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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: April 22, 2005

Subject: Pyrethrins. Response to Error-Only Comments to HED Risk Assessment and Supporting Documents Case No. 2580. DP Barcode No.: D295744

From: Christine Olinger, Risk Assessor
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The Pyrethrins Joint Venture has submitted error-only comments in response to the Preliminary Human Health Risk Assessment for the Reregistration Eligibility Decision and associated supporting documents (C. Olinger, D312613, 1/31/05). Attached is a table listing the comments along with the HED response. Also attached is the revised human health risk assessment incorporating the error-only comments. Supporting documents for this assessment include the following:

J. Deluzio; 12/13/04; DP Barcode: D309021
J. Deluzio; 12/20/04; DP Barcode: D295748
J. Deluzio; 10/12/04; DP Barcode: D295749
M. Lloyd and T. Dole; 4/21/2005; DP Barcode: D315957
J. Blondell; 4/6/2005; DP Barcode: D315643
S. Dutta, 8/19/04, DP Barcode D295750.

Error Only Comments: Pyrethrins DRAFT HED Chapters Pyrethrins. HED Chapter of the Reregistration Eligibility Decision Document (RED) DP Barcode D312613. January 31, 2005			
Header	**Page #, Paragraph**	**Comments**	**HED Response**
Table of Contents	iii-v	Numbering starts to go off actual starting with section 4.2.4, Reproductive Toxicity Study which actually begins on page 22, not 21. All subsequent numbers are increasingly off base to the text.	Pagination errors occurred when document was converted to PDF format.
Executive Summary	1, Paragraph 1	In reference to the commercially available extracts of pyrethrum, it may be helpful to clarify that the extracts at 20-25% are all manufacturing use products, and not end-use products. Nearly all end-use products are low, single digit percent or more typically 0.25-0.5% active ingredient.	Will incorporate suggestion.
Executive Summary - Toxicological Effects	1, Last paragraph	Suggestive evidence of carcinogenicity but is it relevant to humans, etc. at the doses exposed? Why is the "no quantification…" paragraph not used?	The purpose of this paragraph is to describe the toxicological effects seen in the toxicity studies. Discussion on the appropriate quantification method is found in the dose response section.
Executive Summary - Dose Response	2, Paragraph 6	Why is the "no quantification…" paragraph not used?	Will provide additional characterization of the cancer classification.
Dose Response	2, Paragraph 6	Change "Access" to "Assess"	Will change.
Executive Summary - Dietary	3, Paragraph 2	Percent of crop treated data is mentioned – based on what sources of data? California PUR?	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Executive Summary - Residential Exposure	3, Paragraph 5	Metered release systems are noted for outdoor residential settings – metered systems are aerosols! They are confusing metered with residential mosquito misting systems.	The cited use was described in the Master Label provided by the registrant. HED developed exposure scenarios for the RED directly from the Master Label.
Executive Summary - Residential	3, Paragraph 4	Bulb dusters and power dusters are used by PCO, not homeowners.	Will incorporate suggestion.

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.Executive Summary - Aggregate Exposure	4, Paragraph 2	We believe that consumer application rates are not the highest. We believe that the highest rates are coming from PCO uses	The rates on the Master Label do not agree with the rates on the product labels. It is recommended that the master label be revised to reflect the product label rates.
Executive Summary – Occupational Exposure	4, Paragraph 5	We believe that consumer application rates are not the highest. We believe that the highest rates are coming from PCO uses.	The rates on the Master Label do not agree with the rates on the product labels. It is recommended that the master label be revised to reflect the product label rates.
2.0 Ingredient Profile	5, Paragraph 1	Repeat of comment above, that only MUPs are at 20-25% pyrethrins levels, to avoid misunderstanding that commercial end-use products have this high a level. End-use products and applications are at single digit percents or more typically 0.25-0.5% active.	Will incorporate suggestion.
Summary of Registered Uses	5, Paragraph 2	Does not mention domestic, animal, structural, etc.	Will incorporate suggestion.
Summary of Registered Uses	5, Paragraph 5	The product forms attributed to agricultural crop and livestock uses are wrong Typical products for Ag and livestock are emulsifiable concentrates.	Will modify paragraph to state that these formulations represent all uses.
2.2 Structure and Nomenclature	Page 6, 2nd para	The use of the chemical term isomer is incorrect when discussing the components of Pyrethrins I and Pyrethrins II. These are not isomers in the true synthetic chemical sense, these are distinct compounds formed in the plant by highly stereochemically conserved enzymatic esterification of the two stereospecific acids and the three stereospecific alcohols. Unlike synthetic compounds, no chemical	Will incorporate suggestion.

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		isomers are produced because the plant produces only one specific acid or alcohol for enzymatic esterification. These are natural products in the truest sense.	
2.2 Structure and Nomenclature	Page 6, 2nd para	Our understanding of the nomenclature for components of pyrethrum are that the single compound is lower case followed by an Arabic numeral (e.g. pyrethrin 1), and that the class defined by the acid, is capitalized followed by the Roman numeral (e.g. pyrethrin 1 is a component of Pyrethrins I)	Will incorporate suggestion.
3.1.1 Description	9, Paragraph 2	(13.18% TRR) needs to identify TRR upon first use.	Will incorporate suggestion.
3.1.3 Description of Rotational Crop . . .	Page 10, 2nd para	Extra space between “rotational” and “crop”.	Will incorporate suggestion.
3.5.1 Tabutee	Table 3.5	The “NS” under rotational crops is not defined. Footnote 1 should report no data requirement exists.	Will incorporate suggestion.
Modification	13, Paragraph 1	The sentence beginning “Both sexes P” and the next 2 sentences seem to be saying the same thing.	Will incorporate suggestion.
4.1 Hazard and Dose . . .	Page 14, 1st para	Second to last line, extra space between “toxicity” and “is.”	Will incorporate suggestion.
Modification	14, line 6	Change “Access” to “Assess”	Will incorporate suggestion.
Modification	14, last line	Change “Access” to “Assess”	Will incorporate suggestion.
Table 4.1a	15, 870.1300	Rat in brackets [Rat]	Will incorporate suggestion.
Table 4.1a	15, 870.2600	Last field should read “negative”	Will incorporate suggestion.
Table 4.1b	18, 870.7600	0.22% dermal absorption cited earlier.	Will incorporate suggestion.

