toddlers from incidental soil ingestion,
- oral exposures to toddlers from transfer of pesticides from object to mouth on treated lawns following liquid concentrate or wettable powder applications,
- oral exposures to toddlers from transfer of pesticides from hand to mouth on treated lawns following liquid concentrate applications,
- dermal exposures to adults and children from activities on treated indoor surfaces from applications by foggers,
- oral exposures to toddlers from transfer of pesticides from hand to mouth from indoor surfaces from fogger applications, and
- inhalation exposures to adult or toddlers from indoor air following fogger application.

Aggregate Risk Estimates

The current uses for esfenvalerate encompass agricultural use sites and non-occupational (residential) uses. Therefore, when addressing aggregate exposures, the dietary pathways of food and drinking water plus the residential uses were considered, as appropriate.

Acute (food and water) Aggregate

Acute risk estimates associated with exposure to esfenvalerate residues in food do not exceed HED's level of concern. Estimates of exposures from food were taken from the dietary exposure model results described above (Section 4.2.2). These exposure estimates are based on USDA PDP monitoring data, field trial data, estimated percent crop treated information, and processing factors and may be considered highly refined. Based on the highly refined dietary assessment results, the acute dietary risk estimates are below the Agency's level of concern at the 99.9th exposure percentile for the general U.S. population (37% aPAD) and all population subgroups. The most highly exposed population subgroup using PDP monitoring data, percent crop treated data, and processing factors, where available, was children 1-2 years old at 67% aPAD.

The Environmental Fate and Effects Division (EFED) has conducted a drinking water assessment for esfenvalerate on christmas trees in Oregon and cotton in Mississippi. The maximum EEC in surface water is 7.5 ppb and 0.009 ppb in ground water. For the Christmas tree scenario representing the maximum labeled use rate for esfenvalerate, the exposure assessment for surface

water used conservative assumptions for percent cropped area (PCA = 0.87) and surrogate data for the soil water partition coefficient, which is also considered conservative. Although adsorption of esfenvalerate to soil appears to be significant, no soil water adsorption coefficient for esfenvalerate is available from the environmental fate database. Given that the Christmas tree use is limited, representing 12% of the esfenvalerate market, and the conservatisms assumed in the exposure assessment, HED does not consider the lowest acute DWLOC of 6 ppb for acute risk for infants (less than 1 year old) and a peak estimated environmental concentration (EEC) of 7.5 ppb to represent a significant risk.

Cotton represents the next highest labeled use rate for esfenvalerate, and the lowest acute DWLOC of 6 ppb for acute risk for infants (less than 1 year old) is higher than the peak EEC of 2.0 ppb for cotton; therefore, there is no acute aggregate risk of concern for cotton uses of esfenvalerate. Other uses of esfenvalerate with lower use rates are expected to result in EECs below the lowest acute DWLOC of 6ppb, and are not expected to be of concern.

Chronic (food and water) Aggregate

Chronic dietary estimates of exposure from food were taken from the dietary exposure model results described above. The chronic risk estimates are below the Agency's level of concern for the general U.S. population and all population subgroups.

Chronic Estimated Environmental Concentrations (EECs) in surface water (5.32 ppb) and ground water (0.009 ppb) were provided using PRIZM/ EXAMS and SCI-GROW modeling, respectively. For considering chronic exposure to residues of esfenvalerate in drinking water, HED has calculated DWLOCs. Based on dietary exposure estimates and default values for body weight and water consumption, the population subgroup infants (< 1 year) has the lowest DWLOC value of 6 ppb. The chronic DWLOCs for this population, and all other population subgroups, are greater than both the surface water and ground water EECs; therefore, chronic aggregate risk estimates associated with exposure to esfenvalerate residues in food and water do not exceed HED's level of concern.

Short- and Intermediate-Term (food, water, and residential uses) Aggregate

Since the toxicological endpoints of concern are based on the similar adverse effects, dermal and inhalation exposures and risks must be aggregated for occupational scenarios and dermal, inhalation, and incidental oral exposures and risks must be aggregated for nonoccupational scenarios. For non-occupational scenarios, aggregate risks will be estimated using the Aggregate Risk Index (ARI). The aggregate risk index (ARI) method is used to calculate total non-dietary risk estimates, because the uncertainty factors (UFs) are not all the same for all routes of exposure.

The route-specific MOEs are combined using the following formula: $ARI_{total} = 1/((1/ARI_a) + (1/ARI_b) + \dots (1/ARI_n))$; where $ARI_a = MOE_a/UF_a$, $ARI_b = MOE_b/UF_b$, and $ARI_n = MOE_n/UF_n$, which represent MOEs and UFs for each exposure route of concern. An $ARI_{Total} < 1$ exceeds HED's level of concern, and an $ARI_{Total} > 1$ is not of concern. The exposure scenarios that result in aggregated residential risk estimates of concern, i.e., $ARI_{Total} < 1$, include:

- toddlers on turfgrass following applications of the wettable powder formulation: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth
- toddlers on turfgrass following applications of the wettable powder formulation: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth plus exposures from transfer of pesticides from objects to mouth plus exposures from soil ingestion.
- adults who apply indoor broadcast or RTU sprays and perform high contact activities within those premises within 24 hours after treatments.
- toddlers on indoor surfaces from foggers or sprays, including dermal exposures plus exposures from transfer of pesticides from surfaces to hands to mouth.

Because these aggregate residential risk exposures alone exceeds HED's level of concern, additional exposure to esfenvalerate in drinking water and food would cause risk estimates to further exceed the levels of concern. Therefore, HED will not conduct a short- and intermediate-term aggregate risk assessment for the scenarios mentioned above.

The exposure scenarios that result in aggregated residential risk estimates not of concern, i.e., $ARI_{Total} \geq 1$, include:

- toddlers on turfgrass following applications of the liquid concentrate: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth;
- toddlers on turfgrass following applications of the liquid concentrate: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth plus exposures from transfer of pesticides from objects to mouth plus exposures from soil ingestion.
- adults who apply the wettable powder formulation with a pump-trigger sprayer plus either mow the treated lawn or have high contact activities on treated lawns.
- adults who apply the liquid concentrate with a hose-end sprayer plus either mow the treated lawn or have high contact activities on treated lawns.

- adults who apply with an aerosol can to vegetable gardens plus perform gardening tasks.

Since the above uses do not exceed HEDs level of concern, an aggregate short- and intermediate-term risk was conducted with food and water. Upon aggregation with food and water exposures, the liquid formulations used on turf result in risk estimates of concern, i.e. DWLOCs are less than the EECs for water. However, for liquid spray formulations used in gardens, aggregation with food and water exposures result in DWLOCs values above EECs and therefore the risk estimates are not of concern for this scenario.

Occupational Exposure and Risk Estimates - Handlers

When data were available to assess risks, risks to occupational handlers for the proposed new uses of esfenvalerate are below the HED's level of concern for noncancer risk assessments (i.e., MOE \geq 100) at either baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks), or with the addition of personal protective equipment for dermal protection (i.e., chemical-resistant gloves). This exposure/risk assessment includes only those occupational handler scenarios expected to occur with the proposed new use sites.

For the agricultural crop scenarios of the proposed new use sites (i.e. for bok choy, Brussels sprouts, canola, cardoon, pistachios and sweet potato) using PHED data, the risks are not a concern at baseline attire for applying sprays with groundboom and airblast equipment and for flagging to support aerial applications. The risks to handlers mixing and loading to support applications to agricultural crops (including chemigation applications) are not a concern with the addition of chemical-resistant gloves to baseline attire. EPA has insufficient data to assess exposures to pilots in open cockpits. Risks to pilots in enclosed cockpits (engineering control scenario) were not a concern for all agricultural crop scenarios.

For the remaining proposed new uses, there are no appropriate exposure data to assess exposures from applying esfenvalerate indoors with a mechanical fogger/aerosol generator; i.e. for fumigating/treating unshelled peanuts, cocoa beans, and shelled almonds and walnuts. No reasonable surrogate data are available to evaluate risks from this exposure; however, based on the proposed label language, this scenario appears to be more like an aerosol treatment than like a fogger treatment; i.e. the treatment is not meant to be penetrating. Therefore, handler exposures from this scenario (maximum application rate 4.4E-5 lb ai/cu ft) should be more similar to those estimated by the indoor aerosol scenario (maximum application rate 5.875E-4 lb ai/cu ft), than by the indoor fogger scenario (maximum application rate 7.29E-5 lb ai/cu ft); both presented in the residential portion of this risk assessment. For the aerosol residential handler scenario, MOEs of 5,200 (dermal) and 34,000 (inhalation) were estimated; and for the fogger residential handler scenario, MOEs of 1,200 (dermal) and 4,700 (inhalation) were estimated. Therefore, the MOEs estimated under the residential scenario should be conservative and protective of this occupational scenario, since the application rate for these commercial uses is less than the application rate for the residential indoor aerosol scenario by an order of magnitude. Therefore, it seems reasonable to

assume that applying esfenvalerate indoors with a mechanical fogger/aerosol generator are not expected to exceed HED's occupational handler level of concern (i.e. MOE<100).

Occupational Exposure and Risk Estimates - Postapplication

The postapplication occupational assessment for esfenvalerate on agricultural crops is based on chemical-specific dislodgeable foliar residue (DFR) studies on apples, broccoli, and sweet corn (MRID 44852402, MRID 44852401, and MRID 44852403). For the proposed agricultural crops treated with esfenvalerate, risks were not a concern (i.e., MOEs \geq 100) at 12 hours following application (i.e., day 0).

Incident Reports

A review of incident data sources was conducted for esfenvalerate. Relatively few incidents of illness have been reported due to esfenvalerate. Incidents suggest that esfenvalerate can be a source of respiratory distress. In general, esfenvalerate is more likely to cause minor to moderate symptoms than other pesticides, but much less likely to cause serious or major effects which would require hospitalization or critical care. Note that there were relatively few cases involving occupational exposure or children under age six. By far, the most common moderate effects (almost always requiring medical attention) were difficulty breathing and cough in adults, suggesting that esfenvalerate may pose an asthma-like hazard.

Detailed descriptions of 262 cases submitted to the California Pesticide Illness Surveillance Program (1982-2000) were reviewed. In 19 of these cases, esfenvalerate was used alone or was judged to be responsible for the health effects. Only cases with a definite, probable or possible relationship were reviewed. Esfenvalerate ranked 133rd as a cause of systemic poisoning in California based on data for 1982 through 1999. Applicators were associated with more exposures than any other category. These illnesses included symptoms of conjunctiva, skin rashes, headache, dizziness, vomiting, nasal burning, and eye irritation. Effects to the eyes and skin seemed to predominate. One of the difficulties with the California data is that search a large percentage (93%) of cases involved mixtures where the predominate pesticide responsible for the illness was undetermined.

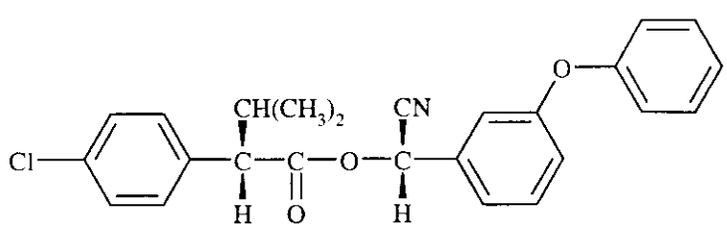
On the list of the top 200 chemicals for which National Pesticide Information Center (NPIC) received calls from 1984-1991 inclusively, esfenvalerate was ranked 155th with 18 incidents in humans reported and three in animals (mostly pets).

No scientific literature was located concerning acute poisoning due to exposure to esfenvalerate.

Data Gaps and Tolerance Reassessment

Refer to Section 8.0 of this document for specific data gaps and tolerance reassessment.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Compound	
Common name	Esfenvalerate
Company experimental name	Asana®
IUPAC name	(S)-α-cyano-3-phenoxybenzyl (S)-2-(4-chlorophenyl)-3-methylbutyrate
CAS name	(S)-cyano(3-phenoxyphenyl)methyl (S)-4-chloro-α-(1-methylethyl)benzeneacetate
CAS #	66230-04-4
Chemical Class	Pyrethroid
End-use formulation (EUP)	Asana® XL (0.66 lbs ai/gallon)

Parameter	Value
Melting point/range	59-60.2 °C
pH	Insoluble in water
Density	1.163 g/mL
Water solubility (25°C)	Insoluble in water (<20 ppb at 20°C)
Solvent solubility (g/100mL at 20°C)	Soluble in acetone, chloroform, DMF, ethanol, hexylene glycol, methanol and xylene (>450 g/L) Hexane (77 g/L at 20°C)
Vapor pressure at 25°C	1.5 x 10 ⁻⁹ mmHg

TABLE 2.2 Physicochemical Properties	
Parameter	Value
Dissociation constant (pK_a)	No dissociation
Octanol/water partition coefficient (K_{ow})	6.5
UV/visible absorption spectrum	$2.3 \times 10^3 \text{ mol}^{-1} \text{cm}^{-1}$ at 278 nm $>10 \text{ mol}^{-1} \text{cm}^{-1}$ at 290 nm

Pure **esfenvalerate** is a white crystalline solid with a melting point of 59-60.2 °C, density of 1.163 g/mL at 23-25 °C, octanol/water partition coefficient ($\log K_{ow}$) of 6.5 at 25 °C, and vapor pressure of 1.5×10^{-9} mm Hg at 25 °C. Technical esfenvalerate is a yellowish viscous liquid or crystalline solid with a density of 1.17 g/mL. Esfenvalerate is practically insoluble in water (<20 ppb at 20 °C) and is soluble in a range of organic solvents including acetone, chloroform, DMF, ethanol, hexylene glycol, methanol, and xylene (>450 g/L), and hexane (77 g/L) at 20 °C. Esfenvalertate has a low vapor pressure and exposure to the gaseous state should be negligible.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

-Acute Toxicity. The data base for acute toxicity for esfenvalerate is considered complete except for an acute inhalation toxicity study.

The acute toxicity data on the esfenvalerate Technical is summarized below in Table 3.1.1.

Table 3.1.1. Acute Toxicity Data on Esfenvalerate

Acute Toxicity of Esfenvalerate (PC Code 109303)

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
870.1100	Acute Oral	00144973	LD ₅₀ = 87.2 mg/kg	II
870.1200	Acute Dermal	00156508	LD ₅₀ > 2000 mg/kg	III
870.1300	Acute Inhalation	Not available	Not available	Not available
870.2400	Primary Eye Irritation	00156509	Mild irritation	III
870.2500	Primary Skin Irritation	00156510	Mild irritation*	IV
870.2600	Dermal Sensitization	41215203	Negative*	N/A

*Esfenvalerate and other type II pyrethroids cause a special type of dermal sensitization on contact that is indicated by tingling and other signs.

-Subchronic/Chronic/Developmental/Reproductive/Carcinogenicity and General Metabolism.

Table 3.1.2. Toxicity profile of esfenvalerate.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity rodents	Accession numbers 257018, 257019 and 257020 - 1984. Acceptable/Guideline Doses 0, 50, 150, 300 or 500 ppm.	NOAEL = 50 ppm LOAEL = 150 ppm based on neurological signs manifested by "jerky leg movements.
870.3100 90-Day oral toxicity in rats	MRID # 40215601 Acceptable/Non-Guideline, Doses 0, 75, 100, 125 or 300 ppm	NOAEL = 125 ppm LOAEL = 300 based on decreased body weight and neurological signs (hyperactivity and jerky leg movements).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100 90-Day oral toxicity in mice.	MRID # 41359701. Acceptable/Non- Guideline. Special study comparing both fenvalerate and esfenvalerate.	<u>Fenvalerate:</u> NOAEL - Not established. LOAEL < 2000 ppm based on clinical signs of neurotoxicity and hepatic effects other effects. <u>Esfenvalerate:</u> NOAEL = 150 ppm LOAEL = 500 ppm based on clinical signs of neuro and hepatic toxicity other signs.
870.3150 90-Day oral toxicity in non-rodents.	No study available. There is a pilot dose range finding study associated with the chronic feeding study in dogs - see below.	
870.3200 21-Day dermal toxicity-rats	MRID # 45275401 (2000). Acceptable/Guideline. Doses 0, 25, 125, 500 and 1000 mg/kg/day.	NOAEL (systemic) 25 mg/kg/day LOAEL (systemic) 125 mg/kg/day (based on abnormal hind limb gait) A NOAEL and LOAEL for special dermal sensitization could not be evaluated.
870.3200 21/28-Day dermal toxicity-rabbit	MRID 43435101 (1992). Acceptable/Guideline Doses 0, 100, 300 or 1000 mg/kg/day.	NOAEL = > 1000 mg/kg/day (HDT) - no systemic effects.
870.3250 90-Day dermal toxicity	No study available.	
870.3465 90-Day inhalation toxicity	No study available.	
870.3700a Prenatal developmental in rodents	MRID 43211502 and 43211504. ACCEPTABLE/Guidelin e (when combined). 0, 1, 2, 2.5, 3, 4, 5, 10 or 20 mg/kg/day (in one or the other studies).	Maternal NOAEL = 2 mg/kg/day LOAEL = 2.5 mg/kg/day based on behavioral/CNS clinical signs. Developmental NOAEL = > 20 mg/kg/day. No effects at 20 mg/kg/day (HDT).