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Executive Summary	28, line 3	"Oppm" repeated – explain or delete. Is this because of 2 control groups of animals?	There were two control groups of animals in this study.
Recommendation	37, Paragraph 2	"As per FQPA (1996)…" use parens rather than commas.	Will incorporate suggestion.
5.1 Incident Report	41, Sentence 2	Pyrethrins are not always used with PBO. What does "10,000 reported exposures" mean? Were there alleged injuries? We question the ragweed sensitivity allegation.	Changed wording. Reported exposures are those exposures reported to Poison Control Centers in the years 1993-2001.
5.1 Incident Reports	41, Paragraph 3	What is the basis (reference) for the suspicion that pyrethrins can cause allergic reactions in individuals sensitive to ragweed? In ragweed allergies it is highly likely those allergens are pollen related proteins, which would be denatured or excluded from the final pyrethrins extracts by the organic extractions. We see no evidence for a connection, particularly with "modern" Pyrethrins.	Recommendations are based on incidents cited in articles by Wagner cited in the revised incident report.
Water Exposure	43	As the in the EFED document, we believe that the estimated water Py concentrations do not take into account Py that would deposit on surface water and very susceptible to photolysis. Specific PJV EFED comments regarding this item as follows "These model assumptions are inconsistent with literature on spray deposition (Mabury and Crosby, 1996), particularly for highly hydrophobic products	Estimated drinking water concentrations were provided by EFED.

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		such as pyrethrins; the literature indicates that pesticides deposited by spray drift form a microlayer on the surface which is highly susceptible to photolysis for those that are susceptible to photolysis. The model assumption of instantaneous, homogeneous mixing throughout the water column is also inconsistent with literature that indicates that pesticides are more slowly distributed from the surface to depth through processes such as diffusion and convection."	
Acute Dietary Exposure	44, last paragraph, line 6	Clarify "…do not exceed equal HED's level of concern." Also, the comment is made that percent of crop treated information represents upper bound estimates. What state or region was used as the basis for % of crop treated? Was <u>any</u> California data used? California law requires reporting of <u>all</u> agricultural use by pounds of AI and acres treated. The 2003 report shows less than 1700 pounds of pyrethrins were used on crops. Specific examples from the report show a total of 164.1 pounds applied to 3983 acres of tomatoes in 102 applications; 152.4 pounds applied to 6985 acres of leaf lettuce in 1210 separate applications, 41.0 pounds applied to 4605 acres of spinach in 664 separate applications. Pyrethrins are simply <u>not</u> used as widely as EPA believes	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III. The word equal will be deleted.

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Residential Exposure	46, Paragraph 2	Application of dust with bulb duster and power duster are PCO applications to non-residential areas not homeowners. No exposure to homeowners or children.	Will incorporate suggestion.
Handler Exposure	46, 2)	"Load/apply dusts" – PCO use, not homeowner	This will be considered during the public comment phase.
Handler Exposure	46, 3)	"Mix/load/apply liquids" not sure if there are any indoor use concentrates used in this manner by homeowner.	This will be considered during the public comment phase.
Handler Exposure	47, 5)	Hose end sprayer for ornamentals, not lawns.	Homeowners often apply products to turf using a hose end sprayer.
Post Application	47, 1) – 7)	Other Task Forces have exposure data relevant to these uses.	Please clarify which data are being referred to in this comment.
Post Application	47, last 2 paragraphs	References SOP 12. Other Task Forces have exposure data relevant to these uses.	Please clarify which data are being referred to in this comment.
6.2.1.2 Residential Exposure Data and Assumptions	47, Paragraph 6	Actually, correct designation of the PBO Task Force II is "PBTFII". (The Task Force has also been making this mistake.)	Will incorporate suggestion.
Post Application	48, first line	There should be a comma following "Kenya"	Will incorporate suggestion.
Post Application	48, Paragraph 3, line 5	Carbarge is not a common mosquito adulticide.	Assume the commenter meant carbaryl. The carbaryl assessment included such a scenario.

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Residential Handler	49, line 1	Is "residential handler" defined? Does it include the homeowner? Homeowners do not spray half acre per day with hose end sprayer or treat 1000 sq. feet of garden daily or use 1 aerosol can per day. Other Task Forces have exposure data relevant to these uses.	The term "residential handler" applies to homeowners who mix, load, and apply pesticide products. The area treated per day values are standard assumptions from SOP 12. Refinement is not necessary because risks are low.
Mosquito Abatement	49, Paragraph 2	Fixed wing release altitude ranges depending on aircraft and terrain. Rotary aircraft release altitude of 30 feet seems a bit low for residential areas.	This release height was used for other assessments such as carbaryl and malathion. Given the low risks, additional refinement is not necessary.
Truck Mounted	49, last bullet	Do not believe that particles will remain in the air for 2 hours	This is accounted for in the 100X dilution factor.
Turf Indoor	49, first bullet	More realistic turf transferable residue data are available via other Task Forces.	These data are not needed because there are no dermal endpoints and the incidental oral risks are low.
Truck Mounted	49, 3rd bullet	EPAs Policy 12 uses 0.7 m3/hr for child light activity breathing rate, substitute for 0.8 m3/hr and adjust exposure calculations accordingly.	Will incorporate suggestion.
Toddler Incidental	49, last line	"100% of AI available in upper 1 cm of soil" would not hold as degradation is rapid – depends on time from spray to ingestion.	This is a standard assumption from SOP 12. Given the low risks for soil ingestion, it is not necessary to refine these values with pyrethrin specific data.
Pet Treatment	50, first bullet	Half of a 16 oz spray bottle is excessive.	This assumption comes from the carbaryl risk assessment.
Pet Treatment	50, second bullet	20% transfer of residue is excessive. Other Task Forces have exposure data relevant to these uses.	This is a standard assumption from SOP 12. Given the low risks, it is not necessary to refine these values with pyrethrin specific data. Please clarify which data are being referred to in the "task force" comment.

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Pet Treatment	50, last bullet	Need to clarify that hand to mouth behavior is for children only.	Table 6.2 "Summary of Residential Risks" indicates that only children are exposed by the incidental oral route
Space Spray	50, second bullet	Use of one can per application is excessive. Other Task Forces have exposure data relevant to these uses.	Master Label has been modified. Assessment reflects revised rate.
Space Spray	50, third bullet	One application per day is excessive. Other Task Forces have exposure data relevant to these uses.	Master Label has been modified. Assessment reflects revised rate.
Space Spray	50, fourth bullet	EPAs Policy 12 uses 0.7 m3/hr for child light activity breathing rate, substitute for 0.8 m3/hr and adjust exposure calculations accordingly	Will incorporate suggestion.
	50, Paragraph3	This paragraph references PBO, not pyrethrins. Is this a cut and past error? Suggest "piperonyl butoxide" be changed to "pyrethrins" and the reference changes to D069001, Dole, 1/31/2005.	Will incorporate suggestion.
	50, Paragraph 5	Again, this paragraph reference PBO	Will incorporate suggestion.
	52, Paragraph 1	We agree with EPAs calculation and logic regarding the aerosol. We suspect that the Master Label is incorrect in that it cites an undiluted PCO product, rather than the actual rate of the diluted product per label instructions.	HED concurs.
Table 6.2	53	The post application exposure numbers would be changed if less than a full can was used for the calculation which is more typical usage.	This comment suggests that the master label needs to be changed to reflect the product labels.
Acute Aggregate	55, Paragraph 5	Percent of crop treated from CA and other areas appears to be ignored.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated