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700b Prenatal developmental in nonrodents	MRID 43211501 and 54311503. ACCEPTABLE/ GUIDELINE (when combined). 0, 2, 3, 4, 4.5, 5, 10 or 20 mg/kg/day.	Maternal NOAEL = 2 mg/kg/day LOAEL = 3 mg/kg/day based on behavioral/CNS clinical signs. . Developmental NOAEL > 20 mg/kg/day. No effects at 20 mg/kg/day (HDT).
870.3800 Reproduction and fertility effects	MRID 43489001. ACCEPTABLE/ GUIDELINE 0, 4.21, 5.55 or 18.8 mg/kg/day in males; 0, 5.56, 7.18 or 25.1 mg/kg/day in females.	Parental/Systemic LOAEL = 4.21 mg/kg/day based on skin condition and decreased body weight. NOAEL not established. Reproductive LOAEL > 25.1 mg/kg/day. No direct adverse effects on reproductive performance. Offspring NOAEL = 5.56 mg/kg/day LOAEL = 7.18 mg/kg/day based on decreased body weight, litter size and subcutaneous hemorrhages.
870.4100a Chronic toxicity rodents	Refer to 870.4300 below.	
870.4100b Chronic toxicity dogs	Range finding study: 00163855 (1986) and definitive study: 40376501 (1985) Acceptable/Guideline when combined. Doses 0, 0.625, 1.25, 5, 7.5 or 12.5 mg/kg/ day in either study.	NOAEL = 5 mg/kg/day LOAEL = 7.5 mg/kg/day based on decreased group body weight and ataxia in one male.
870.4200 Carcinogenicity - mice	MRID 444260607 ACCEPTABLE/ Guideline 0, 4.29 or 18.3 mg/kg/day in males, 0, 5.74 or 24.7 mg/kg/day in females. (A dose of 57 to 58 mg/kg/day was not tolerated.	Systemic toxicity: NOAEL = Not established. LOAEL = 4.29 mg/kg/day in males and 5.74 mg/kg/day in females based on skin lesions. No evidence of carcinogenicity

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300. Combined Chronic Feeding/ Carcinogenicity - rats	MRID 00079877. ACCEPTABLE/Non-Guideline. 0 and 50 mg/kg/day.	NOAEL = Not established. LOAEL = 50 mg/kg/day based on decreased body weight and transient hind limb weakness in males. No evidence of carcinogenicity.
870.6200a Acute neurotoxicity screening battery	MRID 45228301 ACCEPTABLE/ Guideline 0, 1.75, 1.90, 20 or 80 mg/kg/day (in corn oil)	NOAEL = 1.75 mg/kg/day LOAEL = 1.90 mg/kg/day based on tremors in females.
870.6200b Subchronic neurotoxicity screening battery	MRID 45202301 ACCEPTABLE/ Guideline 0, 3, 8.9 or 28.8 mg/kg/day in males; 0, 3.7, 10.7 or 35 mg/kg/day in females. MRID 45157501 ACCEPTABLE/ Guideline 0, 3.22, 6.39 or 20.08 mg/kg/day in males; 0, 3.73, 7.26 or 22.78 mg/kg/day in females.	NOAEL = 3 in males or 3.7 in females mg/kg/day LOAEL = 8.9 in males or 10.7 in females mg/kg/day based on decreased body weight and motor activity in females. NOAEL = 3.22 mg/kg/day in males. LOAEL = 6.39 mg/kg/day based on reduced forelimb grip strength and skin lesions.
870.6300 Developmental neurotoxicity	No study is available. A developmental neurotoxicity study with a special protocol is being requested.	
870.7485 Metabolism and pharmacokinetics - rats and mice.	MRID #s 44679301, 45351601 and 45351602.	Combination of studies demonstrate the absorption, excretion and distribution and identification of the principle metabolites.
870.7600 Dermal penetration	No Study.	

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Special studies		No special studies were required for the registration of esfenvalerate. There were earlier studies which attempted to demonstrate special neuropathological responses at higher doses to fenvalerate. The subchronic neuro-toxicity screen study did not demonstrate any histopathological effects thus establishing a NOAEL for possible neuro histopathological effects.

Table 3.1.2a. Mutagenicity/Genetic Toxicity.

Study	Results
Gene mutation	
Salmonella/mammalian activation gene mutation assay. Takarazuka Research Center, Study No.: LLT-50-0009, December 28, 1985. MRID No.: 41316301.	No evidence of induced mutant colonies up to and including 5000 µg/plate in <i>Salmonella typhimurium</i> strains TA98, TA1537, TA1538 and in <i>Escherichia coli</i> strain WP2 (evrA).
HGPRT locus mammalian cells in culture: gene mutation assay. Takarazuka Research Center, Study LLT-50-0012, December 28, 1985. MRID No.: 41316302.	No evidence of induced mutant colonies in the HGPRT mammalian gene locus in Chinese Hamster V70 cultured cells.
Chromosome aberration	
<i>In vitro</i> mammalian cytogenetic chromosomal aberration study in Chinese Hamster ovary cells. Takarazuka Research Center, Study No.: LLT-50-0010, December 28, 1985. MRID No.: 41215204.	No evidence of induction of chromosomal aberrations or polyploid cells induced by esfenvalerate.
Other mechanism	
No study.	

-Hazard Characterization.

Relationship between esfenvalerate and fenvalerate. Esfenvalerate is a pyrethroid insecticide and is an isomeric enriched technical grade of fenvalerate (PC Code 109301). There are more recent toxicity studies with esfenvalerate and there are also earlier studies with fenvalerate which have been used to characterize the toxicity of esfenvalerate. Fenvalerate use has been withdrawn from the U.S. market.

Esfenvalerate and fenvalerate belong to the Type II subclass of pyrethroids that usually have a cyano group attached to the *alpha* carbon (refer to structure). The type II pyrethroids produce a characteristic toxicity response in both insects and mammals that is distinct from the type I pyrethroids. The Type I pyrethroids produce responses more closely resembling the fine tremors seen with DDT. The type II pyrethroids produce responses that include choreoathetosis writhing in mammals. It is generally recognized that the sodium conductance channel is the site of action of both type I and type II pyrethroids although the kinetics of the interaction between the type I and type II pyrethroids and the channel are different to produce the differences in responses.

Acute Toxicity. Esfenvalerate is considered moderately toxic via the oral route having an LD₅₀ of 87.2 mg/kg (Toxicity Category II) but is less toxic by the dermal route (Toxicity Category III). Esfenvalerate is mildly irritating but not a sensitizer. No acute inhalation study with esfenvalerate was available.

Subchronic and chronic toxicity. In the subchronic toxicity study with esfenvalerate in rats decreased body weight and signs of neurotoxicity (jerky leg movements) were evident. The indications of body weight decrease and signs of neurotoxicity (decreased motor activity and hindlimb grip strength) were also apparent in the two subchronic neurotoxicity studies with esfenvalerate. In a chronic feeding study, dogs demonstrated signs of neurotoxicity as indicated by emesis, head shaking, biting extremities as well as the systemic effects including normocytic anemia, increased serum cholesterol, and possible hepatic microgranulomatosis. Mice also show weight loss and anemia, reactive responses in the lymphatic tissue in multiple locations and hepatic microgranuloma and giant cell formation in the liver and spleen.

Esfenvalerate and other type II pyrethroids produce a dermal "pyrethroid reaction" that leads to a specific type of dermal sensation especially in mice possibly resulting from contact with feed. This sensation results in scratching and skin lesions that can become infected and confounding the results of subchronic and chronic studies.

Dermal application of esfenvalerate for 21 days resulted in "abnormal gait" in females at the lowest test dose. At higher doses all females and most males were affected. This "abnormal gait" persisted for typically 0 to 6 or 7 days and was not seen when an FOB assessment was made prior to sacrifice at 20 days.

Neurotoxicity. Pyrethroids affect the nervous system and following acute oral administration tremors result. Abnormal gait also results following dermal application in rats. Following feeding administration, neurotoxicity may result at higher doses where other systemic signs such as body weight effects also are seen.

Early in the development of pyrethroids there were concerns that higher doses resulted in a specific degeneration of the peripheral nervous system and extensive studies were conducted to attempt to determine the potential for fenvalerate or esfenvalerate to cause this type of

neuropathy. The recently conducted acute and two independent subchronic studies with rats did not indicate neuropathy at the doses tested. The overall current conclusion is that NOAELs have been established for induction of neuropathy (i.e. there was no neuropathy in the recent guideline subchronic neurotoxicity studies and only following higher near lethal doses will a sparse peripheral neuropathy possibly result.)

Developmental and Reproductive Toxicity. The rat and rabbit developmental toxicity studies did not indicate that there was developmental toxicity (either quantitative or qualitative) at dose levels at or below maternal toxicity. There was no increased susceptibility in the rat or rabbit developmental toxicity studies at the highest doses tested.

The rat multi-generation reproduction study did not indicate any adverse effects on reproductive performance and parental toxicity consisted of dermal reactions and body weight effects and at higher doses there was abnormal gait in the P1 generation. At the highest dose, the F1 generation could not tolerate the same dose as the P generation and demonstrated in addition to abnormal gait, tremors, ataxia, hyperactivity, vocalization, hypersensitivity and eventual death even after lowering the dose.

Carcinogenicity. Fenvalerate/esfenvalerate is currently classified as a Group E chemical, no evidence of carcinogenicity in rats or mice. The existing data base consisting mainly of a rat study with fenvalerate and a mouse study with esfenvalerate did not indicate increased incidence of neoplasia. These studies are recognized to have been studied at dose levels considered adequate for carcinogenicity evaluation.

Mutagenicity. There is no mutagenicity concern for fenvalerate/esfenvalerate based on the weight of evidence of the studies submitted thus far. There is, however, no study for the category "other mechanisms" and a study to meet this requirement is needed.

Immunotoxicity. There were no indications that indicate a specific concern for immunotoxicity.

Metabolism and Pharmacokinetics. The metabolism and pharmacokinetics data base for fenvalerate and esfenvalerate demonstrated the absorption, excretion and distribution and identification of the principle metabolites.

3.2 FQPA Considerations.

Special Sensitivity to Infants and Children.

A. Determination of Susceptibility

The HIARC concluded that there is no indication of increased pre- or postnatal qualitative or quantitative susceptibility in either the rat or rabbit developmental toxicity studies or in the 2-generation reproduction study. No developmental toxicity was observed in rats and rabbits in the presence of maternal toxicity (clinical signs of neurotoxicity). In the 2-generation reproduction study, a decrease in mean body weight and skin lesions were observed in the parents at the lowest dose tested (4.21 mg/kg/day); no NOAEL was established. For offspring toxicity, the NOAEL was 5.56 mg/kg/day and the LOAEL was 7.18 mg/kg/day, based on decreases in pup mean body weight and litter size and increases in subcutaneous hemorrhages.

In the 2-generation reproduction study, the HIARC noted a *qualitative* difference in response between the P1 animals (exposed as adults only at 350 ppm or 18.8/25.1 mg/kg/day (M/F)) and the F1 animals (exposed both *in utero* at 350 ppm and perinatally at 150 ppm for an approximate overall mean dose of 19 mg/kg/day). The F1 animals could not tolerate the 350 ppm dose level and it was reduced to 150 ppm. Abnormal gait/mobility was observed in the P1 animals. In the F1 animals, not only was abnormal gait observed, but additional clinical signs of neurotoxicity were noted (tremors, vocalization, ataxia, hyperactivity and hypersensitivity). However, the HIARC concluded that the observed difference between the P1 and F1 generations with regard to the additional clinical signs of neurotoxicity is not a concern for qualitative susceptibility *per se* since these findings have no impact on the regulatory dose selected for risk assessment and these effects occur at the highest dose tested (HDT) and a similar difference in the response was not seen at lower doses.

B. Degree of Concern Analysis and Residual Uncertainties.

There are no concerns or residual uncertainties for pre and/or post natal toxicity following exposure to esfenvalerate/fenvalerate.

C. Special FQPA Safety Factor(s):

The HIARC determined that the special FQPA Safety Factor can be removed (1x) because: 1) there is no evidence of quantitative or qualitative susceptibility following *in utero* exposure to rats or rabbits or pre/postnatal exposure to rats and 2) there are no residual uncertainties for pre/postnatal toxicity.

Note: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or

degradates of concern and does not underestimate the potential risk for infants and children.

Recommendation for a Developmental Neurotoxicity Study

A special developmental neurotoxicity study in rats is required for esfenvalerate.

Summary and basis for recommendation. The HIARC recommended that the DNT study for esfenvalerate be modified to assess potential latent behavioral effects that have been attributed to exposure of rodents to pyrethroids during development (Eriksson and Fredriksson, 1991). This would entail retaining the offspring on study for approximately 4-6 months past cessation of treatment (that is, until at least 90 days of age, instead of 60-70 days of age), and conducting behavioral testing (i.e., motor activity, auditory startle, and cognitive function) and neuropathology assessments at that time. Other assessments that could be considered for addition to the protocol include: a) receptor density of muscarinic and nicotinic cholinergic receptors (mAChR and nAChR) coupled to biochemical measurements of the activity and b) effects on axonal/dendritic growth. For further information that may be useful in designing this modified DNT protocol, it is recommended that the registrant consult the draft Proposal for a Test Protocol on Neurobehavioral Impact Following Direct Exposure of Pyrethroids During Critical Window of Exposure for Brain Development, National Chemicals Inspectorate Sweden (2 May 2002), and comments on this proposal from a Special Meeting of the European Commission to discuss questions related to developmental neurotoxicity (19 June 2002). The registrant should consult with the Agency prior to conducting this study.

Database Uncertainty Factor

In accordance with the 2002, *OPP Guidance Document on Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment*, since there are not sufficient reliable data to assign a different factor than the 10X default factor, the HIARC concluded that a Database Uncertainty Factor (UF_{DB}) of 10X is required until the data from the special DNT study are received and evaluated.

3.3 Dose-Response Assessment.

The short-, intermediate- and long-term (non-cancer) dermal risk assessments for esfenvalerate are based on a 21-day dermal toxicity study in rats (MRID 45275401). The findings from this dermal toxicity study potentiated a revisit of this active ingredient to the HIARC. Previously, HED elected to use the oral endpoint from the acute neurotoxicity study mentioned above (i.e. 1.75 mg/kg/day). A dermal absorption factor of 25 percent was previously selected, based on dermal absorption data available for structurally-related pyrethroids (HIARC document, February 10, 2003). However, since then this dermal toxicity study has been reviewed. The HIARC met on 8/19/03 to re-evaluate the dermal endpoints, dermal absorption and the database uncertainty factor (UF_{db}) for esfenvalerate. Prior to determining the dermal endpoints, the

HIARC discussed the 21-day dermal study and raised the NOAEL/LOAEL in the DER to 25/125 mg/kg/day. With the 21-day dermal study, a revised dermal absorption factor of 2% was then estimated by dividing the LOAEL of 2.5 mg/kg/day from the developmental rat study by the LOAEL of 125 mg/kg/day from the 21-day dermal study. Similar effects had been observed in both studies. This new dermal absorption factor supersedes the previously estimated factor of 25%. The HIARC then determined that all dermal risk assessments (short-, intermediate-, and long-term) should be based on the 21-day dermal rat study with a NOAEL of 25 mg/kg/day, supported by the following rationale: it is a route-specific study; since the effects are not cumulative, it is appropriate for all durations; and, based on the new dermal absorption factor, the HIARC further noted that the oral endpoint from the acute neurotoxicity study of 1.75 mg/kg/day modified by the dermal absorption factor of 2% results in an equivalent dermal dose of 87.5 mg/kg/day which is less conservative than use of the NOAEL of 25 mg/kg/day from the route-specific dermal study for assessing risks from dermal exposures.

Table 3.3.1. Summary of Toxicology Endpoint Selection for Esfenvalerate/Fenvalerate.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary General Population including Infants and Children	NOAEL = 1.75 mg/kg UF = 1000 ^a Acute RfD = 0.0018 mg/kg.	FQPA SF = 1 aPAD = $\frac{\text{Acute RfD}}{\text{FQPA SF}}$ = 0.0018 mg/kg	Acute neurotoxicity screen. LOAEL = 1.90 mg/kg based on tremors.
Chronic Dietary all populations	NOAEL = 1.75 mg/kg/day UF = 1000 ^a Chronic RfD = 0.0018 mg/kg/day	FQPA SF = 1 X cPAD = $\frac{\text{Chronic RfD}}{\text{FQPA SF}}$ = 0.0018 mg/kg/day	Acute neurotoxicity screen. LOAEL = 1.90 mg/kg based on tremors.
Incidental Oral (All Durations)	NOAEL = 1.75 mg/kg/day	Residential LOC for MOE = 1000 ^a Occupational = NA	Acute neurotoxicity screen. LOAEL = 1.90 mg/kg based on tremors.
Dermal (All Durations)	NOAEL = 25 mg/kg/day (dermal absorption rate = 2%)	Residential LOC for MOE = 300 ^a Occupational LOC for MOE = 100	21-Day Dermal in rats. LOAEL = 125 mg/kg based on abnormal hind limb gait.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Inhalation (All Durations)	Oral NOAEL= 1.75 mg/kg/day (Inhalation absorption rate = 100%)	Residential LOC for MOE = 1000 ^a Occupational LOC for MOE = 100	Acute neurotoxicity screen. LOAEL = 1.90 mg/kg based on tremors.
Cancer	Classification: Group "E" chemical.		

^a Additional 10x database uncertainty factor for lack of a special developmental neurotoxicity study applied to oral and inhalation endpoints. A 3X database uncertainty factor for lack of a special developmental neurotoxicity study applied to dermal endpoints.

UF = Uncertainty factor, FQPA SF = Food Quality Protection Act 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.

-Endpoint Selection Rationale and Discussion.

Esfenvalerate is a pyrethroid insecticide that results in tremors following acute oral administration. The evidence of tremors in the acute neurotoxicity study demonstrated the lowest NOAEL (1.75 mg/kg) and LOAEL (1.95 mg/kg) of the available studies regardless of duration and was selected as the RfD to assess risk from acute and chronic exposures as well as from oral incidental and inhalation short-, intermediate- and chronic exposure (no subchronic inhalation study was available). This selection is justified because the lowest combination of NOAEL and LOAEL will protect against toxicity occurring at higher doses and for longer exposures. In the case of esfenvalerate, long term daily exposures are considered as multiple daily exposures with each potentially causing tremors on a daily basis. Current HIARC policy is to use the same endpoint for all oral exposures when the acute NOAEL is lower than the subchronic or chronic NOAEL regardless of gavage or dietary administration unless there is a reasonable basis not to. In the case of esfenvalerate, the potential to cause tremors due to the interaction of esfenvalerate with the nervous system is considered by HIARC as justification for using the acute neurotoxicity NOAEL for the basis of the chronic RfD.

A subchronic dermal toxicity study became available to the team after the initial HIARC meeting. This study was assessed by the HIARC on 10/22/03. The NOAEL/LOAEL were raised to 25/125 mg/kg/day and the study was selected for dermal risk assessment (all durations). A database uncertainty factor of 3X was applied to the dermal endpoint.

3.4 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 scientific bases 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). The studies submitted as guideline studies did not provide any obvious indications that fenvalerate/esfenvalerate have specific endocrine disruptive effects. Some studies appearing in the literature suggest that some pyrethroids and their metabolites may have endocrine disrupting effects. At least one publication (Maitri et al, *Biochem. Biophys. Res. Commun.* 214:905-909, 1995) reports that fenvalerate inhibits thyroid function and depresses 5'D-I activity in mice. Another paper (Tyler et al, *Environmental Toxicology and Chemistry*, 2000, 19:80-809) raised the possibility that pyrethroids and their degradative metabolites as a class have endocrine activities. Fenvalerate/ esfenvalerate may need further assessment for potential endocrine effects when guidelines for testing for endocrine effects are finalized.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Esfenvalerate has registered crop uses on almond, apple, apricot, artichoke, beans (dry and succulent), blackberry, blueberry, boysenberry, broccoli, cabbage, Chinese cabbage, caneberry, carrot, cauliflower, cherry, collards, corn (field, pop, and sweet), cotton, cucumber, dewberry, eggplant, elderberry, filbert, gooseberry, kohlrabi, lentil, lettuce (head lettuce), loganberry, melons (cantaloupe, honeydew, muskmelon, and watermelon), mustard green, nectarine, peach, peanut, pear, pea (including dry pea), pecan, pepper, plum, potato, pumpkin, radish, raspberry, sorghum, soybean, squash (summer and winter), sugar beet, sugarcane, sunflower, tomato, turnip, walnut (black and English), and youngberry.

In addition to the above crop uses, esfenvalerate is registered for use in Food Handling Establishments (FHEs) by McLaughlin Gormley King Company (MGK®).

Crops included in these dietary risk assessments for esfenvalerate include all crops with esfenvalerate tolerances, (including crops currently not included on the label, such as okra), import crops with fenvalerate tolerances, crops with pending petitions (IR-4: canola, sweet potato, cardoon, Brussels sprouts, bok choy; and pistachios), as well as MGK's tolerances for post-harvest treatment (cocoa, almond, peanut, walnut). The following petitions were withdrawn by the registrant: celery (PP#4F3023, withdrawn on 7/30/02) cranberries (PP#E3697, withdrawn on 5/7/98), leaf lettuce (PP#1E3958, withdrawn on 2/10/03) and kale (PP#1E3957, withdrawn on 2/10/03).

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Tolerances are established for residues of esfenvalerate under 40 CFR §180.533 and are expressed in terms of esfenvalerate [(S)-cyano(3- phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl)benzene-acetate] in/on the following: artichoke, globe; kohlrabi; lettuce, head; mustard greens; sorghum, fodder; sorghum, forage; sorghum, grain; sugar beet pulp; sugar beet, root, and sugar beet, top, eggs, whole; poultry, fat; poultry, meat; poultry, mbyp (except liver), poultry, liver, kiwi, and sugar beet pulp. Also, all of the registered uses for fenvalerate have been transferred to esfenvalerate after its cancellation in the U.S.

HED recommends that the tolerance expression under 40 CFR §180.533 be amended to specify that the residues to be regulated are: esfenvalerate [(S)-cyano(3-phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl) benzeneacetate] and its non-racemic isomer [(R)-cyano-(3-phenoxyphenyl)methyl-(R)-4-chloro- α -(1-methylethyl) benzeneacetate] and its diastereomers [(S)-cyano(3-phenoxyphenyl)methyl-(R)-4-chloro- α -(1-methylethyl) benzeneacetate and (R)-cyano(3-phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl) benzeneacetate].

For tolerance enforcement, the Pesticide Analytical Manual, Vol. II lists two similar gas liquid chromatography methods for the determination of fenvalerate residues. These methods are also applicable to esfenvalerate. Method I (MMS-R-478-1) determines residues in/on crops, animal tissues, and water. Method II (MMS-R-447-3) determines residues in animal tissue, milk, milk fat, cream, and eggs. The second method differs from the first in that final clean-up procedures use a capillary column rather than a packed column. Fenvalerate and esfenvalerate residues are composed of two pairs of diastereoisomers (RS, SR and SS, RR) which appear as two GLC peaks in both methods. The limit of detection (LOD) is approximately 0.01 ppm.

The registrant has submitted an addendum (AMR 717-87: Supplement 1) to the enforcement methods published in PAM Vol. II. The incorporation of these changes into the PAM Vol. II method produced Method AMR 750-87 which was the data-collection method used in more recent esfenvalerate field trials. The major changes include improvements in both the liquid partitioning, the liquid-solid chromatography clean-up steps, and the use of a capillary column instead of a packed column. The method changes do not affect the LOD of fenvalerate or esfenvalerate in crops or animal tissue, which is 0.01 ppm; the limit of quantitation (LOQ) was listed as 0.02 to 0.05 ppm, depending on the matrix. Both GLC methods resolve the four fenvalerate isomers into two diastereomeric peaks. The RS, SR pair elutes first from the column followed by the SS, RR pair. The typical peak ratio for fenvalerate is 54:46, and the ratio for esfenvalerate is 15:85. The amended method can distinguish between fenvalerate and esfenvalerate. The supplemental method has been forwarded to FDA for inclusion in PAM Volume II as letter method A.

The above-described enforcement methods (or its modifications) were the data-collection methods used for the analysis of samples collected from studies pertaining to magnitude of the residue in plants and animals as well as storage stability. In all cases, adequate concurrent method recovery data were provided.

A highly refined probabilistic dietary exposure and risk assessment was conducted for fenvalerate and esfenvalerate. Chronic and acute exposure estimates were based on data from (1) field trial studies for esfenvalerate, (2) USDA's Pesticide Data Program (PDP) monitoring data for fenvalerate and esfenvalerate (for the years 1998 to 2001), (3) estimates of percent crop treated for esfenvalerate, and (4) the USDA Continuing Survey of Food Intake by Individuals (CSFII) conducted from 1994 through 1996 and 1998. PDP data for esfenvalerate and fenvalerate are available for the following commodities: apples, green beans, canned sweet peas, broccoli, carrots, cherries, canned sweet corn, cucumbers, cantaloupe melons, head lettuce, nectarines, peaches, peanut butter, pears, peppers, potatoes, winter squash, strawberries, and tomatoes.

Estimates of chronic and acute dietary exposure were calculated using Novigen's Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.33). For the chronic analysis, mean anticipated residues calculated from PDP data were used. For the acute analysis, the distribution of the residues in PDP (substituting half the limit of detection for non-detectable values and adjusted for percent crop treated data) were used to create RDFs. Conservative assumptions were made in the calculation of anticipated residues (i.e. PDP data

reported as total fenvalerate (the sum of fenvalerate and esfenvalerate residues for PDP commodities, thus leading to an overestimation of the residue values), use of esfenvalerate field trials on several commodities, use of tolerance level residues for the food handling establishments using esfenvalerate data only). Since the PDP data used was reported as total fenvalerate, this dietary assessment is overly conservative. Further refinement can be conducted if the imported uses on fenvalerate are cancelled (i.e. esfenvalerate PDP only may be used, therefore the residue levels would be lower for PDP commodities).

HED SOP 99.6 was used for the classification of food forms with respect to level of blending (8/20/99). The appropriate use of these data in the DEEM™ software depends in part on the classification of each commodity as “blended-B”, “partially blended-PB”, or “not blended-NB”. Monitoring data were translated to similar crops when possible, generally according to the HED SOP 99.3 “Translation of Monitoring Data”, and adjusted for percent crop treated for the crop for which translation is being conducted.

A cancer dietary risk assessment was not required since esfenvalerate is currently classified as a Group E carcinogen.

4.2.2 Acute Dietary

The acute dietary risk estimates are below the Agency’s level of concern (<100% aPAD) at the 99.9th exposure percentile for the general U.S. population (37% aPAD) and all other population subgroups. The most highly exposed population using PDP and field trial data was children 1-2 years at 67% aPAD.

Table 4.2.2. Results of Acute Dietary Exposure Analysis						
Population Subgroup	95 th Percentile		99 th Percentile		99.9 th Percentile	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.000059	3	0.000187	10	0.000662	37
All Infants (< 1 year old)	0.000106	6	0.000343	19	0.000954	53
Children 1-2 years old	0.000127	7	0.000348	19	0.001203	67
Children 3-5 years old	0.000108	6	0.000283	16	0.000942	52
Children 6-12 years old	0.00074	4	0.000204	11	0.000714	40
Youth 13-19 years old	0.000052	3	0.000154	9	0.000600	33
Adults 20-49 years old	0.000050	3	0.000160	9	0.000603	34
Females 13-49 years old	0.000047	3	0.000159	9	0.000589	33
Adults 50+ years old	0.000053	3	0.000164	9	0.000604	34

4.2.3 Chronic Dietary

The chronic dietary risk estimates are below the Agency's level of concern (<100% cPAD) for the general U.S. population (33% cPAD) and all population subgroups. The most highly exposed population using PDP and field trial data was children 1-2 years at 66% cPAD.

Table 4.2.3. Results of Chronic Dietary Exposure Analysis		
Population Subgroup	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.000588	33
All Infants (< 1 year old)	0.000293	16
Children 1-2 years old	0.001182	66
Children 3-5 years old	0.001146	64
Children 6-12 years old	0.000768	43
Youth 13-19 years old	0.000488	27
Adults 20-49 years old	0.000513	29
Females 13-49 years old	0.000537	30
Adults 50+ years old	0.000527	29

4.2.4 Cancer Dietary

Esfenvalerate has been classified a Group "E" carcinogen (no evidence of carcinogenicity). As such, a cancer dietary risk assessment is not warranted.

4.3 Water Exposure/Risk Pathway

Environmental Fate

The Environmental Fate and Effects Division (EFED) has conducted a drinking water assessment for esfenvalerate on christmas trees in Oregon and cotton in Mississippi (EFED memo D280680, I. Saheb, 2/04/02).

According to the EFED, esfenvalerate may contaminate surface waters via application spray drift and runoff in areas with large amount of annual rainfall. Esfenvalerate dissipates in the environment primarily by soil metabolism, with half-life of 95 days. Adsorption to soil appears to be significant, but EFED has no studies measuring k_d . Esfenvalerate degrades by photolysis in water with a half-life of 9 days at pH 5 which is more acidic than natural surface water, but appears to resist

photolysis in soil. The difference between in the photolytic behaviors is probably due to soil binding. Aerobic soil metabolism is a slower process, with a half-life of 95 days in silt loam soil. Anaerobic soil metabolism has a similar half-life of 77 days in the same soil. Although the isomer will racemize in solution, detectable hydrolysis at pH 5, 7, or 9 did not take place. In the field, esfenvalerate dissipated with a half-life of 14 days. No significant concentration of esfenvalerate (<0.01 - 0.02 ppm) were detected below the 0-15 cm depth. EFED currently has no monitoring data for esfenvalerate in surface or groundwater.

Estimated Environmental Concentrations (EECs)

Surface Water

The Tier II screening models PRIZM and EXAMS with the Index Reservoir and Percent Crop Area adjustment were used. Monitoring data were not available for esfenvalerate in surface water. Because EFED lacks partition coefficient data (k_d) for esfenvalerate, the k_d values measured for λ -cyhalothrin, a closely related chemical, were used instead.

Table 4.3.1 Estimated Environmental Concentrations in Surface Water for Esfenvalerate

Application Scenario	Model EECs (ug/L)	
	Christmas Trees	Cotton
Christmas Trees - 8 applications @ 0.19 lbs ai/acre, aerial application		
Cotton - 10 applications @ 0.05 lb ai/acre, aerial applicationn		
Peak (90 th percentile annual daily max)	7.54	2.0
90 th percentile annual mean	5.32	1.13
36-year overall mean	4.96	0.95

The peak EECs for esfenvalerate use on christmas trees may be used for the acute surface water-based drinking water risk assessment. The annual mean EECs may be used for the chronic surface water-based drinking water risk assessment.

Ground Water

The SCI-GROW model was used to estimate potential groundwater concentrations of esfenvalerate. Given the current maximum application rate on christmas trees (8 applications @ 0.19 lbs ai/acre, aerial application), and the linear nature of the SCI-GROW modeling, a ground water EEC of 0.009 ppb is appropriate for use in the chronic and acute exposure assessments.

4.4 Residential Exposure/Risk Pathway

Handlers Exposure

It has been determined there is a potential for exposure in residential settings during the application process for homeowners who use products containing esfenvalerate. There is also a potential for exposure from entering areas treated with esfenvalerate, such as lawns, home gardens, and inside homes that could lead to exposures for adults and children. As a result, risk assessments have been completed for both residential handler and postapplication scenarios.

It has been determined that exposure to pesticide handlers is likely during the residential use of esfenvalerate in a variety of environments, including on lawns, ornamentals, and treatments in and around homes. The anticipated use patterns and current labeling indicate several major residential exposure scenarios based on the types of equipment and techniques that can potentially be used to make esfenvalerate applications. The quantitative exposure/risk assessment developed for residential handlers is based on these scenarios. [Note: The scenario numbers correspond to the tables of risk estimate calculations included in the appendices.]

- (1) Liquid concentrates: mixing/loading/applying with low-pressure handwand sprayer,
- (2) Liquid concentrates: mixing/loading/applying with backpack sprayer,
- (3) Liquid concentrates: mixing/loading/applying with hose-end sprayer,
- (4) Liquid concentrates: mixing/loading/applying with watering can,
- (5) Wettable Powders: mixing/loading/applying with trigger pump sprayer,
- (6) Liquid ready-to-use: applying with aerosol can,
- (7) Liquid ready-to-use: applying with fogger, and
- (8) Liquid ready-to-use: applying with trigger pump sprayer.

A series of assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption and factor is detailed below. In addition to these factors, unit exposure values were used to calculate risk estimates. These unit exposure values were taken from the Pesticide Handlers Exposure Database (PHED) or from Outdoor Residential Exposure Task Force (ORETF) data.

Assumptions and Factors: The assumptions and factors used in the risk calculations include:

- Exposure factors used to calculate daily exposures to handlers were based on applicable data if available. For lack of appropriate data, values from a scenario deemed similar enough were used. In this assessment ORETF mixer/loader/applicator data for hose-end sprayers were used to assess watering can applications and ORETF mixer/loader/applicator data for pump-trigger sprayer applications is used to assess ready-to-use (RTU) pump-trigger sprayer applications. The nature of these application methods are believed to be similar enough to bridge the data.

- The HED always considers the maximum application rates allowed by labels in its risk assessments to consider what is legally possible based on the label (see Table 11).
- Residential risk assessments were not based on what could be applied in a typical workday like with the occupational risk assessments presented above. Instead, the HED based calculations on what would reasonably be treated by homeowners, such as the size of a lawn, or the size of a garden. This information was used by the HED to define chemical throughput values for handlers, which in turn were coupled with unit exposure values to calculate risks. The factors used for the esfenvalerate assessment were those dictated in the Health Effects Division Science Advisory Committee *Policy 12: Recommended Revisions To The Standard Operating Procedures For Residential Exposure Assessment*, which was completed on February 22, 2001. The following daily volumes handled and area treated, excerpted from the policy and used in each residential scenario, include:
 - One eight ounce ready-to-use aerosol can;
 - Two 7 ounce ready-to-use indoor fogger cans;
 - One one-gallon pump trigger sprayer container;
 - One bottle ready-to-use (RTU) pump sprayer;
 - 1000 square feet for premise treatments and 0.5 acres for lawn treatments for hose-end sprayers;
 - 5 gallons when mixing/loading/applying liquids outdoors with a backpack sprayer, a low pressure handwand sprayer, or watering can; and
 - 0.5 gallons when mixing/loading/applying liquids indoors with low-pressure handwand sprayer.
- The assumptions and formulae for calculating dermal and inhalation exposures from the use of ready-to-use (RTU) pressurized indoor total-release foggers were taken from the EPA's Risk Assessment for Extension of Tolerances for Synthetic Pyrethroids (11/14/97), EPA's Standard Operating Procedures for Residential Exposure Assessments (December 18, 1997), and HED's Science Advisory Council for Exposure Policy 11 (February 22, 2001). Esfenvalerate air concentration estimates are based on the findings of an air monitoring study using a cyfluthrin total-release fogger (Eberhart, D. C., Exposure Evaluation During Homeowner Use of LASER Products. January 22, 1987). ***Data compensation may be required for use of data from this study.*** Cyfluthrin is a pyrethroid which, when applied by a total-release fogger, is presumed to behave in a very similar manner to esfenvalerate. Both compounds are very non volatile (vapor pressure 5.0E-7 mm Hg at 25 degrees C (esfenvalerate) and 2.03E-9 mm Hg at 25 degrees C (cyfluthrin)), and their application rates, container sizes and fumigation procedures are identical. Use of the cyfluthrin fogger study data as a surrogate for esfenvalerate is a reasonable surrogate compared to HED SOPs.