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			values will be considered in Phase III.
7.2 Short-term Aggregate	55, Paragraph 6	Same comment as above (page 52, 1st para).	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
7.3 Intermediate-Term Aggregate Risk	56, Paragraph 2	First line, remove "a" between "the" and "systemic".	Will incorporate suggestion.
7.5 Cancer Risk	56	Change "Access" to "Assess"	Will incorporate suggestion.
9.1.2.2 Exposure	61, 6)	The aerial acres per day are virtually equal to California acres per year. The mosquito control acres are also very high. Not sure how much turf is presently treated. Animal groomers/vet techs are not likely to use 8 fl. oz. per animal.	The values are standard assumptions for aerial treatment, mosquito control and turf treatment. The assumption of 8 animals treated per day is from the carbaryl risk assessment. Refinement is not needed because the risks are low.
Occupational Handler	63	The low MOEs for the agricultural scenarios are partially a result of overestimating of crop use. All 4 are based on WP form, which may not be in general use today.	This suggests that cancellation of the WP labels for agricultural use might be a feasible mitigation option.
Occupational Handler	63, Paragraph 3	Why are SOP values used?	The SOP values are used in Tier 1 risk assessments to streamline the risk assessment process and conserve Agency resources. Tier 2 risk assessments are performed to refine risks of concern identified in a Tier 1 assessment.
Occupational Handler	64, Paragraph 2	Acknowledge overestimation of exposure for workers.	This acknowledgement is included in risk characterization at the end of the ORE chapter.
9.2.2. Post Application . .	65, Paragraph 3	Fourth line, extra spaces between "is" and "ventilated".	Will incorporate suggestion.
Assumptions	65	Typical Dairy Barn Spray Systems have spray heads in each stall to treat the	HED assumed that the metered release systems act as a space spray rather than a surface spray

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		animals. The exposure is minimal to workers.	intended for direct animal treatment.
Table 1	96	In second line, numbers and words are overwritten over each other.	Will correct this typographical error.

Pyrethrins. Acute and Chronic Dietary Exposure Assessments for the Reregistration Eligibility Decision (RED) Document. DP Barcode D295748. December 20, 2004			
Header	**Page #, Paragraph**	**Comments**	**HED Response**
Executive Summary	2, Paragraph 3	"The previous hypothesis that sample would most…"; change to: "The previous hypothesis that sample residues would most…"	A new dietary assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Acute Dietary	2, Last Paragraph	% of CT estimates may be incorrect. See recent California DPR Pesticide Use Report (Jun '05).	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Chronic Dietary Exposure Results and Characterization	3, Paragraph 1	"…from a spray food handling study,…"; change to: "…from a spray application-based food handling establishment study…"	A new dietary assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
II. Introduction	3, Paragraph 4	"This is the most recent dietary assessment."; change to: "This is the most recent dietary assessment guidance."	A new dietary assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Table 1	5,6	The last 2 columns which represent that 100% of almond and barley treated is completely wrong. See California PUR report (January, 2005). California grows the bulk of almonds in the U.S. and in 2003, there were two (2) applications of a total of 1.1 pounds AI to a total of 158 acres. There was no report in 2003 of any California barley being treated with pyrethrin.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Table 1	7	Under "Beans, succulent" the table show 100% of crop treated. In California in 2003 "Beans, succulent" received 5 applications on 45.70 total acres with 0.9 pounds AI of pyrethrins. Blackberry also	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.

Pyrethrins. Acute and Chronic Dietary Exposure Assessments for the Reregistration Eligibility Decision (RED) Document. DP Barcode D295748. December 20, 2004			
Header	**Page #, Paragraph**	**Comments**	**HED Response**
		shows 100% CT yet California DPR data shows 88 applications to 84 acres for a total of 4.5 pounds AI. Blueberry and Buckwheat similarly show 100% CT but California shows 1 application to 84 acres of blueberries and no buckwheat applications.	
Table 1	7	Buckwheat is not 100% treated. Cattle also are not 100% treated. Coca bean and Coconut meat (COPRA) are listed as 100% CT but this is not correct. Crabapple shows 100% CT, but this is also in error.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Table 1	8	Figs and goats also show 100% CT in error. The listing of Guava, Hogs, Horses, Mango, Mur fat and Oats are also listed in error as 100% CT. (10 acres of oats in CA in 2005).	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Table 1	9	Peanuts, Peas and Pineapple all show 100% CT and this is incorrect.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Table1	10	Pineapple, Plum, Prune and Rice all show 100% CT and this is incorrect. No California report of any rice acreage being treated in 2003.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Table 1	11	Rice, Rye, Sheep all show 100% CT and this is incorrect. California is the leading rice producer in the U.S. and no rice was treated in 2003. No rye was treated in CA in 2003. A total of 14.7 pounds AI of Pyrethrins was applied to <u>all</u> livestock in 2003. Walnut, post harvest shows 100%	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.

Pyrethrins. Acute and Chronic Dietary Exposure Assessments for the Reregistration Eligibility Decision (RED) Document. DP Barcode D295748. December 20, 2004			
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		CT however the California DPR report shows 4 applications in 36 acres of 0.4pounds AI.	
Table 1	12	Apricot shows 100% CT but California reports no pounds applied in 2003. Asparagus also incorrect with NO California use. Avocado shows 100% CT but the California data shows 4 applications to 524 acres for a total of 6.2 pounds AI. Banana shows 100% CT but is not correct. Beet shows 100% CT but California data shows 122 applications to 188.4 acres of 2.9 pounds AI. Brazil nut, Butternut are also probably incorrect listed at 100% CT.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Table 1	13	Carob bean, Carrots, Cashews, Cherimoya, Coffee beans, Cranberries, and Dates also show 100% CT. The listings are incorrect.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Table 1	14	Feijoa, Filberts, Food handling, Garlic, Grapefruit, Hickory nut, Joioba, Lemon, Loquat, Lychee, and Millet (grain) also show 100% CT incorrectly.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Table 1	15	Mustard greens, Papaya, Passionfruit, Pecans, Persimmon, Pistachio and Radish all incorrectly show 100% CT.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Table 1	16	Radish, Safflower, Shallot, Starfruit and Sugarcane all incorrectly show 100% CT.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
Table 1	17	Sunflower, Tea, Triticale, and Wild Rice also incorrectly show 100% CT.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated

Pyrethrins. Acute and Chronic Dietary Exposure Assessments for the Reregistration Eligibility Decision (RED) Document. DP Barcode D295748. December 20, 2004			
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			values will be considered in Phase III.
III Drinking Water	18	The DEEM-FCIO model will be based on incorrect % CT data which will create errors in the result.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
IV. DEEM-FCID Program and Consumption Information	18, Paragraph 2	"For acute exposure assessments, maximum consumption data are used…"; change to: "For acute exposure assessments, the entire distribution of consumption data are used…"	A new dietary assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Table 4	20	The children 1-2 % a PAD at 100% as well as all of the other calculations are based on faulty assumptions of % CT and presence of Pyrethrins in water that are unsupported by CA EPA.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.
		The overall comment is that dietary exposure calculations are based on faulty premises that numerous crops are 100% treated with Pyrethrins. That is complicated by models predicting surface water/drinking water contamination from ag drift or runoff and erosion. The California PUR data shows no or minimal use of Pyrethrins on commodities listed as 100% CT.	Percent crop treated data were provided by BEAD. Modifications to percent crop treated values will be considered in Phase III.

Pyrethrins. Residue Chemistry Considerations for Reregistration Eligibility Decision (RED) Document. DP Barcode D295749. October 12, 2004			
Header	**Page #, Paragraph**	**Comments**	**HED Response**
	10, Table 2	The water solubility used in other EPA Assessments is 0.2 PPM.	Please clarify which assessments.
	89, Paragraph 1	Method A is an assay for technical Pyrethrins. Other active ingredients such as PBO and MGK 264 which are frequently formulated with Pyrethrins, will cause interferences with Method A.	Will clarify in revised chapter after phase 3.
	155, Paragraph 2, line 6	The pre-harvest trials involved ten applications at the maximum use rate – not one (IX).	1x refers to the use rate, not the number of applications.
Executive Summary	2, Paragraph 2	Are the residential use on garden crops included here? Residential use is not specifically mentioned here.	Residential uses are not included.
Executive Summary	2, Paragraph 5	Combustible coil, dust, impregnated mat, RTU, shampoo, and towelette are not typically used in Ag or livestock.	Uses are cited from Master Label.
Executive Summary	3, Paragraph 1	Identify “TRR”	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Executive Summary	3, Paragraph 2	Identify “OWR”	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Executive Summary	3, Last Paragraph	Identify “PAM”	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Executive Summary	4, Paragraph 1	Identify “LOQ”	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Residue Chemistry	7, Paragraph 1	Identify “ILV”	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial

Pyrethrins. Residue Chemistry Considerations for Reregistration Eligibility Decision (RED) Document. DP Barcode D295749. October 12, 2004			
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			changes in Phase 3.
Background	8, Paragraph 1	Identify "TGAI"	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
860.1200 Directions	11, Paragraph 2	If there are no registrations of pyrethrin coils, why were they noted on page 2, paragraph 2?	HED concurs with change. A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
	11, Paragraph 3	The information in the Master Label was derived from some basic labels, not hundreds of products, and submitted with the caveat that it did NOT cover all current cases.	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
	11, Paragraph 4	Identify "MAI"	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Crop Group 3	12, last line	"Onion, welsh;" should read "Welsh"	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Crop Group 6	14, second line	Should read "Guar, gum, edible"	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Crop Group 14	20, second category	Not sure that any tree nuts are hydroponically grown. Delete the "application to hydroponically grown" comments.	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Crop Group 16	22	Not sure any of these grain crops are hydroponically grown. Is it necessary to list hydroponic restrictions?	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Crop Group 17	22	Not sure any of these grasses are hydroponically grown. Is it necessary to list hydroponic limitations?	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.

Pyrethrins. Residue Chemistry Considerations for Reregistration Eligibility Decision (RED) Document. DP Barcode D295749. October 12, 2004			
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Crop Group 18	24	Not sure that any of these non-grass animal feeds are grown hydroponically. Is it necessary to list restrictions?	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.
Direct Application To Animals	29	Not sure if exotics would be used for human food.	Master label was used as provided to HED.
860.1400 Water, Fish	99, Paragraph 2, line 3	10-day holding interval for rice.	A new residue chemistry assessment is not needed in Phase 2. Will incorporate editorial changes in Phase 3.

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Header	**Page #, Paragraph**	**Comments**	**HED Response**
1.2 Use Patterns and	3	Pyrethrins are NOT always used with PBO. Pyrethrin does kill.	HED concurs with this comment and the appropriate changes have been made.
Section 1.3	3	"…21-day dermal absorption study in rabbits…"; change "absorption" to "toxicity"	HED concurs with this comment and the appropriate changes have been made.
Section 1.3	3	"A LOAEL of 2.56 mg/kg/day…"; this value, i.e., 2.56 is referred to as "2.57" in some instances in the HED RED chapter (e.g., Section 4.4.7.2, p. 35); the correct value should be used consistently throughout all chapters	HED concurs with this comment and the appropriate changes have been made.
	3, Paragraph 2	We are not aware of any granular formulations that contain Pyrethrins. Is it possible that EPA is referring to some of the dust formulations, such as pyrethrins on diatomaceous earth?	EcoPCO G/X (67425-17) is an active registration granular formulation that is registered for PCO use.
Section 1.3	4	"…DNT…"; DNT should be defined (i.e.., Developmental Neurotoxicity (DNT) study)	HED concurs with this comment and the appropriate changes have been made.
1.3 Hazard Identification	4, Paragraph 2	Extra space between end of second sentence and beginning of third.	HED concurs with this comment and the appropriate changes have been made.
Endpoints Selected	4, Paragraph 2	The PJV disagrees with the Agency's concern that the lack of a NOAEL for Inhalation Exposure and will be submitting a paper explaining our position.	This is a toxicology-related question. It will be addressed by the toxicologist.
Occupational Handler	4, 4 bullet points	The agricultural field crop exposure is in error because of actual reduced % crop treated and less actual acreage than assumed. See California PUR report 1/24/05. Will the structural MOEs change with a respirator requirement?	This is accounted for in the risk characterization section of the ORE chapter. The structural MOEs would be 10x greater if a PF10 respirator is worn.
1.4 Occupational and Residential Exposure and Risk	5, Paragraph 1	The Agency starts discussing indoor metered spray systems found predominantly in restaurants and food processing areas, but then diverges into using a dairy barn scenario to cover all of these indoor use exposure scenarios. We believe the Agency continues to confuse the dairy barn mister spray systems with the smaller compact metered spray systems which a completely different. We do not feel the dairy barn scenario is relevant to the single unit indoor metered spray system scenario.	The dairy barn scenario is based upon the metered release for ag premises in the master label (Table A6). The master label has the same parameters for domestic dwellings and indoor sites (Table C5). There is no indication that a different system would be used in domestic dwellings.
Section 1.4 and Section 6	5, Paragraph 2 and 16, Last Paragraph	"…however, the maximum MOE with an infinite amount of ventilation is 410 because the first minute dose at the target concentration generates an MOE of 410." This statement is misleading and erroneous and should be deleted (it also appears in the last paragraph on p. 16). First, it is inappropriate to compare an inhaled dose obtained in one minute post-metered release in a dairy barn to a subchronic (intermediate-term NOAEL). Further, it appears (based on Appendix A, p. 6) that to derive	HED concurs with the transcription errors cited in appendix A and has made corrections. The issue of comparing one minute exposures to sub-chronic endpoints will be addressed by the toxicologist in the public comment phase.