Residential Handler, Pressurized Total-Release (RTU) Fogger: Use of total-release foggers involves placing the fogger unit in the middle of a room on sheets of newspaper to contain any heavy fall-out or drip from the unit during fogging operation. The applicator leaves the home immediately after activating the fogger. The applicator returns to the home two hours following activation to open up windows and doors and turn the HVAC unit back on. The applicator then picks up the fogger unit and newspapers for disposal. Fogger activation is not anticipated to result in exposure. However, the retrieval and disposal of the fogger unit may result in potential short-term dermal and inhalation exposure to esfenvalerate. Handlers are assumed to make a maximum of 2 applications per day.

In EPA's Risk Assessment for Extension of Tolerances for Synthetic Pyrethroids (11/14/97), it used a "film-thickness" method for determining dermal exposure from handling and disposing of the spent total-release fogger unit and newspapers upon which the unit was placed for activation. The method was taken from EPA's, "Methods for Assessing Exposure to Chemical Substances, Vol 7: Methods for Assessing Consumer Exposure to Chemical Substances, OTS, 560/5-85-007." (EPA 1987). The method assumes that a 0.002 cm film of the pesticide residue coats half of the surface area of both hands (396.5 cm²). A product density of 800 mg/cm³ is assumed as a standard value for organic solvent-based aerosol foggers (EPA Draft Standard Operating Procedures for Residential Exposure Assessments, December 1997). The formulas for determining the daily dermal and inhalation doses from retrieving and disposing of the spent total-release fogger unit is as follows:

$$\text{Dermal Dose} = [\text{SA} \times \text{D} \times \text{FT} \times \text{WF} \times \text{FA} \times \text{F}] / \text{BW}$$

where: SA = hand surface area (396.5 cm²)
 D = density (800 mg/cm³)
 FT = film thickness (0.002 cm)
 WF = weight fraction of ai (0.1% or 0.001)
 FA = fraction absorbed (25% or 0.25)
 F = use frequency (2 per day)
 BW = body weight (60 kg)

$$\text{Dermal Dose} = \frac{(396.5 \text{ cm}^2) \times (800 \text{ mg/cm}^3) \times (0.002 \text{ cm}) \times (0.001) \times (0.25) \times (2)}{60 \text{ kg}}$$

$$= 0.005287 \text{ mg/kg/day}$$

Inhalation Exposure

$$\text{Potential inhalation dose rate (PDR}_{\text{inhal}}) = [\text{C} \times \text{IR} \times \text{ET}] / \text{BW}$$

where: C = airborne concentration (0.0446 mg/m³), based on average airborne concentration of cyfluthrin for the 106 minutes immediately following the two-hour treatment period (Eberhart, 1987);
 IR = inhalation rate (1 m³/hour); based on NAFTA rate for workers engaged in light activity;
 ET = exposure time (0.5 hours)

BW = body weight (60 kg)

$$PDR_{\text{inhal}} = (0.0446 \text{ mg/m}^3) \times (1 \text{ m}^3/\text{hour}) \times (0.5 \text{ hour})/60 \text{ kg}$$

$$PDR_{\text{inhal}} = 0.0003717 \text{ mg/kg/day}$$

Residential Handler Exposure Studies: Non-cancer risk estimates were calculated using the Margin of Exposure (MOE) approach. Much of the process for residential uses is identical to that considered for the occupational assessment with a few notable exceptions (e.g., all are short-term exposures and people wear shorts and short-sleeved shirts with no gloves). The other major difference with residential risk assessments is that the uncertainty factors which define the level of risk concern also have the additional FQPA safety factor applied. In the case of esfenvalerate, the overall uncertainty factor applied to residential handler risk assessments is 300 for dermal exposures and 1000 for inhalation exposures, due to the lack of a developmental neurotoxicity study with a special protocol for pyrethroids. Therefore, a dermal MOE ≥ 300 does not exceed the HED's level of concern and an inhalation MOE ≥ 1000 does not exceed the HED's level of concern.

Since the toxicological endpoints of concern are based on the similar adverse effects, dermal and inhalation exposures and risks must be aggregated for occupational scenarios and dermal, inhalation, and incidental oral exposures and risks must be aggregated for nonoccupational scenarios. To calculate an aggregate dermal plus inhalation risk estimate, the aggregate risk index (ARI) method is used, because the uncertainty factors (UFs) are not the same for these routes of exposure. The route-specific MOEs are combined using the following formula: $ARI_{\text{total}} = 1/((1/ARI_a) + (1/ARI_b) + \dots (1/ARI_n))$; where $ARI_a = MOE_a/UF_a$, $ARI_b = MOE_b/UF_b$, and $ARI_n = MOE_n/UF_n$, which represent MOEs and UFs for each exposure route of concern. An $ARI_{\text{Total}} < 1$ exceeds HED's level of concern, and an $ARI_{\text{Total}} > 1$ is not of concern. None of the exposure scenarios result in aggregated residential handler risk estimates of concern, i.e., all $ARI_{\text{Total}} > 1$.

Non-cancer Risk Summary: The noncancer risk calculations for residential esfenvalerate handlers are included in Table 4.4.1 and summarized below.

Table 4.4.1: Esfenvalerate Residential Handler Risks Summary

Exposure Scenario	Crop or Target	Application Directed At	Application Rate ^a (lb ai/unit)	Amount Handled/day ^b	Dermal MOE ^c	Inhalation MOE ^d	Aggregate Risk Index ^e
Mixer/Loader/Applicator							
Mixing/Loading/Applying Emulsifiable Concentrates with Low Pressure Handwand (1)	indoor surfaces	indoor surfaces	0.0047 lb ai/gal dilute treats 1000 sq ft	0.5 gallons	6,400	1,500,000	21
	12-18 inch band of soil adjacent to building; 2-3 feet in height on foundation	perimeter treatments	0.0047 lb ai/gal dilute treats 1000 sq ft	5 gallons	640	150,000	2.1
	buildings, patios, porches, garages, and other areas	outdoor surfaces	0.0047 lb ai/gal dilute treats 1000 sq ft	5 gallons	640	150,000	2.1
	residential turf	foliar	0.00028 lb ai/gal treats 500 sq ft	5 gallons	11,000	2,500,000	36
	garden vegetables	foliar	0.00028 lb ai/gal dilute treats 1000 sq ft	5 gallons	11,000	2,500,000	36
Mixing/Loading/Applying Emulsifiable Concentrates with Backpack Sprayer (2)	12-18 inch band of soil adjacent to building; 2-3 feet in height on foundation	perimeter treatments	0.0047 lb ai/gal dilute treats 1000 sq ft	5 gallons	13,000	150,000	34
	buildings, patios, porches, garages, and other areas	outdoor surfaces	0.0047 lb ai/gal dilute treats 1000 sq ft	5 gallons	13,000	150,000	34
	residential turf	foliar	0.00028 lb ai/gal treats 500 sq ft	5 gallons	210,000	2,500,000	550
	garden vegetables	foliar	0.00028 lb ai/gal dilute treats 1000 sq ft	5 gallons	210,000	2,500,000	550
Mixing/Loading/Applying Emulsifiable Concentrates with Hose-End Sprayer (ORETF data) (3)	12-18 inch band of soil adjacent to building; 2-3 feet in height on foundation	perimeter treatments	0.0047 lb ai/gal dilute treats 1000 sq ft	1 gallon	29,000	1,400,000	90
	buildings, patios, porches, garages, and other areas	outdoor surfaces	0.0047 lb ai/gal dilute treats 1000 sq ft	1 gallon	29,000	1,400,000	90
	residential turf	foliar	0.034 lb ai/acre	0.5 acre	8,000	390,000	25
	garden vegetables	foliar	0.00028 lb ai/gal dilute treats 1000 sq ft	1 gallon	490,000	23,000,000	1,500
Mixing/Loading/Applying Emulsifiable Concentrates with a Watering Can (ORETF Hose-End Sprayer data) (4)	12-18 inch band of soil adjacent to building; 2-3 feet in height on foundation	perimeter treatments	0.0047 lb ai/gal dilute treats 1000 sq ft	5 gallon	5,800	280,000	18
	buildings, patios, porches, garages, and other areas	outdoor surfaces	0.0047 lb ai/gal dilute treats 1000 sq ft	5 gallon	5,800	280,000	18

Exposure Scenario	Crop or Target	Application Directed At	Application Rate ^a (lb ai/unit)	Amount Handled/day ^b	Dermal MOE ^c	Inhalation MOE ^d	Aggregate Risk Index ^e
Mixing/Loading/Applying Wettable Powders with a Pump Sprayer (5)		indoor surfaces	0.0022 lb ai/gal dilute treats 1000 sq ft	0.5 gallon	6,200	40,000	14
	12-18 inch band of soil adjacent to building; 2-3 feet in height on foundation	perimeter treatments	0.0022 lb ai/gal dilute treats 500 sq ft	1 gallon	3,100	20,000	6.8
	buildings, patios, porches, garages, and other areas	outdoor surfaces	0.0022 lb ai/gal dilute treats 500 sq ft	1 gallon	3,100	20,000	6.8
	residential turf	foliar	0.0022 lb ai/gal dilute treats 500 sq ft	1 gallon	3,100	20,000	6.8
Applying Ready to Use Formulations with Aerosol Cans (6)	indoor surfaces	indoor surfaces	0.0013 lb ai/eight ounce can	1 can	5,200	34,000	11
	outdoor surfaces	outdoor surfaces	0.00053 lb ai/eight ounce can	1 can	13,000	83,000	28
Applying Ready to Use Formulations with Foggers (7)	indoor spaces	indoor spaces	5.83E-7 lb ai/seven ounce fogger	2 foggers	1,200	4700	2.2
Applying Ready to Use Formulations with Pump Sprayers (8)	indoor surfaces	indoor surfaces	0.021 lb ai/gal RTU	0.5 gallon	2,600	150,000	8.3
	12-18 inch band of soil adjacent to building; 2-3 feet in height on foundation	perimeter treatment	0.0022 lb ai/gal dilute treats 500 sq ft	1 gallon	13,000	710,000	41
	garden vegetables	foliar	0.00028 lb ai/gal RTU	1 bottle	99,000	5,600,000	310

Footnotes:

- a Application rates are the maximum application rates determined from EPA registered labels.
- b Amount handled per day values are EPA estimates of acreage treated or gallons applied, as found in the Residential SOPs (revised 2/01).
- c Dermal MOE = NOAEL (25 mg/kg/day) / absorbed dermal daily dose (mg/kg/day), where absorbed dermal dose = daily unit exposure (mg/lb ai) x application rate x amount handled per day / body weight (60 kg adult).
- d Inhalation MOE = NOAEL (1.75 mg/kg/day) / inhalation daily dose (mg/kg/day), where absorbed inhalation dose = daily unit exposure (µg/lb ai) x application rate x amount handled per day x conversion factor (1mg/1,000 µg / body weight (60 kg adult).
- e The aggregate risk index (ARI) method is used to calculate total non-dietary risk estimates, because the uncertainty factors (UFs) are not all the same for all routes of exposure; where an $ARI_{Total} < 1$ exceeds HED's level of concern, and an $ARI_{Total} \geq 1$ is not of concern. The following formula is used to combine the route-specific MOEs: $ARI_{Total} = 1/((1/ARI_a) + (1/ARI_b) + \dots (1/ARI_n))$; where $ARI_a = MOE_a/UF_a$, $ARI_b = MOE_b/UF_b$, and $ARI_n = MOE_n/UF_n$, which represent MOEs and UFs for each exposure route of concern.

In residential settings, the HED does not consider the use of personal protective equipment (PPE) to limit exposures as a viable mitigation approach, because its use is viewed as impractical and not enforceable. As such, risk estimates are based on handlers wearing short-sleeve shirts, short pants, shoes, and socks. For residential handlers, all scenarios are **not** of concern (i.e., dermal MOEs \geq 300 and inhalation MOEs \geq 1000).

Indoor crack and crevice applications were not assessed, since the scenarios involving broadcast indoor applications using the same equipment and solutions are not of concern; i.e. with low-pressure handwand or pump-trigger applications. Exposures from crack and crevice applications should be considerably less.

Post-Application Exposure

Esfenvalerate uses are varied and include vegetable gardens, lawns, and indoor and outdoor premises treatments. As a result, a wide array of individuals of varying ages can potentially be exposed when they do activities in areas that have been previously treated or have contact with treated companion animals. In the residential exposure assessment, dermal exposures were assessed for adults and children of differing ages. Additionally, oral non-dietary ingestion exposures were assessed for children (i.e. soil ingestion, and hand-/object-to-mouth).

When the guidance in current labels and these documents is considered, it is clear that the HED should consider children of differing ages as well as adults in its assessments. It is also clear that different age groups should be considered in different situations. The populations that were considered in the assessment include:

- **Residential Adults (Homeowner):** These individuals are members of the general population that are exposed to chemicals by engaging in activities at their residences (e.g., in their lawns or gardens) and also in areas not limited to their residence (e.g., parks) previously treated with a pesticide. These kinds of exposures are attributable to a variety of activities and usually addressed by the HED in risk assessments by considering a representative activity as the basis for the exposure calculation.
- **Residential Children:** Children are members of the general population that can also be exposed in their residences (e.g., on lawns, in gardens, or inside homes) as well as other areas previously treated with a pesticide (e.g., parks). These kinds of exposures are attributable to a variety of activities such as playing outside, or playing indoors on carpet or hard flooring. Toddlers have been selected as a sentinel (or representative) population for turf and indoor surface assessments.

A series of assumptions and exposure factors served as the basis for completing the residential postapplication risk assessments. Each assumption and factor are detailed below.

The assumptions and factors used in the risk calculations are consistent with current HED policy for completing residential exposure assessments (i.e., *SOPs For Residential Exposure Assessment*). [Note: More detail about the origin of each factor can be obtained in the SOP document and associated documents such as the HED's 1999 Overview document presented to the FIFRA SAP.] The values used in this assessment include:

- There are many factors that are common to the occupational and residential postapplication risk assessments such as body weights for adults, analysis of residue dissipation data, and transfer coefficients used for the garden exposure scenarios. Please refer to the assumptions and factors in Section 2.1.2 for further information concerning these common values. [Note: The transfer coefficients have not been adjusted for the clothing that someone working in their home garden might be anticipated to wear such as shorts and short-sleeved shirt.]
- In residential settings, the HED does not use REIs or other mitigation approaches to limit exposures, because they are viewed as impractical and not enforceable. As such, risk estimates on the day of application are the key concern and the risk estimates are based on persons wearing short-sleeve shirts, short pants, shoes, and socks. The postapplication residential assessment for esfenvalerate on home lawns is based on data from a chemical-specific turfgrass transferable residue (TTR) study (MRID 45013501) and the assessment for home gardens is based on data from a chemical-specific dislodgeable foliar residue (DFR) study on broccoli (MRID 44852402).
- The HED combines or aggregates risks resulting from exposures to individual chemicals when it is likely they can occur simultaneously based on the use pattern and the behavior associated with the exposed population. Within a residential assessment, this can take two forms. The first is to add together risks for individual exposure scenarios from all likely sources of exposure such as after an application to turf or inside a home. For esfenvalerate, the HED has added together risk values (i.e., MOEs) for different kinds of exposures within the turf (dermal, hand-to-mouth, object-to-mouth, and soil ingestion) and indoor surface (dermal and hand-to-mouth) scenarios. These represent the standard set of exposures that are typically added together when chemicals are used on turf or inside, because it is logical they can co-occur. The second is to add exposures from different residential exposure scenarios that can possibly co-occur such as when a homeowner makes an application and then checks their garden for bugs a few hours later on the same day.
- Exposures to children playing on treated turf as well as adults on turf (lawn care and exercising) have been addressed using the latest HED approaches for these scenarios including:
 - 5 percent of the application rate has been used to calculate the 0-day residue levels used for defining risks from hand-to-mouth behaviors, measured TTR values are

- not used because of differences in transferability versus what would be expected during hand-to-mouth behaviors;
 - 20 percent of the application rate has been used to calculate the 0-day residue levels used for defining risks from object-to-mouth behaviors, measured TTR values are not used because of differences in transferability versus what would be expected during hand-to-mouth behaviors, a higher percent transfer has been used for object-to-mouth behaviors because it involves a teething action believed to be more analogous to DFR/leaf wash sample collection where 20 percent is also used;
 - the average predicted TTR value quantified in MRID 451143-01 has been used to complete the dermal exposure calculations;
 - the transfer coefficients used are those presented at the 1999 HED presentation before the FIFRA Science Advisory Panel that have been adopted in routine practice by the HED;
 - toddlers are expected to weigh 15 kg;
 - hand-to-mouth exposures are based on a frequency of 20 events/hour and a surface area per event of 20 cm² representing the palmar surfaces of three fingers;
 - saliva extraction efficiency is 50 percent meaning that every time the hand goes in the mouth approximately ½ of the residues on the hand are removed;
 - object-to-mouth exposures are based on a 25 cm² surface area;
 - exposure durations are expected to be 2 hours based on information in the HED's *Exposure Factors Handbook*;
 - soil residues are contained in the top centimeter and soil density is 0.67 mL/gram; and
 - dermal, hand- and object-to-mouth, and soil ingestion are added together to represent an overall risk from exposure to turf while granular ingestion is considered to be a much more episodic behavior and is considered separately by the HED.
- Exposures to youths and adults working in home gardens have been addressed using the latest HED approaches for this scenario including:
 - youth-aged children are considered along with adults;
 - 12 year old youth are expected to weigh 39.1 kg;
 - exposure durations are expected to be 40 minutes;
 - transfer coefficients for youth were calculated by adjusting the appropriate adult transfer coefficients by a 50% factor as has been done by the HED since the inception of the *SOPs For Residential Exposure Assessment*;
 - the combination of adjusting transfer coefficients for youth-aged children and using appropriate body weights for the age group results in dose levels that are slightly lower than that of adults in the same activity (the TC reduction and body weight reduction is essentially a 1:1 ratio); and
 - the DFR data used for the assessments are based on a chemical-specific broccoli DFR study.