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		the intermediate term MOE value of 410 (which was based on an incorrect LOAEL value of 2.67 – see Appendix A, p. 6), the dose obtained in one minute was multiplied by 2 (presumably as part of the calculations tracking minute by minute dose) to account for 2 metered releases in a 8-hr work period; thus, the dose estimated was not correctly represented for the "first minute" as stated. Appendix A, p. 6, cites an incorrect inhalation value of "0.000694 m3 per minute"; it appears that the calculations were based on the correct value of 1 m3/hr or 0.0167 m3/min. Appendix A, p. 6, also cites the ventilation rate incorrectly, i.e., it is cited as "Ventilation Rate (Q) = 500 cfm"; the correct value is "5000 cfm"	
Occupational Post Application	6, Paragraph 1	Bulb Dusters & Power Dusters are not used in residential settings.	HED concurs with this comment and the appropriate changes have been made.
Section 2.2	7, Last Paragraph	"The target MOE for intermediate/long term incidental oral exposures is 1000."; The value of 1000 should be corrected to "100" [see "Residential MOE = 100" as presented in Table 2 on page 8, for "Incidental Oral – Intermediate-Term (1 - 6 months)"]	HED concurs with this comment and the appropriate changes have been made.
	9, Section 3.2	Pressurized gases should be aerosols & emulsifiable concentrates should be added.	HED concurs with this comment and the appropriate changes have been made.
4 Incident Report	10	Second sentence is incorrect in that Pyrethrins are NOT always used with PBO. Need to clarify that 10,000 exposures is NOT 10,000 poisonings. Pyrethrins do not have a clear association for causing allergic responses in people allergic to ragweed.	HED acknowledges that pyrethrins are not always used with PBO. However, comments pertaining to the incident report will be addressed by the epidemiologist in the incident report response to comments.
Section 5	10	"…thirty occupational exposure scenarios have been assessed for this RED."; the next page, i.e., p. 11, lists 28 scenarios	HED concurs with this comment and the appropriate changes have been made.
5.1 Occupational	10, Last Paragraph	Bulb and power dusters are PCO equipment, not residential	The cited paragraph refers to occupational handler exposure.
Ag Handling Scenarios	11	Most if not all Ag products with Pyrethrins are emulsifiable concentrates, of these, 90% of applications are by ground boom and 10% are by aerial application. The only air blast applications are for orchards.	Does this mean that the wettable powder/dust formulations could be cancelled for agricultural uses, thus eliminating the handler risks of concern?
Section 5.2.1.2	12	"Default application assumptions…are documented in HED Science Advisory Committee on Exposure's SOP 9…(7/5/2000)"; this is not the most recent version of the SOP; the most recent version should be cited, i.e., SOP 9.1, revised September 25, 2001	SOP 9 was last revised on 7/5/2000. HED is not aware of a version 9.1 dated September 25, 2001.
Section 5.2.1.2	13, Paragraph 2	"(D. Brassard, date)"; the "date" should be removed and replaced with the	HED concurs with this comment and the

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		actual calendar date for the personal communication or document, e.g., memorandum, being cited	appropriate changes have been made.
Section 5.2.2	13 - 14	"The values for areas treated or amounts used per day were generally taken from ExpoSAC Policy #9, except as noted." The values that originate from Policy #9, versus other sources should be more clearly indicated. The Sept 25, 2001 version of Policy #9 does not address "animal groomers and veterinary technicians" or "pest control operator applications". While the subsection "Non-Standard Exposure Assumptions" (p. 14) provides additional documentation (e.g., for pest control applicators), it does not elaborate on the source of assumptions specific to animal groomers and veterinary technicians"	The source of the non-standard assumptions will be clarified in the ORE chapter. The assumption of 8 animals treated per day is from the carbaryl risk assessment. The assumptions for PCO applications are from a PCO survey reviewed by BEAD.
5.22 Exposure	13, Bullet 4	Rates are referenced "in Table 3 above" which there is no "Table 3" in the above part of the document.	Table 3 is located on page 9. This will noted in the ORE document.
5.22 Exposure	13, Bullet 5	The acreages listed may be overly high. The number of animals treated by a vet tech may also be high and the amount used per animal is definitely excessive.	The acreages listed are taken from SOP 9 (July 5, 2000) and given the low risks, additional refinement is not necessary.
5.22 Exposure	13, Last Bullet	Animal Groomers & Veterinary Technicians are more likely to use a dip or a shampoo on animals rather than an aerosol. Also, animals typically do not like the sound of an aerosol & would not stand still long enough to spray out an entire 16 oz. can.	The aerosol can scenario was assessed because there are labels for aerosol can products.
	13, Section 5.2.2	Most of the assumptions of acres treated per day are too high. Typical Ag aerial applications treat about 16 acres & typical ground applications treat about 13 acres.	Assumptions are standard values from SOP 9. Refinement is unnecessary given the risk profile particularly if the WP/Dust formulations are not used.
5.22 Exposure	14, First Bullet	1000 gallons per day for hand wand is high.	This assumption is taken from SOP 9 and is based on PHED application data normalized to an 8 hour day and cultural use patterns.
5.22 Exposure	14, 7th Bullet	A PCO Operator might be able to treat 7 homes in a day, but would be pushed to treat two commercial buildings in a day.	The National Pest Management Association survey data reviewed by BEAD indicate that PCO's spend approximately the same amount of time applying general pest control formulations to residential and commercial buildings.
	14, Last Bullet	Air blast applications are only used for treating orchards and we question their relevance to mosquito adulticide ULV applications.	"A search of PHED and a general literature search revealed no exposure monitoring data for truck-mounted ULV applications. The most directly analogous and still conservative