- Postapplication residential risks are based generally on maximum application rates or values specified in the *SOPs For Residential Exposure Assessment*.
- The Jazzercise approach is the basis for the dermal transfer coefficients as described in the Agency's Series 875 guidelines, *SOPs For Residential Exposure Assessment*, and the 1999 FIFRA SAP Overview document
- For space, surface and crack and crevice broadcast sprays, the labels indicate that solutions are mixed, loaded and applied in an identical manner using similar equipment, and at the same maximum application rate. The only discernible difference in exposure characteristics among these application scenarios is the amount of space treated. Therefore, the same HED residential SOP was used to calculate risk estimates for broadcast sprays versus crack and crevice sprays. It is reasonable to assume that exposures from indoor crack and crevice sprays would be considerably lower than those for the indoor broadcast space and surface sprays, because a much smaller area is treated. Based on conversations with senior HED exposure science advisory committee (ExpoSAC) staff, HED assumed that the crack and crevice sprays would result in 50% of the exposure from broadcast space and surface sprays. Therefore, the MOEs for crack and crevice uses are simply double those for the broadcast space and surface sprays. However, please note that the risk estimates for crack and crevice uses should be considered to be very conservative estimates, since actual exposures may be considerably less.

Postapplication Studies: Two esfenvalerate-specific studies were used in the postapplication residential exposure and risk assessment: a turf transferable residue study (MRID 450135-01) and a dislodgeable foliar residue study on broccoli (MRID 448524-02). The broccoli study is summarized in the section on occupational postapplication studies above. The turf study, which is briefly summarized below, quantifies esfenvalerate-specific turf transferable residues in three different states.

MRID 45013501 (turf transferable residue data): A TTR study was conducted at individual sites in California using the ORETF roller sampling method. Evercide® Esfenvalerate 35% WP, a wettable powder containing 35 percent active ingredient (ai), was applied twice using a tractor outfitted with a pump and hydraulic boom to a dwarf turf grass test plot. The maximum application rate of 0.188 lb ai/acre was applied. Turf transferable residues (TTR) were sampled as soon as the spray dried and 1, 2, 5, 7, 14, 21, 28, and 35 days after the final treatment (DAT). At each sampling interval, three samples were randomly collected from each of the three treated and one untreated turf plots for each sampling period. The study author reported that detectable TTR values were found on turf samples on the day of application ($374.56 \mu\text{g}$ or $0.0672 \mu\text{g}/\text{cm}^2$) and up to 35 days after treatment (DAT). TTR values for esfenvalerate declined to $5.71 \mu\text{g}$ or $0.001 \mu\text{g}/\text{cm}^2$ by DAT-35. In calculating mean residues, the registrant used the limit of quantitation

(LOQ) for values below the LOQ. The data and the results of the pseudo-first order statistical analysis are summarized below in Table 12. The predicted DAT-0 residue value of 0.038 $\mu\text{g}/\text{cm}^2$ was used to estimate risk on turf.

3.2.3 Residential Postapplication Exposure and Non-cancer Risk Estimates

The residential postapplication exposure and non-cancer risk calculations are presented in this section. Non-cancer risks were calculated using the Margin of Exposure (MOE), which is a ratio of the body burden to the toxicological endpoint of concern. Exposures were calculated by considering the potential sources of exposure (i.e., DFRs on garden plants, TTRs on lawns, and transferable residues on indoor surfaces) then calculating dermal and non-dietary ingestion exposures. The major difference with residential risk assessments is that the uncertainty factor which defines the level of risk concern also has to consider application of the additional FQPA special safety and uncertainty factors specified by the legislation. The overall uncertainty factors applied to esfenvalerate for residential postapplication risk assessments are 300 for dermal exposure and 1000 for oral and inhalation exposures, due to the lack of a developmental neurotoxicity study with a special protocol for pyrethroids.

Table 3.2.3: Residential Risk Estimates for Postapplication Exposure to Esfenvalerate

Exposure Scenario	Route of Exposure	Population	Application Rate ^a	MOE ^b
Outdoors				
Hand to Mouth Activity on Turf ^c	Oral	Toddler	0.19 lb ai/acre	620
			0.034 lb ai/acre	3,400
Object to Mouth Activity on Turf ^d	Oral	Toddler	0.19 lb ai/acre	2,500
			0.034 lb ai/acre	14,000
Incidental Soil Ingestion ^e	Oral	Toddler	0.19 lb ai/acre	180,000
			0.034 lb ai/acre	1,000,000
High Contact Activities on Turf ^f	Dermal	Toddler	0.19 lb ai/acre	940
			0.034 lb ai/acre	5,200
		Adult	0.19 lb ai/acre	1,300
			0.034 lb ai/acre	7,500
Mowing Turf ^g	Dermal	Adult	0.19 lb ai/acre	39,000
			0.034 lb ai/acre	220,000
Gardening ^h	Dermal	Adult	0.012 lb ai/acre	6,700

Exposure Scenario	Route of Exposure	Population	Application Rate ^a	MOE ^b
		Youth (10-12 yrs)	0.012 lb ai/acre	17,000
Indoors				
Hand to Mouth Activity from Indoor Carpet or Hard Surfaces from Broadcast Surface Sprays ^c	Oral	Toddler	0.0000047 lb ai/sq ft	140
Hand to Mouth Activity from Indoor Carpet or Hard Surfaces from Crack and Crevice Sprays ^c	Oral	Toddler	0.0000047 lb ai/sq ft	280
Hand to Mouth Activity from Indoor Carpet or Hard Surfaces from Broadcast Surface Sprays ^d	Dermal	Toddler	0.0000047 lb ai/sq ft	68
		Adult	0.0000047 lb ai/sq ft	97
Hand to Mouth Activity from Indoor Carpet or Hard Surfaces from Crack and Crevice Sprays ^d	Dermal	Toddler	0.0000047 lb ai/sq ft	140
		Adult	0.0000047 lb ai/sq ft	200
High Contact Activity on Treated Indoor Carpets and Hard Surfaces from RTU Fogger ^e	Dermal	Toddler	5.83E-7 lb ai/sq ft	550
		Adult	5.83E-7 lb ai/sq ft	790
Exposure from RTU Fogger ^e	Inhalation	Toddler	Airborne Concentration 0.00018 mg/cu m	15,000
		Adult	Airborne Concentration 0.00018 mg/cu m	49,000
Hand to Mouth Activity from Indoor Carpets and Hard Surfaces from RTU Fogger ^e	Oral	Toddler	5.83E-7 lb ai/sq ft	1,100

Footnotes:

- ^a Application rates represent maximum label rates from current EPA registered labels.
- ^b Margins of exposure (MOEs) calculated using residues which would be found on day of treatment. MOE = NOAEL (25 or 1.75 mg/kg/day)/Exposure Dose (mg/kg/day).
- ^c Hand-to-Mouth on Turf Dose Calculation: oral dose to child (1-6 year old) on the day of treatment (mg/kg/day) = [Application rate lb ai/A] x conversion factor (11.2) to convert lb ai/A to $\mu\text{g}/\text{cm}^2$ (1 lb ai/A x $4.54\text{E}+8 \mu\text{g}/\text{lb}$ x $2.47\text{E}-8\text{cm}^2 = 11.2$) x fraction of residue dislodgeable (5%) x median surface area for 1-3 fingers (20 cm^2 /event) x hand-to-mouth rate (20 events/hour) x exp. time (2 hr/day) x 50% saliva extraction factor x 0.001 mg/ μg / bw (15 kg child).
- ^d Object to Mouth Activity on Turf Dose Calculation: oral dose to child (1-6 year old) on the day of treatment = [Application rate (lb ai/A) x conversion factor (11.2) to convert lb ai/A to $\mu\text{g}/\text{cm}^2$ (1 lb ai/A x $4.54\text{E}+8 \mu\text{g}/\text{lb}$ x $2.47\text{E}-8\text{cm}^2 = 11.2$) x fraction of residue dislodgeable (20%) x ingestion rate of grass (25 cm^2 /day) x 0.001 mg/ μg] / bw (15 kg child).
- ^e Incidental Soil ingestion - Dose Calculation: oral dose to child (1-6 year old) on the day of treatment (mg/kg/day) = [(application rate (lb ai/acre) x fraction of residue retained on uppermost 1 cm of soil

(100% or 1.0/cm) x 4.54E+08 $\mu\text{g}/\text{lb}$ conversion factor x 2.47E-08 acre/cm² conversion factor x 0.67 cm³/g soil conversion factor) x 100 mg/day ingestion rate x 1.0E-06 g/ μg conversion factor] / bw (15 kg).

High Dermal Contact on Turf - Absorbed Dose Calculation: $\text{TTR}_{\text{normalized}} (\mu\text{g}/\text{cm}^2)$ x Transfer Coefficient (14,500 cm²/hr for adults and 5,200 cm²/hr for children (1-6 year old)) x conversion factor (1 mg/1,000 μg) x exposure time (2 hrs/day) / body weight (60 kg adult or 15 kg child). TTR source: Esfenvalerate study MRID 45013501.

Low Dermal Contact on Turf (Mowing) - Absorbed Dose Calculation: $\text{TTR}_{\text{normalized}} (\mu\text{g}/\text{cm}^2)$ x Transfer Coefficient (500 cm²/hr) x conversion factor (1 mg/1,000 μg) x exposure time (2 hrs/day) / body weight (60 kg adult). TTR source: Esfenvalerate study MRID 45013501.

Gardening - Absorbed Dose Calculation: DFR ($\mu\text{g}/\text{cm}^2$) x Transfer Coefficient (adult = 10,000 cm²/hr and youth = 5,000 cm²/hr) x conversion factor (1 mg/1,000 μg) x exposure time (0.67 hrs/day for adults and 0.33 hrs/day for youth) / body weight (60 kg adult or 39 kg youth (10-12 year old)). DFR source: Esfenvalerate broccoli study MRID 44852402.

Hand to Mouth Activity from Indoor Carpet and Hard Surfaces from Aerosol - Dose Calculation: oral dose to child (1-6 year old) on the day of treatment (mg/kg/day) = [application rate (lb ai/acre) x fraction of residue dislodgeable from potentially wet hands (5%) x 4.95E+5 (conversion factor to convert lb ai/square feet to $\mu\text{g}/\text{cm}^2$)] x median surface area for 1-3 fingers (20 cm²/event) x hand-to-mouth rate (20 events/hour) x exp. time (4 hr/day) x 50% saliva extraction factor x 0.001 mg/ μg] / bw (15 kg child). *

Deposition of residues from crack and crevice applications is assumed to result in only 50% as much residue as compared to broadcasted sprays.

High Contact Activity on Treated Indoor Carpet - Absorbed Dose Calculation: [application rate (lb ai/square feet) x fraction of application rate available as dislodgeable residue (5%) x Transfer Coefficient (16,700 cm²/hr for adults or 6,000 cm²/hr for child (1-6 year old)) x exposure time (8 hours/day for carpets and 4 hours/day for hard surfaces) x conversion factor (4.54E+8 $\mu\text{g}/\text{lb}$) x conversion factor (1.08E-3 ft²/cm²) x 1 mg/1,000 μg] x / body weight (60 kg adult or 15 kg child). * ***Deposition of residues from crack and crevice applications is assumed to result in only 50% as much residue as compared to broadcasted sprays.***

High Contact Activity on Treated Indoor Hard Surfaces & Carpets from RTU Foggers - Dose Calculation: [application rate (lb ai/square feet) x fraction of application rate available as dislodgeable residue (10%) x Transfer Coefficient (16,700 cm²/hr for adults or 6,000 cm²/hr for child (1-6 year old)) x exposure time (4 hours/day) x conversion factor (4.54E+8 $\mu\text{g}/\text{lb}$) x conversion factor (1.08E-3 ft²/cm²) x 1 mg/1,000 μg] / body weight (60 kg adult or 15 kg child).

Indoor Inhalation Exposure from RTU Fogger - Dose Calculation: [airborne concentration from a cyfluthrin study (mg/cu m) x inhalation rate (0.5 cu m/hr for adults, 0.4 cu m/hr for children) x exposure time (24 hours) / body weight (60 kg adult or 15 kg child).

Hand to Mouth Activity from Indoor Carpet and Hard Surfaces from RTU Fogger - Dose Calculation: oral dose to child (1-6 year old) on the day of treatment (mg/kg/day) = [application rate (lb ai/acre) x fraction of residue dislodgeable from potentially wet hands (5%) x 4.95E+5 (conversion factor to convert lb ai/square feet to $\mu\text{g}/\text{cm}^2$)] x median surface area for 1-3 fingers (20 cm²/event) x hand-to-mouth rate (20 events/hour) x exp. time (4 hr/day) x 50% saliva extraction factor x 0.001 mg/ μg] / bw (15 kg child).

The HED considered a number of residential postapplication exposure scenarios covering different segments of the population, including toddlers, youth-aged children, and adults. MOEs are of concern for several scenarios, because they exceed the HED's level of concern (i.e., Oral MOE < 1000; Dermal MOE < 300) for non-cancer risk assessments in non-occupational settings. These scenarios include applications to lawns using the wettable powder formulation and applications indoors from space, surface and crack and crevice broadcast sprays. Exposures of concern include:

- dermal exposures to adults and children from activities on treated indoor surfaces from applications by broadcast sprays (MOEs of 97 for adults and 68 for toddlers) or crack and crevice sprays (MOEs of 200 for adults and 140 for toddlers),
- oral exposures to toddlers (MOE of 620) from transfer of pesticide from lawns to hand to mouth following wettable powder applications,
- oral exposures to toddlers from transfer of pesticide from indoor surfaces to hand to mouth from broadcast spray (MOE of 140) and crack and crevice spray (MOE of 280) applications.

The residential postapplication scenarios where risks are not of concern (i.e., Oral and Inhalation MOEs \geq 1000; Dermal MOEs \geq 300) include:

- dermal exposures to adults and children from high contact activities on treated lawns following liquid concentrate applications,
- dermal exposures to adults and children from high contact activities on treated lawns following wettable powder applications,
- dermal exposures to adults from mowing lawns,
- dermal exposures to adults and youth from gardening,
- oral exposures to toddlers from incidental soil ingestion,
- oral exposures to toddlers from transfer of pesticides from object to mouth on treated lawns following liquid concentrate or wettable powder applications,
- oral exposures to toddlers from transfer of pesticides from hand to mouth on treated lawns following liquid concentrate applications,
- dermal exposures to adults and children from activities on treated indoor surfaces from applications by foggers,
- oral exposures to toddlers from transfer of pesticides from hand to mouth from indoor surfaces from fogger applications, and
- inhalation exposures to adult or toddlers from indoor air following fogger application.

Aggregate Risk Estimates for Residential Scenarios

The HED aggregates risk values resulting from separate handler plus postapplication exposure scenarios when it is likely they can occur simultaneously based on the use-pattern and the behavior associated with the exposed population. These aggregated values are conservative screening level risk estimates. For esfenvalerate, the HED aggregated risk values (i.e., MOEs) for postapplication exposures of toddlers associated with turf applications by combining risks from dermal exposures to turfgrass with risks from oral exposures via transfer of residues from turf to hands to mouth. In a second tier aggregation, HED combined the above toddler turfgrass aggregated risks with risks from oral exposures via transfer from turf directly to mouth, and risks from oral exposures via incidental soil ingestion. Similarly, HED aggregated risk values for postapplication exposures to toddlers associated with indoor surface treatments by combining risks from dermal exposure to carpet or hard surfaces with risks from oral exposures via transfer from indoor surfaces to hands to mouth.

For adults, the HED aggregated risks from handler exposures to adults applying esfenvalerate to turfgrass with risks from postapplication exposures from mowing turfgrass and with risks from postapplication exposures through high contact activities on turfgrass. In addition, HED aggregated risks from handler exposures to adults applying esfenvalerate to vegetable gardens with risks from postapplication exposures to adults involved in gardening tasks.

The aggregate risk index (ARI) method is used to calculate total non-dietary risk estimates, because the uncertainty factors (UFs) are not all the same for all routes of exposure. The route-specific MOEs are combined using the following formula: $ARI_{total} = 1/((1/ARI_a) + (1/ARI_b) + \dots (1/ARI_n))$; where $ARI_a = MOE_a/UF_a$, $ARI_b = MOE_b/UF_b$, and $ARI_n = MOE_n/UF_n$, which represent MOEs and UFs for each exposure route of concern. An $ARI_{Total} < 1$ exceeds HED's level of concern, and an $ARI_{Total} > 1$ is not of concern. The exposure scenarios that result in aggregated residential risk estimates of concern, i.e., $ARI_{Total} < 1$, include:

- toddlers on turfgrass following applications of the wettable powder formulation: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth
- toddlers on turfgrass following applications of the wettable powder formulation: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth plus exposures from transfer of pesticides from objects to mouth plus exposures from soil ingestion.
- adults who apply indoor broadcast or RTU sprays and perform high contact activities within those premises within 24 hours after treatments.
- toddlers on indoor surfaces from foggers or sprays, including dermal exposures plus exposures from transfer of pesticides from surfaces to hands to mouth.