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			scenario that could be used as a surrogate for truck-mounted ULV is airblast application from a closed cab (PHED Scenario #12)." Pg. 16. *Evaluation of the Potential Health Risks Associated with Occupational Exposures to Pyrethrins and Piperonyl Butoxide. Volume IV: Products for Mosquito Use.*
5.22 Exposure	14, Last Line	We believe that carbaryl is not used for mosquito adulticide anymore.	Use as a mosquito adulticide remains on the carbaryl labels and therefore was assessed.
Non-Standard Exposure Assumption	14	Carbaryl & Cyfluthrin are fairly residual compounds and are quite dissimilar to Pyrethrins.	It is unclear as to how this would affect the handler assessment because the application methods are similar. The longer residual times would only affect post application exposures.
6.1 Exposure Data	16, First Paragraph	No exposure data? Other Task Forces have exposure data relevant to these uses.	Please clarify which data are being referred to in this comment.
6.1 Exposure Data	16, Assumption	No respirator is also assumed? Will that mitigate?	A PF10 respirator would reduce the risk by a factor of 10. However, we do not feel that the use of respirators in dairy barns is practical or enforceable.
6.2 Post-Application Exposure and Risk Estimates	16, Paragraph 4	5th line, extra space between "is" and "ventilated"	HED concurs with this comment and the appropriate changes have been made.
6.2 Post Application	18, Paragraph 1 & 2	Why were default factors used? Other Task Forces have Exposure data relevant to these uses.	The NDETF data is used as appropriate in place of default factors. Any additional data will be considered upon submission.
6.2 Post Application	18, Paragraph 3	Insert comma to separate "Kenya Prentiss"	HED concurs with this comment and the appropriate changes have been made.
7.2.1.3 Post Application Exposure Data	18, Paragraph 4	While it is true that NDETF did measurements of air concentrations after aerosol application, the study did NOT follow label directions to vacate the room for a period of time and to ventilate the room before re-entry of people. This seems a far too conservative use of the data and does not reflect the reality of the use of aerosol sprays. It is also a very unreasonable assumption that a person will empty an entire 16 ounce can into a room. Use Directions almost always indicate a spray time between 3 and 10 seconds.	The NDETF data is adjusted to account for rates listed on the master label. These rates appear to be much higher than rates listed on actual product labels. The use directions are inconsistent with the master label.

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Spray Drift	19, Paragraph 1	Reference to carbaryl as a mosquito adulticide?	Use as a mosquito adulticide remains on the carbaryl labels and therefore was assessed.
Spray Drift	19, Paragraph 1	Other Task Forces have exposure data relevant to these uses.	Please clarify which data are being referred to in this comment. Any additional data will be considered upon submission.
	19, Paragraph 1	Typical Mosquito Adulticide ULV applications are applied in early morning or at dusk when mosquitoes are active and few people are outdoors where they would be exposed.	Many people enjoy sitting on their decks or patios in the evening particularly when the mosquito population is kept under control.
Residential Handler	19, Second Set Bullets	Half acre treated per day at residence? 1000 SF of garden treated per day? 1 aerosol can per day used indoors? Other Task Forces have exposure data relevant to these uses.	These are standard assumptions taken from SOP 12. Any additional data will be considered upon submission.
Turf & Indoor	20, first point	Estimate of transferable turf residue of 5% is SOP, NOT ORETF generic numbers of 22%.	HED used 5% as the transferable turf residue. This comment is unclear.
Turf & Indoor	20, Toddler	100% of soil fraction and 100 mg/day are high and do not account for rapid degredation.	These are standard assumptions from SOP 12. Given the low risks for soil ingestion, it is not necessary to refine these values with pyrethrin specific data.
Pet Treatment	20, first point	8 ounces of product per animal is excessive.	This is a standard assumption from the residential SOPs. Given that the calculated risks are very low, refinement is not necessary.
Section 7.2.2	20, Middle of Page	"Toddler Object to Mouth Scenario"; re-state as "Toddler Object to Mouth Scenario - Turf Reentry"; similarly, "Toddler Incidental Soil Ingestion Scenario" should be re-stated as "Toddler Incidental Soil Ingestion Scenario – Turf Reentry"	HED concurs with this comment and the appropriate changes have been made.
Section 7.2.2	21, Paragraph 2 under "Data Used for Assessing Post Application Exposures"	"Post-fogger release floor concentration was assumed to be 10 ug/cm2." The value used in Appendix A, p. 10, was 9 ug/cm2.	This value has been corrected to 9.77 ug/cm2.
7.2.2. Exposure Assumptions	21, Paragraph 2	PBO is mentioned yet this document is supposed to about pyrethrins. Is this a cut and paste mistake?	HED concurs with this comment and the appropriate changes have been made.
	21, Paragraph 5	Again, should data from a scenario that did not follow label use directions be used for this risk assessment?	HED concurs that this study did not follow the master label because the rates were much lower. Therefore, the data was adjusted to account for the master label rates.

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Section 7.2.2	21, Last Paragraph	"Indoor air concentration for the period during and after aerosol space spray application was assumed to be 0.47 mg per cubic meter (mg/m3) based on data…"; It is unclear how this value was derived from the cited NDETF study. The air concentration of pyrethrins at a 5 ft sampling height, during the 90 – 120 minute sampling period, was 0.0117 ug/L (or 0.0117 mg/m3). This was resultant from the release of 9.31 gm of formulation containing 0.5% pyrethrins (or 0.0465 gm pyrethrins) into a 2048 cubic foot environmental chamber (not "9.3 grams of a 1% pyrethrin formulation" as stated in the first paragraph on p. 22). The 2-hr TWA for pyrethrins in this study was approximately 0.005 mg per cubic meter (mg/m3) at the 5 ft sampling height. Finally, the scenario being addressed, i.e., space spraying for target pests such as flying insects, would typically not involve the use of the entire contents of one 16 oz can in a 2000 cubic foot room. Further, per "use restriction" instructions for space sprays and foggers, on the master label: "Do not remain in the treated area" and "Do not allow adults, children, or pets to enter until treated area has been thoroughly ventilated." Therefore, a more appropriate use of the NDETF aerosol study data would be to use TWA values estimated following a reasonable reentry interval, e.g., TWA for 2 to 10 hrs post-application. In the case of pyrethrins, the 8 hr TWA between 2 and 10 hrs post application was 0.0000024 mg/m3 at the 5 ft sampling height, clearly indicating negligible post-application inhalation exposure potential.	The 2 hr TWA air concentration of 0.019 mg/m3 was adjusted to account for the master label application rate of 0.00033 lb ai/1000 cf. This rate is much higher than the study application rate of 0.00010 lb ai/1000 cf. If the study application rate is more reflective of the actual use, then the master label should be revised. This issue of room ventilation will be addressed in the public comments after the application rate discrepancy is corrected.
	22, Paragraph 1	The use of an entire 16 ounce can is inconsistent with label directions which recommends a ten second burst to treat a typical 12' x 12' room.	Again, the label directions are not consistent with the Master label.
Uncertainties	24, Paragraph 1	Not even 1 can would be used!	It would be necessary to use one can to achieve the master label rate.
Uncertainties	24, Paragraph 2	Most pyrethrin liquid products are RTU, not concentrates	This information will be used for risk characterization.
	24, Paragraph 24	Brad has found that the percent of crop treated for field crops are generally less than 2.5 percent which is inconsistent with percent of crop treated in the Dietary Assessment in a separate document. The EPA should consistently use the Brad findings.	The issue of percent crop treated is discussed in the Dietary response to comments document.
Appendix, Table 6	7 of Appendix	Column "Amount a.i. Used per Day", bottom box. Line goes through the middle of the cell. Should this line be there?	This will be corrected.