The exposure scenarios that result in aggregated residential risk estimates not of concern, i.e., $ARI_{Total} \geq 1$, include:

- toddlers on turfgrass following applications of the liquid concentrate: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth;
- toddlers on turfgrass following applications of the liquid concentrate: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth plus exposures from transfer of pesticides from objects to mouth plus exposures from soil ingestion.
- adults who apply the wettable powder formulation with a pump-trigger sprayer plus either mow the treated lawn or have high contact activities on treated lawns.
- adults who apply the liquid concentrate with a hose-end sprayer plus either mow the treated lawn or have high contact activities on treated lawns.
- adults who apply with an aerosol can to vegetable gardens plus perform gardening tasks.

Table 14: Aggregate Risk Estimates for Esfenvalerate Residential Scenarios

Exposure Scenario				Margins of Exposure (MOEs)			ARI Total Non-Dietary Risk ^a
				Dermal (UF=300)	Inhalation (UF=1000)	Oral (Non-Dietary) (UF=1000)	
Indoor Surface Spray (0.0000047 lb ai/sq ft)	Adult	Handler	Broadcast Spray	6400	1,500,000	N/A	0.32
		Postapp	High Contact Activity	97	N/A	N/A	
	Adult	Handler	RTU Spray	2,600	4200	N/A	0.29
		Postapp	High Contact Activity	97	N/A	N/A	
	Toddler	Postapp	High Contact Indoor Activity on Treated Carpet or Hard Surface	68	N/A	N/A	0.14
			Hand to Mouth	N/A	N/A	140	
Indoor Fogger (5.83E-7 lb ai/sq ft)	Adult	Handler	Fogger	1200	4700	N/A	1.2
		Postapp	High Contact Activity	790	49,000	N/A	
	Toddler	Postapp	High Contact Activity	550	N/A	N/A	0.66
			Breathing	N/A	15000	N/A	
			Hand to Mouth	N/A	N/A	1100	
Garden: spray (0.012 lb ai/acre) on gardens	Adult	Handler	Hose-end Application	490,000	23,000,000	N/A	22
		Postapp	Gardening	6700	N/A	N/A	
Turf: homeowner applied wettable powder with trigger pump sprayer + post-application activities (0.19 lb ai/acre)	Adult	Handler	Trigger Pump Sprayer Application	3100	20,000	N/A	6.5
		Postapp	Mowing	39,000	N/A	N/A	
	Adult	Handler	Trigger Pump Sprayer Application	3100	20,000	N/A	2.6
		Postapp	High Contact Activity on Treated Turf	1300	N/A	N/A	
Turf: wettable powder (0.19 lb ai/acre) on turf	Toddler	Postapp	High Contact Activity on Treated Turf	940	N/A	N/A	0.52
			Hand to Mouth	N/A	N/A	620	
	Toddler	Postapp	High Contact Activity on Treated Turf	940	N/A	N/A	0.43
			Hand to Mouth	N/A	N/A	620	
			Object to Mouth	N/A	N/A	2500	
Turf : homeowner applied spray with hose-end + postapplication activities (0.034 lb ai/acre)	Adult	Handler	Hose-end Application	8000	390,000	N/A	24
		Postapp	Mowing	220,000	N/A	N/A	
	Adult	Handler	Hose-end Application	8000	390,000	N/A	12
		Postapp	High Contact Activity on Treated Turf	7500	N/A	N/A	

Exposure Scenario				Margins of Exposure (MOEs)			ARI Total Non-Dietary Risk ^a
				Dermal (UF=300)	Inhalation (UF=1000)	Oral (Non-Dietary) (UF=1000)	
Turf: spray (0.034 lb ai/acre) on turf	Toddler	Postapp	High Contact Activity on Treated Turf	5200	N/A	N/A	2.8
			Hand to Mouth	N/A	N/A	3400	
	Toddler	Postapp	High Contact Activity on Treated Turf	5200	N/A	N/A	2.4
			Hand to Mouth	N/A	N/A	3400	
			Object to Mouth	N/A	N/A	14,000	
			Incidental Soil Ingestion	N/A	N/A	1000000	

^aThe aggregate risk index (ARI) method is used to calculate total non-dietary risk estimates, because the uncertainty factors (UFs) are not all the same for all routes of exposure; where an $ARI_{Total} < 1$ exceeds HED's level of concern, and an $ARI_{Total} \geq 1$ is not of concern. The following formula is used to combine the route-specific MOEs: $ARI_{total} = 1 / ((1/ARI_a) + (1/ARI_b) + \dots (1/ARI_n))$; where $ARI_a = MOE_a / UF_a$, $ARI_b = MOE_b / UF_b$, and $ARI_n = MOE_n / UF_n$, which represent MOEs and UFs for each exposure route of concern.

4.5 Spray Drift

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 ground application methods. 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. 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 air-blast 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 and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

The current uses for esfenvalerate encompass agricultural use sites and non-occupational (residential) uses. Therefore, when addressing aggregate exposures, the dietary pathways of food and drinking water plus the residential uses were considered.

Under OPP's aggregate risk assessment for esfenvalerate, HED has compared estimates of concentrations of esfenvalerate in drinking water to Drinking Water Levels of Comparison (DWLOCs). A DWLOC is the portion of the acute PAD or chronic PAD remaining after estimated dietary (food only) exposures have been subtracted and the remaining exposure has been converted to a concentration (ppb). This concentration value (DWLOC) represents the available or allowable exposure through drinking water for esfenvalerate. Under the acute risk assessment, the remaining portion of the acute PAD is based on dietary exposures at the 99.9th percentile of exposure for each relevant population subgroup considered. Under the chronic risk assessment, the remaining portion of the chronic PAD is based on average dietary exposures for each relevant population subgroup considered. Maximum concentrations of esfenvalerate that are less than acute DWLOCs, and average concentrations of esfenvalerate that are less than chronic DWLOCs, do not exceed HED's level of concern. DWLOC values vary for population subgroups depending on dietary exposure through foods for each subgroup, and the assumptions made about drinking water consumption, and body weights for each subgroup.

5.1 Acute Aggregate Risk

Acute risk estimates associated with exposure to esfenvalerate residues in food do not exceed HED's level of concern. Estimates of exposures from food were taken from the dietary exposure model results described above (Section 4.2.2). These exposure estimates are based on USDA PDP monitoring data, field trial data, estimated percent crop treated information, and processing factors and may be considered highly refined. Based on the highly refined dietary assessment results, the acute dietary risk estimates are below the Agency's level of concern at the 99.9th exposure percentile for the general U.S. population (37% aPAD) and all population subgroups. The most highly exposed population subgroup using PDP monitoring data, percent crop treated data, and processing factors, where available, was children 1-2 years old at 67% aPAD.

For the Christmas tree scenario representing the maximum labeled use rate for esfenvalerate, the exposure assessment for surface water used conservative assumptions for percent cropped area (PCA = 0.87) and surrogate data for the soil water partition coefficient, which is also considered conservative. Although adsorption of esfenvalerate to soil appears to be significant, no soil water adsorption coefficient for esfenvalerate is available from the environmental fate database. Given that the Christmas tree use is limited, representing 12% of the esfenvalerate market, and the conservatisms assumed in the exposure assessment, HED does

not consider the lowest acute DWLOC of 6 ppb for acute risk and a peak estimated environmental concentration (EEC) of 7.5 ppb to represent a significant risk.

Cotton represents the next highest labeled use rate for esfenvalerate, and the lowest acute DWLOC of 6 ppb for acute risk is higher than the peak EEC of 2.0 ppb for cotton; therefore, there is no acute aggregate risk of concern for cotton uses of esfenvalerate. Other uses of esfenvalerate with lower use rates are expected to result in EECs below the acute DWLOC of 6ppb, and should not be of concern.

5.2 Short- and Intermediate-Term Aggregate Risk

Since the toxicological endpoints of concern are based on the similar adverse effects, dermal and inhalation exposures and risks must be aggregated for occupational scenarios and dermal, inhalation, and incidental oral exposures and risks must be aggregated for nonoccupational scenarios. For non-occupational scenarios, aggregate risks will be estimated using the Aggregate Risk Index (ARI). The aggregate risk index (ARI) method is used to calculate total non-dietary risk estimates, because the uncertainty factors (UFs) are not all the same for all routes of exposure. The route-specific MOEs are combined using the following formula: $ARI_{total} = 1/((1/ARI_a) + (1/ARI_b) + \dots (1/ARI_n))$; where $ARI_a = MOE_a/UF_a$, $ARI_b = MOE_b/UF_b$, and $ARI_n = MOE_n/UF_n$, which represent MOEs and UFs for each exposure route of concern. An $ARI_{Total} < 1$ exceeds HED's level of concern, and an $ARI_{Total} > 1$ is not of concern. The exposure scenarios that result in aggregated residential risk estimates of concern, i.e., $ARI_{Total} < 1$, include:

- toddlers on turfgrass following applications of the wettable powder formulation: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth
- toddlers on turfgrass following applications of the wettable powder formulation: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth plus exposures from transfer of pesticides from objects to mouth plus exposures from soil ingestion.
- adults who apply indoor broadcast or RTU sprays and perform high contact activities within those premises within 24 hours after treatments.
- toddlers on indoor surfaces from foggers or sprays, including dermal exposures plus exposures from transfer of pesticides from surfaces to hands to mouth.

Because these aggregate residential risk exposures alone exceeds HED's level of concern, additional exposure to esfenvalerate in drinking water and food would cause risk estimates to further exceed the levels of concern. Therefore, HED will not conduct a short- and intermediate-term aggregate risk assessment for the scenarios mentioned above.

The exposure scenarios that result in aggregated residential risk estimates not of concern, i.e., $ARI_{Total} \geq 1$, include:

- toddlers on turfgrass following applications of the liquid concentrate: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth;
- toddlers on turfgrass following applications of the liquid concentrate: dermal exposures plus exposures from transfer of pesticides from turf to hands to mouth plus exposures from transfer of pesticides from objects to mouth plus exposures from soil ingestion.
- adults who apply the wettable powder formulation with a pump-trigger sprayer plus either mow the treated lawn or have high contact activities on treated lawns.
- adults who apply the liquid concentrate with a hose-end sprayer plus either mow the treated lawn or have high contact activities on treated lawns.
- adults who apply with an aerosol can to vegetable gardens plus perform gardening tasks.

Since the above uses do not exceed HEDs level of concern, an aggregate short- and intermediate-term risk was conducted with food and water. Upon aggregation with food and water exposures, the liquid formulations used on turf result in risk estimates of concern, i.e. DWLOCs are less than the EECs for water. However, for liquid spray formulations used in gardens, aggregation with food and water exposures result in DWLOCs values above EECs and therefore the risk estimates are not of concern for this scenario. Results are show in Table 5.2.1.

Table 5.2.1 Short- and Intermediate-Term DWLOC Calculations.							
Population Subgroup	cPAD mg/kg/day	Food Exp mg/kg/day	Aggregate Residential Exp mg/kg/day	Max Water Exp mg/kg/day ^a	Ground Water EEC (µg/L)	Surface Water EEC (µg/L)	DWLOC (µg/L) ^b
Liquid Formulations Used on Turf							
General U.S. Population	0.0018	0.000588	0.003	0	0.009	5.32	0
Children 1-2 years old	0.0018	0.001182	0.0053	0	0.009	5.32	0
Females 13-49 years old	0.0018	0.000537	0.003	0	0.009	5.32	0
Liquid Spray for Use in Gardens							
General U.S. Population	0.0018	0.000588	0.00373	0.001	0.009	5.32	38
Females 13-49 years old	0.0018	0.000537	0.00373	0.0012	0.009	5.32	35

^a Maximum water exposure (mg/kg/day) = [(chronic PAD (mg/kg/day) - food exposure (mg/kg/day))]

^b DWLOC(µg/L) = [maximum water exposure (mg/kg/day) x body weight (kg)] ÷ [water consumption (L) x 10⁻¹ mg/µg]. Consumption = 1 L/day for populations <13 years old and 2 L/day for populations ≥ 13 years old. Default body weights = 70 kg for adult male population groups greater than 19 yrs and general U.S. population, 60 kg for females (13-49) and youth (13-19) ≥ 13 years old, and 10 kg for all others. Values are rounded to 2 significant figures.

5.3 Chronic Aggregate Risk

Chronic aggregate risk estimates associated with exposure to esfenvalerate residues in food and water do not exceed HED's level of concern. Estimates of exposure from food were

taken from the dietary exposure model results described above (Section 4.2.3). These exposure estimates are based on USDA PDP monitoring data, field trial data, estimated percent crop treated information, and processing factors and may be considered highly refined.

For considering exposure to residues of esfenvalerate in drinking water, HED has calculated Drinking Water Levels of Comparison (DWLOCs). These values are the maximum concentration of a chemical that can occur in drinking water after taking into account exposures to residues from other pathways and sources. The DWLOCs are compared against the modeled EECs provided by the EFED (see Section 4.3). DWLOC values that are greater than the EECs indicate that aggregate exposures are unlikely to exceed HED’s level of concern.

As shown in Table 5.3.1, the chronic DWLOCs for the general U.S. population and all of the representative population subgroups modeled by DEEM-FCID are greater than both the surface water and ground water EECs. Chronic aggregate risk estimates associated with exposure to esfenvalerate residues in food and water do not exceed HED’s level of concern.

Population Subgroup	cPAD mg/kg/day	Food Exp mg/kg/day	Max Water Exp mg/kg/day ^a	Ground Water EEC (µg/L)	Surface Water EEC (µg/L)	DWLOC (µg/L) ^b
General U.S. Population	0.0018	0.000588	0.001212	0.009	5.32	42
All Infants (< 1 year old)	0.0018	0.000293	0.001507	0.009	5.32	15
Children 1-2 years old	0.0018	0.001182	0.000618	0.009	5.32	6
Children 3-5 years old	0.0018	0.001146	0.000654	0.009	5.32	7
Children 6-12 years old	0.0018	0.000768	0.001032	0.009	5.32	10
Youth 13-19 years old	0.0018	0.000488	0.001312	0.009	5.32	46
Adults 20-49 years old	0.0018	0.000513	0.001287	0.009	5.32	45
Females 13-49 years old	0.0018	0.000537	0.001263	0.009	5.32	38
Adults 50+ years old	0.0018	0.000527	0.001273	0.009	5.32	45

^aMaximum water exposure (mg/kg/day) = [(chronic PAD (mg/kg/day) - food exposure (mg/kg/day)]

^b DWLOC(µg/L) = [maximum water exposure (mg/kg/day) x body weight (kg)] ÷ [water consumption (L) x 10⁻³ mg/µg]. Consumption = 1 L/day for populations <13 years old and 2 L/day for populations ≥ 13 years old. Default body weights = 70 kg for adult male population groups greater than 19 yrs and general U.S. population, 60 kg for females (13-49) and youth (13-19) ≥ 13 years old, and 10 kg for all others. Values are rounded to 2 significant figures.

5.5 Cancer Risk

Esfenvalerate has been classified a Group “E” carcinogen (no evidence of carcinogenicity). As such, a cancer aggregate risk assessment is not warranted.

6.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of the FFDCFA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Esfenvalerate is a member of the pyrethroid class of pesticides. This class also includes permethrin, cypermethrin, cyfluthrin, fluvalinate, bifenthrin, fenpropathrin, and lambda-cyhalothrin among others. The pyrethroids, as a group, have been determined to share a common mechanism of toxicity (July 2001 memo from Office Director Marcia Mulkey). However, a cumulative risk assessment has not been performed as part of this review because the Agency is currently examining approaches for completing this type of assessment. EPA's Office of Research and Development is currently investigating the pharmacokinetics and pharmacodynamics of pyrethroids which will provide a more solid scientific foundation for the cumulative assessment of these pesticides in the future.

7.0 OCCUPATIONAL EXPOSURE AND RISK

7.1 Occupational Handler

For the agricultural crop scenarios of the proposed new use sites (i.e. for bok choy, Brussels sprouts, canola, cardoon, pistachios and sweet potato) using PHED data, the risks are not a concern at baseline attire for applying sprays with groundboom and airblast equipment and for flagging to support aerial applications. The risks to handlers mixing and loading to support applications to agricultural crops (including chemigation applications) are not a concern with the addition of chemical-resistant gloves to baseline attire. EPA has insufficient data to assess exposures to pilots in open cockpits. Risks to pilots in enclosed cockpits (engineering control scenario) were not a concern for all agricultural crop scenarios.

When data were available to assess risks, risks to occupational handlers from proposed new uses of esfenvalerate are below the HED's level of concern for noncancer risk assessments (i.e., $MOE \geq 100$) at either baseline attire (i.e., long-sleeve shirt, long pants, shoes, and socks), or with the addition of personal protective equipment for dermal protection (i.e., chemical-resistant gloves).

Table 7.1 Esfenvalerate Occupational Handler Risk Summary for Proposed New Uses

Exposure Scenario	Crop or Target	Application Directed At	Application Rate ^a (lb ai/unit)	Units Treated Daily ^b	Baseline Dermal + Baseline Inhalation MOE ^c	PPE-G Dermal + Baseline Inhalation MOE ^d	PPE-G,DL Dermal + Baseline Inhalation MOE ^e	Combined Eng Cont Dermal + Inhalation MOE ^f
Mixer/Loader								
Mixing/Loading Emulsifiable Concentrates for Aerial Application (1a)	canola	foliar	0.05 lb ai/acre	1200 acres	8.6	630	-	-
	pistachios	foliar	0.1 lb ai/acre	350 acres	15	1100	-	-
	cardoons, brussel sprouts, sweet potato	foliar	0.05 lb ai/acre	350 acres	30	2100	-	-
Mixing/Loading Emulsifiable Concentrates for Chemigation Application (1b)	pistachios	foliar	0.1 lb ai/acre	350 acres	15	1100	-	-
	cardoons, bok choy, brussel sprouts, canola, sweet potato	foliar	0.05 lb ai/acre	350 acres	30	2100	-	-
Mixing/Loading Emulsifiable Concentrates for Groundboom Application (1c)	canola	foliar	0.05 lb ai/acre	200 acres	50	3700	-	-
	cardoons, bok choy, brussel sprouts, sweet potato	foliar	0.05 lb ai/acre	80 acres	130	-	-	-
Mixing/Loading Emulsifiable Concentrates for Airblast Application (1d)	pistachios	foliar	0.1 lb ai/acre	40 acres	130	-	-	-
Applicator								
Applying Sprays with an Airplane (2)	canola	foliar	0.05 lb ai/acre	1200 acres	see Eng. Controls	see Eng. Controls	see Eng. Controls	4,200
	pistachios	foliar	0.1 lb ai/acre	350 acres	see Eng. Controls	see Eng. Controls	see Eng. Controls	7,200
	cardoons, brussel sprouts, sweet potato	foliar	0.05 lb ai/acre	350 acres	see Eng. Controls	see Eng. Controls	see Eng. Controls	14,000
Applying Sprays with a Groundboom (3)	canola	foliar	0.05 lb ai/acre	200 acres	6,100	-	-	-
	cardoons, bok choy, brussel sprouts, sweet potato	foliar	0.05 lb ai/acre	80 acres	15,000	-	-	-
Applying Sprays with an	pistachios	foliar	0.1 lb ai/acre	40 acres	880	-	-	-

Exposure Scenario	Crop or Target	Application Directed At	Application Rate ^a (lb ai/unit)	Units Treated Daily ^b	Baseline Dermal + Baseline Inhalation MOE ^c	PPE-G Dermal + Baseline Inhalation MOE ^d	PPE-G.DL Dermal + Baseline Inhalation MOE ^e	Combined Eng Cont Dermal + Inhalation MOE ^f
Airblast (4)								
Flagger								
Flagging for Aerial Sprays (5)	pistachios	foliar	0.1 lb ai/acre	350 acres	2,700	-	-	-
	cardoons, bok choy, brussel sprouts, canola, sweet potato	foliar	0.05 lb ai/acre	350 acres	5,300	-	-	-
Mixer/Loader/Applicator								
Mixing/Loading/Applying Emulsifiable Concentrate with Fogger Equipment (6)	Peanuts: unshelled; Cocoa beans; Almonds & Walnuts: shelled	indoor spaces	0.0000441 lb ai/1000 cu feet	No Data	No Data	No Data	No Data	No Data

Footnotes

aApplication rates are the maximum application rates determined from EPA registered labels for esfenvalerate.

bAmount handled per day values are EPA estimates of acreage treated or gallons applied based on Exposure SAC Policy #9 "Standard Values for Daily Acres Treated in Agriculture".

cCombined dermal and inhalation MOE = 1 / [(1/Dermal MOE) + (1/Inhalation MOE)]. Target MOE is 100.

dCombined dermal with gloves plus baseline inhalation MOE = 1 / [(1/Dermal-gloves MOE) + (1/Inhalation-baseline MOE)]. Target MOE is 100.

eCombined dermal with gloves and double layers plus baseline inhalation MOE = 1 / [(1/Dermal-gloves + double layers MOE) + (1/Inhalation-baseline MOE)]. Target MOE is 100.

fCombined engineering controls dermal plus engineering controls inhalation MOE = 1 / [(1/Dermal-EngControls MOE) + (1/Inhalation-EngControls MOE)]. Target MOE is 100. Only necessary for applying via fixed wing airplane scenarios.

All the occupational handler scenarios have risks associated with them that are below the HED's level of concern for noncancer risk assessments at some level of risk mitigation (i.e. PPE or engineering controls). There is a data gap for evaluating exposures and risks when applying esfenvalerate using mechanical fogger/aerosol generator equipment, i.e. for fumigating/treating unshelled peanuts, cocoa beans, and shelled almonds and walnuts. No reasonable surrogate data are available to evaluate risks from this exposure; however, based on the proposed label language, this scenario appears to be more like an aerosol treatment than like a fogger treatment; i.e. the treatment is not meant to be penetrating. Therefore, handler exposures from this scenario (maximum application rate 4.4E-5 lb ai/cu ft) should be more similar to those estimated by the indoor aerosol scenario (maximum application rate 5.875E-4 lb ai/cu ft), than by the indoor fogger scenario (maximum application rate 7.29E-5 lb ai/cu ft); both presented in the residential portion of this risk assessment. For the aerosol residential handler scenario, MOEs of 5200 (dermal) and 34,000 (inhalation) were estimated; and for the fogger residential handler scenario, MOEs of 1200 (dermal) and 4700 (inhalation) were estimated. Therefore, the MOEs estimated under the residential scenario should be conservative and protective of this occupational scenario, since the application rate for these commercial uses is less than the application rate for the residential indoor aerosol scenario by an order of magnitude. Therefore, it seems reasonable to assume that applying esfenvalerate indoors with a mechanical fogger/aerosol generator are not expected to exceed HED's occupational handler level of concern (i.e. MOE<100).

7.2 Occupational Postapplication Worker

HED assessed occupational postapplication risks to agricultural workers following treatments to the proposed new agricultural crops. For these agricultural crop scenarios, HED uses restricted-entry intervals as a risk mitigation method when risks are of concern at 12 hours following application (i.e., day 0). Under the Worker Protection Standard for Agricultural Pesticides, restricted-entry intervals are the time immediately after a pesticide application when entry into the treated area is limited. In general, during a restricted-entry interval, agricultural workers are prohibited from entering treated areas and contacting treated surfaces. Risk estimates for occupational workers are based on persons wearing long-sleeve shirts, long pants, shoes, and socks. The postapplication occupational assessment for esfenvalerate on the proposed new agricultural crops is based on chemical-specific dislodgeable foliar residue (DFR) studies on apples, broccoli, and sweet corn (i.e., MRIDs 44852402, 44852401, and 44852403). For the proposed new agricultural crops treated with esfenvalerate, risks were not a concern (i.e., MOEs ≥ 100) at 12 hours following application (i.e., day 0).

Table 7.2: Esfenvalerate Occupational Postapplication Risks

Crop	Activity ^a	Transfer Coefficient ^a (cm ² /hr)	Maximum Application Rate ^b (lb ai/acre)	DAT ^c (days)	Short Dermal MOE ^d (UF=100)
Sweet Corn Study (MRID 448524-03)					
canola	scouting (full crop development)	1,500	0.05	0	1,250
	scouting (minimum crop development)	100	0.05	0	19,000
Broccoli Study (MRID 448524-01)					

Crop	Activity ^a	Transfer Coefficient ^a (cm ² /hr)	Maximum Application Rate ^b (lb ai/acre)	DAT ^c (days)	Short Dermal MOE ^d (UF=100)
cardoons	hand harvesting, hand pruning	1,000	0.05	0	1,300
	irrigating, scouting	500	0.05	0	2,700
	hand weeding, scouting, thinning, irrigating	300	0.05	0	4,500
bok choy	hand harvesting, hand pruning, thinning	2,500	0.05	0	540
	irrigating and scouting (full crop development)	1,500	0.05	0	890
	hand weeding, scouting and thinning and irrigating (minimum crop development)	500	0.05	0	2,700
brussel sprouts	hand harvest, irrigating, topping	5000	0.05	0	270
	scouting	4000	0.05	0	330
	weeding-hand, scouting, thinning	2,000	0.05	0	670
sweet potato	hand harvesting	2,500	0.05	0	150
	irrigating, scouting	1,500	0.05	0	890
	hand weeding, irrigating, scouting, thinning	300	0.05	0	4,500
Apple Study (MRID 448524-01)					
pistachios	hand harvesting, hand pruning, thinning	2,500	0.10	0	610
	scouting	500	0.1	0	3,100

Footnotes:

- a Crop-specific activities and transfer coefficients from Science Advisory Council for Exposure Policy Number 3.1, Agricultural Transfer Coefficients adopted May 7, 1998, and revised August 7, 2000.
- b Maximum application rates from Dupont Asana XL Insecticide (EPA registration number 352-515).
- c DAT is days following treatment. Zero days is considered to be 12 hours after treatment.
- d Dermal MOE is calculated using the following formulas:

$$DE_{t_i} \text{ (mg ai/day)} = (TR_{t_i} \text{ (}\mu\text{g/cm}^2\text{)} \times TC \text{ (cm}^2\text{/hr)} \times \text{Hr/Day})/1000 \text{ (}\mu\text{g/mg)}$$

Where:

- DE(t) = Daily exposure or amount deposited on the surface of the skin at time (t) attributable for activity in a previously treated area, also referred to as potential dose (mg ai/day);
- TR(t) = Transferable residues that can either be dislodgeable foliar or turf transferable residue at time (t) where the longest duration is dictated by the decay time observed in the studies ($\mu\text{g/cm}^2$);
- TC = Transfer Coefficient (cm²/hour); and
- Hr/day = Exposure duration meant to represent a typical workday (hours).

and

$$\text{ADD}(t) \text{ (mg ai/kg/day)} = \text{DE}(t) \div \text{BW (kg)}$$

Where:

- ADD(t) = Average Daily Dose: The amount as absorbed dose received from exposure to a pesticide on a given day (mg pesticide active ingredient/kg body weight/day, also referred to as ADD);
- DE(t) = Daily Exposure: Amount deposited on the surface of the skin on a given day that is available for dermal absorption (mg ai/day); and
- BW = Body weight: determined to represent the population of interest in a risk assessment (60 kg).

and

$$\text{Dermal MOE (t)} = \text{NOAEL (mg ai/kg/day)} \div \text{ADD (mg ai/kg/day)}$$

Where:

- MOE = Margin of exposure: value used by the HED to represent risk or how close a chemical exposure is to being a concern (unitless);
- ADD = Average Daily Dose on a given day: the amount of absorbed dose received from exposure to a pesticide on a given day (mg pesticide active ingredient/kg body weight/day); and
- NOAEL = Dose level in an acute neurotoxicity toxicity study rats, where no observed adverse effects occurred (NOAEL) in the study

7.3 Incident Data

A review of incident data sources was conducted for esfenvalerate. Relatively few incidents of illness have been reported due to esfenvalerate. Incidents suggest that esfenvalerate can be a source of respiratory distress. In general, esfenvalerate is more likely to cause minor to moderate symptoms than other pesticides, but much less likely to cause serious or major effects which would require hospitalization or critical care. Note that there were relatively few cases involving occupational exposure or children under age six. By far, the most common moderate effects (almost always requiring medical attention) were difficulty breathing and cough in adults, suggesting that esfenvalerate may pose an asthma-like hazard.

Detailed descriptions of 262 cases submitted to the California Pesticide Illness Surveillance Program (1982-2000) were reviewed. In 19 of these cases, esfenvalerate was used alone or was judged to be responsible for the health effects. Only cases with a definite, probable or possible relationship were reviewed. Esfenvalerate ranked 133rd as a cause of systemic poisoning in California based on data for 1982 through 1999. Applicators were associated with more exposures than any other category. These illnesses included symptoms of conjunctiva, skin rashes, headache, dizziness, vomiting, nasal burning, and eye irritation. Effects to the eyes and skin seemed to predominate. One of the difficulties with the California data is that search a large percentage (93%) of cases involved mixtures where the predominate pesticide responsible for the illness was undetermined.

On the list of the top 200 chemicals for which National Pesticide Information Center (NPIC) received calls from 1984-1991 inclusively, esfenvalerate was ranked 155th with 18 incidents in humans reported and three in animals (mostly pets).

No scientific literature was located concerning acute poisoning due to exposure to esfenvalerate.

8.0 DATA NEEDS, LABEL REQUIREMENTS, AND TOLERANCE REASSESSMENT

Toxicology

The following studies need to be conducted with **esfenvalerate**:

870.1300. Acute Inhalation Toxicity - required to satisfy the 870.1300 data gap.

870.3465. 90-day inhalation study - required because of the concern for repeated inhalation exposure from the greenhouse uses of formulated esfenvalerate. The protocol should include FOB measures and motor activity.

870.3200. 21/28-day dermal toxicity in rats - is required to ascertain the neurotoxic and systemic toxicity potential. The protocol should include FOB measures and motor activity.

870.6300. Developmental neurotoxicity-with special protocol for pyrethroids. It is recommended that the registrant contact the Agency to discuss the test protocol (Draft OECD TG 426) with special emphasis on neonatal administration to pups by gavage as well as other possible modifications).

Note: The acute toxicity data base for technical fenvalerate could not be verified from the files. The need for replacement studies will be determined in the process of RED development.

Chemistry

Residue Chemistry Deficiencies-

- 860.1200 Directions for use- The registered uses of esfenvalerate on livestock animal premises (including dairy farm milk storage rooms), feed mills, feed processing plants and feed storage areas for contact, surface, space, and crack and crevice treatments should be deleted from all product labels because these uses are not supported by adequate residue data and no registrants have committed to support these uses.
- 860.1500 Crop Field Trials- Tolerances will be reassessed upon receipt and acceptance of the following outstanding data:

Soybean Aspirate Grain Fractions: The registrant is required to submit data depicting residues of esfenvalerate (as determined by the enforcement method) in/on aspirated grain fractions of soybeans following application of the EC formulation (Asana® XL) according to the maximum registered use pattern. The number of field trials and geographic locations of trial sites should be in compliance with the current guidance. When the requested aspirated grain fraction data on corn, sorghum, and soybean have been received and evaluated, HED will recommend an appropriate tolerance level for aspirated grain fractions as a RAC based on the highest residues measured in the dust.

Pea (field) vines and hay: The registrant is required to submit data depicting residues of esfenvalerate (as determined by the enforcement method) in/on pea vines and hay following

application of the EC formulation (Asana® XL) according to the maximum registered use pattern. The number of field trials and geographic locations of trial sites should be in compliance with the current guidance. When the requested data have been received and evaluated, HED will:

(i) recommend appropriate tolerance levels for pea vines and hay; and (ii) require the registrant to delete the existing feeding/grazing restrictions for pea vines from the product labels.

Sorghum Aspirated Grain Fractions: The registrant is required to submit data depicting residues of esfenvalerate (as determined by the enforcement method) in/on aspirated grain fractions of sorghum following application of the EC formulation (Asana® XL) according to the maximum registered use pattern. The number of field trials and geographic locations of trial sites should be in compliance with the current guidance. When the requested aspirated grain fraction data on corn, sorghum, and soybean have been received and evaluated, HED will recommend an appropriate tolerance level for aspirated grain fractions as a RAC based on the highest residues measured in the dust.

Cotton Gin Products: The registrant is required to submit data depicting residues of esfenvalerate (as determined by the enforcement method) in/on cotton gin byproducts following application of the EC formulation (Asana® XL) according to the maximum registered use pattern. The number of field trials and geographic locations of trial sites should be in compliance with the current guidance. When the cotton gin byproduct data have been received and evaluated, HED will recommend an appropriate tolerance level for this RAC.

Chinese Cabbage: Provided that label revisions are made for the EC (Asana® XL) formulation to specify a geographically limited use of esfenvalerate on Chinese cabbage (areas east of the Mississippi River only) and a 7-day PHI, no additional residue data for Chinese cabbage will be required for registration. The available data will support an esfenvalerate tolerance of 1.0 ppm. The registrant should submit a revised Section F proposing a tolerance of 1.0 ppm.

Kiwi: There are no registered uses of esfenvalerate on kiwifruit. Therefore, the established esfenvalerate tolerance on kiwifruit must be revoked.

Brussel Sprouts (PP#9E6061): A revised Section B and Section F need to be submitted in support of the establishment of a regional tolerance for residues of esfenvalerate at 0.20 ppm.

Post Harvest applications in/on almonds, cocoa beans, peanut kernels, and walnuts (PP#0F6110): A revised Section B and Section F need to be submitted.

Product Chemistry Deficiencies

Product chemistry data requirements are not satisfied for the DuPont **esfenvalerate** TGAI/technical; additional data are required concerning discussion of formation of impurities (dioxins), enforcement analytical method, physical state, odor, and UV/visible absorption (OPPTS 830.1670, 1800, 6303, 6304, and 7050). Product chemistry data requirements are satisfied for the Sumitomo **esfenvalerate** technical concerning OPPTS 830.1550-1800; the Sumitomo technical is a “me-too” registration and is relying on data submitted by DuPont to support data requirements pertaining to physical/chemical properties.

Provided that the registrants submit the data required in the attached data summary tables for the TGAI/technicals, and either certify that the suppliers of beginning materials and the manufacturing processes for the fenvalerate and esfenvalerate technical products have not changed since the last comprehensive product chemistry reviews or submit complete updated product chemistry data packages, the Agency has no objections to the registration of esfenvalerate with respect to product chemistry data requirements.

Occupational

None.

9.0 TOLERANCE CONVERSION AND REASSESSMENT

9.1. Tolerance Conversion and Reassessment for Esfenvalerate

Esfenvalerate tolerances are established under 40 CFR §180.533 and are expressed in terms of esfenvalerate [(S)-cyano(3- phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl)benzene-acetate].

HED recommends that the tolerance expression under 40 CFR §180.533 be amended to specify that the residues to be regulated are: esfenvalerate [(S)-cyano(3-phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl) benzeneacetate] and its non-racemic isomer [(R)-cyano-(3-phenoxyphenyl)methyl-(R)-4-chloro- α -(1-methylethyl) benzeneacetate] and its diastereomers [(S)-cyano(3-phenoxyphenyl)methyl-(R)-4-chloro- α -(1-methylethyl) benzeneacetate and (R)-cyano(3-phenoxyphenyl)methyl-(S)-4-chloro- α -(1-methylethyl) benzeneacetate].

Esfenvalerate Tolerances Listed Under 40 CFR §180.533 (a)

Adequate residue data are available to support the established esfenvalerate tolerances on the following raw agricultural commodities for: artichoke, globe; kohlrabi; lettuce, head; mustard greens; sorghum, fodder; sorghum, forage; sorghum, grain; sugar beet pulp; sugar beet, root, and sugar beet, top.