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Incident Data System	2, Paragraph 5	There are registrations of Pyrethrin only products for use on agricultural crops, contrary to the statement that the Pyrethrin only products are MUP products.	Change wording of sentence to be clearer "*Only about 120 products (nearly half are intermediates, intended for use in formulation) are registered containing just pyrethrins as the active ingredient.*"
	5, Paragraph 3	Eye irritation from a shampoo product is not unexpected and is not due to pyrethrins but the surfactants and detergents in the shampoo. These are defatting agents which are expected to produce all of the eye symptoms noted. Data on Pyrethrin Technical does not present such ocular symptoms.	Not an error. An incident review always reviews the product as formulated and not the technical.
	6, Paragraph 2	Four (4) confirmed incidents in California over a 20 year period is inconsequential.	Not an error. To know whether four is inconsequential or not, we would need to know the number of applications of pyrethrins alone without any other ingredients involved. This information is not available.
	6, Paragraph 3	The NPTN incidents are also reflective of low toxicity and irritation potential.	Speculation rather than an error. Without knowing the denominator of cases and the proportion of reported cases exhibiting irritation, this comment cannot be supported.
V NIOSH Sensor	6, Last Paragraph	10 cases reported from California does not agree with California's 4 incidents between 1982-2002 – why?	Agree. The following explanatory note has been added: *"Note that the California reports come from the California Department of Health Services which use different criteria for listing an incident as due to*

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			pyrethins than the California Department of Pesticide Regulation (cited in section III above) which reported only 4 cases where pyrethrins was determined to be the primary pesticide responsible for the illness in their data from 1982 to 2002."
	8 & 9	Pyrethrins are not pyrethroids.	This beginning of this section states: "The following information was copied from the Hazardous Substances Databank (HSDB), a database of the National Library of Medicine's TOXNET system (http://toxnet.nlm.nih.gov) on April 2, 2003." Then it goes on to quote the following concerning pyrethroids: "Chronic respiratory disease: In persons with chronic respiratory disease, especially asthma, the inhalation of /pyrethroids/ might cause exacerbation of symptoms due to its sensitizing properties. Skin disease: /Pyrethroids/ can cause dermatitis which may be allergic in nature. Persons with pre-existing skin disorders may be more susceptible to the effects of this agent. Any employee developing the above-listed conditions should be referred for further medical examination. /Pyrethrum/" "The allergenic properties of pyrethroids /with early pyrethrum preparations/ are marked in comparison with other pesticides. Many cases of contact dermatitis and respiratory allergy have been reported. Persons sensitive to ragweed pollen are particularly prone to such reactions. Preparations containing synthetic

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			pyrethroids are less likely to cause allergic reactions than are the preparations made from pyrethrum powder. /Pyrethroids/" "Initial medical screening: Employees should be screened for history of certain medical conditions ... which might place the employee at increased risk from /pyrethroid/ exposure. Chronic respiratory disease: In persons with chronic respiratory disease, especially asthma, the inhalation of /pyrethroids/ might cause exacerbation of symptoms due to its sensitizing properities. Skin disease: /Pyrethroids/ can cause dermatitis which may be allergic in nature. Persons with pre-existing skin disorders may be more susceptible to the effects of this agent. Any employee developing the above-listed conditions should be referred for further medical examination. /Pyrethrum/" HED agrees that the authors of these quotes appear to have confused pyrethrins and pyrethroids in their review statements. This is a fault of the Hazardous Substances Databank and does not significantly alter any of the conclusions derived from it.
VI Conclusions	9	We disagree with the conclusion (general) that pyrethrins "can be a skin or eye irritant from direct exposure", as the six pack of	One of the primary purpose of an incident review is to identify shortcomings of "the six pack of acutes"

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		acutes will accurately define the acute toxicological properties of a product. The acutes should continue to be the factual information upon which precautions are based.	performed on animal data. This review successfully did that and the conclusion will not be altered. Note that the conclusion applies to products as formulated and not the technical ingredient.
VII Recommendations	9, First Paragraph	We disagree with the suggestion from Mosby's Master Degree Thesis that labels need to carry additional warnings connecting ragweed allergy to potential consequences of inhalation of product containing pyrethrins. Not sufficient data.	The suggestion from the Mosby thesis is her opinion. The HED recommendation based on her thesis and other sources was " Patients with a history of asthma or ragweed allergy should consult their physician prior to use" should be considered. Such warnings should only apply to products used in enclosed spaces." Note that HED was careful to advise that this recommendation be "considered" not adopted because HED agrees the data is not sufficient.

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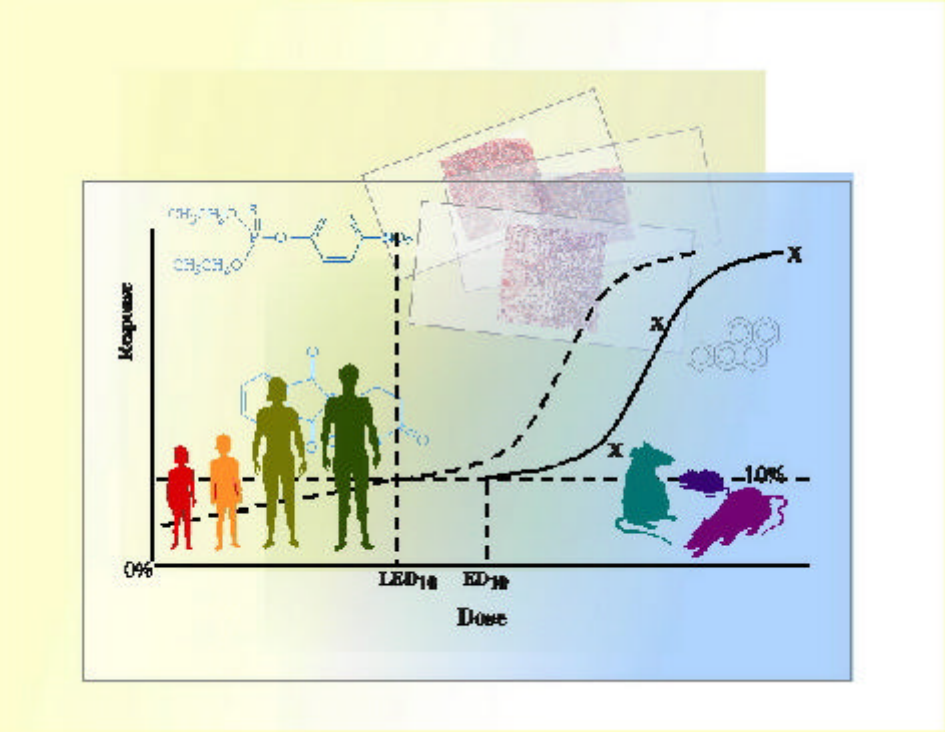
	9, Last Paragraph	The acute toxicity studies should continue to define the toxicity category and precautionary statements that are appropriate for a product. We disagree with the recommendation.	As stated above: One of the primary purpose of an incident review is to identify shortcomings of "the six pack of acutes" performed on animal data. The recommendation: "Pyrethrins products should include label warnings of their risk to skin, eye, or respiratory effects if used in enclosed spaces" is clearly warranted by the evidence provided in this review. As safe as pyrethrins are, they are not perfect and some people will react to them as clearly demonstrated by the reports. There is no reason that these people shouldn't have the benefit of a simple warning, same as any other pesticide.
References	10	Wagner is listed as a reference, but it is not cited in the document.	Agree. Paragraph has been added to include this reference.