Adequate residue data are also available to support the established esfenvalerate tolerances on the following poultry commodities: eggs, whole; poultry, fat; poultry, meat; poultry, mbyp (except liver); and poultry, liver.

The established esfenvalerate tolerances on kohlrabi and head lettuce should be moved under 40 CFR §180.533 (c) because the labeled uses of esfenvalerate on these crops are for regional registrations.

We recommend the revocation of the esfenvalerate tolerance on kiwifruit, unless an interested party proposes uses and submits supporting residue data.

The established tolerance for sugar beet root should be lowered from 0.5 ppm to 0.05 ppm based on nondetectable (<0.01 ppm) residues in/on the RAC following application at 1.0x. The reassessed esfenvalerate tolerance for sugar beet root will be in harmony with fenvalerate Codex MRL for root and tuber vegetables.

The established tolerance for sugar beet pulp should be revoked because the reassessed tolerance for the RAC (sugar beet root) should sufficiently cover expected esfenvalerate residues in sugar beet pulp resulting from registered use.

A summary of esfenvalerate tolerance reassessments is presented in Table 9.2.1.

Converted Esfenvalerate Tolerances To Be Proposed Under 40 CFR §180.533 (a)

For crops with fenvalerate tolerances for which esfenvalerate uses are supported, HED (DP Barcode D213050, 2/12/96, S. Willett) has previously determined that the fenvalerate tolerances under 40 CFR §180.379 can be converted to esfenvalerate. In 1994, the basic registrant submitted a petition, PP#4F4329, to convert fenvalerate tolerances to esfenvalerate (still to be expressed as the sum of all isomers) based on the use rates for esfenvalerate (Asana®). The use rate for esfenvalerate (Asana®) is four times lower than that for fenvalerate (Pydrin®). In support of this petition, the registrant submitted bridging residue comparison studies on: almond, apple, bean, cabbage, corn (field and sweet), cottonseed, cucurbits, soybean, peanut, pear, stone fruits, sugarcane, sunflower, tomato, and several commodities not currently registered (alfalfa, barley, celery, hay, grass, wheat). These bridging studies indicate that esfenvalerate (Asana®) residues are 3-4 times lower than fenvalerate (Pydrin®) residues. The average ratio (fenvalerate to esfenvalerate) based on field data with quantifiable residues (i.e., 0.1 ppm) is 3.3-3.5 to 1.

HED agrees that a conversion ratio (i.e., 3.3 to 1) based on the results of the bridging studies could be used to satisfy registration requirements for certain crop commodities. Specifically, HED will use the tiered approach originally proposed by DuPont in PP#4F4329 (and re-iterated below) in converting fenvalerate crop tolerances to esfenvalerate crop tolerances based on bridging data.

- For fenvalerate tolerances greater than 2.0 ppm, divide the tolerance by 3 and round to the nearest whole number;
- For fenvalerate tolerances less than or equal to 2.0 ppm, and greater than or equal to 1.0 ppm, divide the tolerance by 2; and
- For fenvalerate tolerances less than 1.0 ppm, leave the numerical value unchanged due to the increased variability in analytical data as the limit of quantitation is approached.

Pending label amendments and revised Section F for some crops, we recommend the establishment of esfenvalerate tolerances on the following raw agricultural commodities (with recommended tolerance level in parenthesis) based on the available bridging data and using the registrant's tiered approach of residue conversion: almond, hulls (5.0 ppm); almond, nutmeat (0.2 ppm); almonds (50 ppm, post-harvest uses); apple (1.0 ppm); bean, dry (0.25 ppm); bean, succulent (1.0 ppm); blueberry (1.0 ppm); bok choy (1.0 ppm); broccoli (1.0 ppm); brussel sprouts (0.20 ppm); cabbage (except Chinese cabbage) (3.0 ppm); cabbage, Chinese (1.0 ppm); caneberry (Crop Subgroup 13-A) (1.0 ppm); cardoon (1.0 ppm); carrot (0.5 ppm); cauliflower (0.5 ppm); cocoa beans (1.0 ppm, post-harvest); collard (3.0 ppm); corn, field, forage (15.0 ppm); corn, field, grain (0.02 ppm); corn, field, stover (15.0 ppm); corn, pop, grain (0.02 ppm); corn, pop, stover (15.0 ppm); corn, sweet, forage (15.0 ppm); corn, sweet, K + CWHR (0.1 ppm); corn, sweet, stover (15.0 ppm); cotton, undelinted seed (0.2 ppm); cucumber (0.5 ppm); eggplant (0.5 ppm); elderberry (1.0 ppm); filbert, nutmeat (0.2 ppm); gooseberry (1.0 ppm); lettuce, head (5.0 ppm); muskmelon (0.5 ppm); pea, dry (0.25 ppm); pea, succulent (1.0 ppm); peanut kernels (0.20 ppm, post-harvest); peanut, nutmeat (0.02 ppm); pear (1.0 ppm); pecan, nutmeat (0.2 ppm); pepper (0.5 ppm); pistachios (0.10 ppm); potato (0.02 ppm); pumpkin (0.5 ppm); radish, root (0.3 ppm); radish, tops (3.0 ppm); soybean, seed (0.05 ppm); squash, summer (0.5 ppm); squash, winter (0.5 ppm); stone fruits (Crop Group 12) (3.0 ppm); sugarcane (1.0 ppm); sunflower, seed (0.5 ppm); sweet potato (0.05 ppm); tomato (0.5 ppm); turnip, root (0.5 ppm); turnip, tops (7.0 ppm); walnut, nutmeat (0.2 ppm); walnuts (15 ppm, post-harvest); and watermelon (0.5 ppm).

According to 40 CFR §180.1 (h), tolerances established for the general category of peas would apply to the specific commodity lentil. Since the registered uses of lentil and dry peas are identical, the reassessed tolerance (0.25 ppm) on dry peas would be sufficient to cover residues of esfenvalerate on lentils.

According to 40 CFR §180.1 (h), tolerances established for the general category of muskmelons would apply to the specific commodities cantaloupe and honeydew melon. Since the registered uses of cantaloupe, honeydew melon, and muskmelon are identical, the reassessed tolerance (0.5 ppm) on muskmelon would be sufficient to cover residues of esfenvalerate on cantaloupe and honeydew melon.

We recommend the establishment of esfenvalerate tolerances on for milk (0.3 ppm), milk fat (7.0 ppm), and the fat, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep (1.5 ppm each).

As a result of changes to Table 1 of OPPTS 860.1000, the registrant is required to propose tolerances on the following commodities following submission and evaluation of adequate residue data: aspirated grain fractions; cotton gin byproducts; and pea vines and hay. The tolerance for aspirated grain fractions will be based on the highest esfenvalerate residues measured in the grain dust of corn, sorghum, and soybean.

Esfenvalerate tolerances on peanut hay, soybean forage, and soybean hay are not required because forage/hay feeding restrictions appear on the basic registrant's product label; these restrictions are allowed by the Agency for peanut and soybeans.

Current and Pending Esfenvalerate Petitions

PP#9E6061. IR-4 submitted this petition for the establishment of a tolerance for residues of esfenvalerate in/on Brussels sprouts grown in all states except CA at 0.2 ppm. Pending submission of a revised Section B and a revised Section F, HED can recommend for the establishment of a regional tolerance of 0.2 ppm for residues of esfenvalerate and its isomers in/on brussel sprouts (DP Barcode D259703, J. Morales, 3/1/03).

PP#4F3023. DuPont Agricultural Products submitted this amended petition for the establishment of a tolerance for residues of esfenvalerate in/on celery at 5.0 ppm. The petitioner withdrew this petition on 7/30/02.

PP#7F4859. DuPont Agricultural Products submitted this petition for the establishment of a tolerance for residues of esfenvalerate in/on pistachios at 0.1 ppm. HED recommends for the establishment of a tolerance of 0.1 ppm for residues of esfenvalerate and its isomers in/on pistachios (DP Barcode D238338, J. Morales, 3/1/03).

PP#0F06110. IR-4 submitted this petition for the establishment of tolerances for residues of esfenvalerate in/on almonds at 50 ppm, cocoa beans at 1.0 ppm, peanut kernels at 0.20 ppm, and walnuts at 15.0 ppm resulting from postharvest applications. Pending submission of a revised Section B and a revised Section F, HED can recommend for the establishment of a tolerance of 50 ppm in/on almonds, cocoa beans at 1.0 ppm, peanut kernels at 0.20 ppm, and walnuts at 15.0 ppm (resulting from postharvest applications of esfenvalerate) for residues of esfenvalerate and its isomers (DP Barcode D274838, J. Morales, 3/1/03).

PP#9E5075. IR-4 submitted this petition for the establishment of a tolerance for residues of esfenvalerate in/on canola seed at 0.3 ppm. HED cannot recommend for the establishment of a tolerance for residues of esfenvalerate and its isomers in/on canola at this moment (DP Barcode D257618, J. Morales, 3/1/03) at HED.

PP#E3697. IR-4 submitted this amended petition for the establishment of a tolerance for residues of esfenvalerate in/on cranberries at 0.2 ppm. The petitioner withdrew this petition on 5/7/98.

PP#4F4329. DuPont Agricultural Products submitted this petition to propose the conversion of tolerances for fenvalerate (40 CFR 180.379) to esfenvalerate tolerances. The original notice of filing was published in the Federal Register on July 13, 1994 (59 FR 35719). At this time HED can recommend for the tolerance conversion from fenvalerate to esfenvalerate.

PP#2F4082. The McLaughlin Gormley King (MGK) Company submitted this petition for the establishment of a tolerance for residues of esfenvalerate and piperonyl butoxide in/on stored cocoa beans at 1.0 ppm. Residue data, submitted by the petitioner in support of this petition, were deemed inadequate (DP Barcode D174163, 9/29/92, N. Dodd).

PP#0F3852. DuPont Agricultural Products submitted this petition for the establishment of a tolerance for residues of esfenvalerate in/on alfalfa green forage at 15.0 ppm, alfalfa hay at 15.0 ppm, alfalfa seed at 1.0 ppm, and head lettuce at 5.0 ppm. Residue data submitted by the petitioner were deemed adequate for head lettuce (CB No. 6524, 4/10/91, M. Flood). The alfalfa portion of the petition was withdrawn on 4/30/85.

PP#1E3958. IR-4 submitted this petition for the establishment of a tolerance for residues of esfenvalerate in/on leaf lettuce at 15.0 ppm. The petitioner withdrew this petition on 2/10/03.

PP#1E3957. IR-4 submitted this petition for the establishment of a tolerance for residues of esfenvalerate in/on kale at 5.0 ppm with regional registration east of the Rocky Mountains. The petitioner withdrew this petition on 2/10/03.

PP#0E3912. IR-4 submitted this petition for the establishment of a tolerance for residues of esfenvalerate in/on cardoon at 1.0 ppm. Although residue data submitted by the petitioner in support of this petition were deemed adequate (CB No. 7132, 1/28/91, S. Bacchus), the tolerance request has not been established.

PP#9E3810. IR-4 submitted this petition for the establishment of a tolerance for residues of esfenvalerate in/on bok choy at 2.0 ppm with regional registration, east of the Mississippi River only. Residue data submitted by the petitioner in support of this petition were deemed adequate (CB No. 5896, 1/3/90, F. Toghrol) provided the petitioner submit a revised Section F to specify a new tolerance level of 1.0 ppm based on the review of supporting data.

PP#9E3813. IR-4 submitted this petition for the establishment of a tolerance for residues of esfenvalerate in/on sweet potato at 0.05 ppm. Although residue data submitted by the petitioner were deemed adequate (CB No. 6419, 3/22/90, L. Rodriguez), the tolerance request has not been established.

9.2. Table for New , Converted, and Reassessed Tolerances

Table 9.2.1 provides the **reassessed** tolerances for esfenvalerate currently listed under 40 CFR 180.553(a).

Table 9.2.1. Tolerance Reassessment Summary for Esfenvalerate			
Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/ [Correct Commodity Definition]
Tolerances Listed Under 40 CFR §180.533 (a)			
Artichoke, globe	1.0	1.0	
Eggs, whole	0.03	0.03	[Eggs]
Kiwifruit	0.5	Revoke	No registered uses.
Kohlrabi	2.0	2.0	This tolerance supports a regional registration and should be moved under 40 CFR §180.533 (c).
Lettuce, head	5.0	5.0	This tolerance supports a regional registration and should be moved under 40 CFR §180.533 (c).
Mustard greens	5.0	5.0	
Poultry, fat	0.3	0.3	
Poultry, meat	0.03	0.03	
Poultry, mby (except liver)	0.3	0.3	
Poultry, liver	0.03	0.03	
Sorghum, fodder	10.0	10.0	[Sorghum, stover]
Sorghum, forage	10.0	10.0	
Sorghum, grain	5.0	5.0	
Sugarbeet pulp	2.5	Revoke	The reassessed RAC tolerance of 0.05 ppm should sufficiently cover esfenvalerate residues in sugar beet pulp resulting from registered use.
Sugarbeet, root	0.5	0.05	The reassessed esfenvalerate tolerance for sugar beet root will be in harmony with fenvalerate Codex MRL for root and tuber vegetables. [Beet, sugar, root]
Sugarbeet, top	5.0	5.0	[Beet, sugar, tops]

Table 9.2.2 provides **new** tolerances for esfenvalerate and tolerances **converted** from fenvalerate to esfenvalerate to be established under 40 CFR§1803533 (a).

Table 9.2.2 New or Converted Tolerances that need to be Established under 40 CFR §180.533(a)			
Commodity	Current Tolerance (ppm)	New or Converted Tolerance (ppm)	Comment/ [Correct Commodity Definition]
Almond, hulls	None	5.0	
Almond, nutmeat	None	0.2	
Almonds (Post-Harvest)	None	50	
Apple	None	1.0	
Aspirated grain fractions	None	TBD ¹	HED will base the tolerance on the highest residue of aspirated grain fractions from studies conducted on soybeans, corn, and sorghum.
Bean, dry	None	0.25	
Bean, succulent	None	1.0	
Blueberry	None	1.0	
Broccoli	None	1.0	
Brussels Sprouts	None	0.20	
Cabbage (except Chinese cabbage)	None	3.0	
Cabbage, Chinese	None	1.0	Regional Registration
Caneberry (Crop Subgroup 13-A)	None	1.0	
Cardoon	None	1.0	
Carrot	None	0.5	
Cattle, fat	None	1.5	
Cattle, mbyb	None	1.5	
Cattle, meat	None	1.5	
Cauliflower	None	0.5	
Cocoa Beans (Post-Harvest)	None	1.0	
Collards	None	3.0	
Corn, field, forage	None	15.0	
Corn, field, grain	None	0.02	
Corn, field, stover	None	15.0	
Corn, pop, grain	None	0.02	
Corn, pop, stover	None	15.0	
Corn, sweet, forage	None	15.0	
Corn, sweet, K + CWHR	None	0.1	
Corn, sweet, stover	None	15.0	
Cotton gin byproducts	None	TBD ¹	
Cotton; undelinted seed	None	0.2	The recommended tolerance is in harmony with Codex and Mexican MRLs.

Table 9.2.2 New or Converted Tolerances that need to be Established under 40 CFR §180.533(a)			
Commodity	Current Tolerance (ppm)	New or Converted Tolerance (ppm)	Comment/ [Correct Commodity Definition]
Cucumber	None	0.5	
Eggplant	None	0.5	
Elderberry	None	1.0	
Filbert, nutmeat	None	0.2	
Goats, fat	None	1.5	
Goats, mbyop	None	1.5	
Goats, meat	None	1.5	
Gooseberry	None	1.0	
Hogs, fat	None	1.5	
Hogs, mbyop	None	1.5	
Hogs, meat	None	1.5	
Horses, fat	None	1.5	
Horses, mbyop	None	1.5	
Horses, meat	None	1.5	
Lettuce, Head	None	5	
Milk	None	0.3	
Milk, fat	None	7.0	
Muskmelon	None	0.5	The recommended tolerance for muskmelon will cover registered uses on cantaloupe and honeydew melon.
Pea, dry	None	0.25	The recommended tolerance for dry pea will cover registered uses on lentils.
Pea, succulent	None	1.0	
Pea, vines	None	TBD ¹	
Pea, hay	None	TBD ¹	
Peanuts (Post-Harvest)	None	0.20	
Peanut, nutmeat	None	0.02	
Pear	None	1.0	
Pecan, nutmeat	None	0.2	
Pepper	None	0.5	
Pistachios	None	0.1	
Potato	None	0.02	
Pumpkin	None	0.5	
Radish, root	None	0.3	
Radish, tops	None	3.0	
Sheep, fat	None	1.5	
Sheep, mbyop	None	1.5	
Sheep, meat	None	1.5	
Soybean, seed	None	0.05	

Table 9.2.2 New or Converted Tolerances that need to be Established under 40 CFR §180.533(a)			
Commodity	Current Tolerance (ppm)	New or Converted Tolerance (ppm)	Comment/ [Correct Commodity Definition]
Squash, summer	None	0.5	
Squash, winter	None	0.5	
Stone fruits group (Crop Group 12)	None	3.0	
Sugarcane	None	1.0	
Sunflower, seed	None	0.5	
Sweet Potato	None	0.05	
Tomato	None	0.5	
Turnip, root	None	0.5	
Turnip, tops	None	7.0	
Walnuts (Post-Harvest)	None	15	
Walnut, nutmeat	None	0.2	
Watermelon	None	0.5	

¹ TBD = To be determined. Additional data are required for: aspirated grain fractions; cotton gin byproducts; pea vines; and pea hay.



13544

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Chemical: Esfenvalerate

PC Code:
109303

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