HUMAN HEALTH RISK ASSESSMENT

Pyrethrins



U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)
Christine Olinger, Chemist/Risk Assessor
Date: April 21, 2005

HUMAN HEALTH RISK ASSESSMENT

Pyrethrins

Risk Assessment Team:

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1.0 Executive Summary

This risk assessment is being conducted in association with the Reregistration Eligibility Decision for the pyrethrins. Pyrethrins are botanical insecticides with mixed active ingredients present in commercially available extracts of the pyrethrum flower, largely *Chrysanthemum cinerariaefolium*. Such extracts, used for formulating the final product, contain 20-25% total pyrethrins, the main active constituents being pyrethrin 1 and pyrethrin 2 plus smaller amounts of the related cinerins and jasmolins. Formulated products generally contain 0.25 - 0.5 % active ingredients.

The Pyrethrin Joint Venture (PJV) is supporting the reregistration of pyrethrins. The food/feed uses of pyrethrins which are being supported by PJV include: (i) preharvest and postharvest uses on many agricultural crops; (ii) direct and indirect treatments of livestock animals and premises; (iii) treatments of commercial and industrial facilities and storage areas where raw and processed food/feed commodities are stored or processed; and (iv) mosquito abatement areas including aquatic areas; (v) structural treatments; and (vi) treatment of domestic animals. The Master Label submitted by PJV, presented in Appendix 1, shows that there are at least 19 crop groups and several miscellaneous commodities that will be supported for reregistration.

Pyrethrum is considered an axonic poison. The axon of a nerve cell is vital in the transmission of nerve impulses from one cell body to other cells, and chemicals that affect this impulse transmission are referred to as axonic poisons. The fast knockdown of flying insects is the result of rapid muscular paralysis, making it appear to have its effect on the ganglia of the insect central nervous system. There is also evidence that its effects are on the neurons. Pyrethrins, along with pyrethroids, appear to affect the sodium channel.

Sufficiency of Hazard Data The toxicological database, with the exception of a developmental neurotoxicity study [and a comparative thyroid study], is adequate to support the reregistration of pyrethrins. Evidence of quantitative susceptibility was found following *in utero* and/or pre-/postnatal exposure in the 2-generation reproduction study in rats. However, except for the data needs described below, data are sufficient for important endpoints and dose-response evaluation for three species [rat, mouse, dog]. Data are sufficient for all exposure scenarios and for FQPA evaluation. Due to the finding of neuropathology in rats following acute exposure, a developmental neurotoxicity study is required. Due to thyroid effects observed following chronic exposure, a comparative thyroid study in adult and young animals is required. This request stems from concerns regarding the possible impact of perturbations of thyroid function on the development of the young.

Toxicological Effects The critical effects are (1) neurobehavioral [rat, mouse] following acute, short-term, and chronic exposure, with neuropathological lesions following acute exposure; (2) thyroid [rat, dog] following chronic exposure; and (3) liver [rat, dog, mouse] following short- and long-term exposure. Following inhalation exposure, neurobehavioral effects were observed initially, and histopathological lesions of the lungs/respiratory tract were observed at all dose levels. The neurobehavioral effects and the mode of action are considered relevant to humans as the effects are observed in the rat and mouse, and the mode of

action affects a basic function of the nervous system that is common to all animals.

There is suggestive evidence that pyrethrins are carcinogenic in rats based on the weight-of-the-evidence considerations, which include the occurrence of benign liver tumors only in female rats. No treatment-related increase in tumors in male rats [other than thyroid adenomas] or mice of either sex was observed, and there is no concern for mutagenicity. The finding of thyroid tumors in rats of both sexes is not of concern for humans based on the differences of the possible modes of carcinogenic action in humans and rats. Pyrethrins show no significant teratogenic or reproductive effects in rats, although quantitative susceptibility was observed in the reproduction study where decreased pup body weight occurred at a dose level where no maternal effects were observed. Although one abortion and one full litter resorption were seen in the rabbit developmental toxicity study, relevance of these findings in ascribing evidence of developmental toxicity is equivocal since it is not uncommon for rabbits to abort/resorb their litters.

Dose - Response Assessment Toxicity data are available for selecting endpoints and doses for risk assessment. Studies demonstrating body-weight decrements [rat and rabbit], neurobehavioral effects [rat and rabbit], and thyroid effects [rat] were considered.

The oral Point of Departure [POD] for the acute RfD [general population, including infants and children] was based on an acute neurotoxicity study in rats. No appropriate single-dose endpoint was available specifically for the acute oral exposure of females 13-49 years old. The combined chronic toxicity/carcinogenicity study in rats was used as the basis for selecting the NOAEL for the chronic RfD. Also considered for this exposure scenario was the 2-generation reproduction study in rats. The chronic toxicity study was used because it provided the lowest NOAEL for an endpoint of concern [thyroid effects]. The rabbit developmental toxicity study was selected for the short-term incidental oral exposure scenario, and the 2-generation reproduction study in rats was selected for the intermediate-term incidental oral exposure scenario. Other studies considered for the latter scenario included the rabbit developmental toxicity study and a mechanistic study in rats. The selected study provides a POD that is protective of effects observed in the other studies.

Dermal risk assessments are not required due to negligible dermal absorption and dermal toxicity. There is an acceptable 21-day dermal toxicity study in rabbits in which no systemic or dermal toxicity was observed at the limit dose [1000 mg/kg/day]. Additionally, there is an acceptable human dermal penetration study available that demonstrates absorption of less than 0.22%.

The inhalation POD's were based on clinical signs and body-weight effects early [short-term] in the study and respiratory tract lesions observed at study termination [intermediate and long-term] in the 90-day inhalation toxicity study. The study was an appropriate route-specific study and was used for all exposure durations.

No quantification of cancer risk is required, based on the "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" classification.

The uncertainty factors used in determining the acute RfD exposure limits were: 10X for interspecies extrapolation; 10X for intraspecies extrapolation; and 3X for database uncertainty factor [UF_{DB}]. The uncertainty factors used in determining the chronic RfD exposure limits were: 10X for interspecies extrapolation and 10X for intraspecies extrapolation.

FQPA No evidence of increased susceptibility of rats or rabbits was seen in developmental toxicity studies. Although there was evidence of increased quantitative susceptibility following *in utero* and/or pre-/postnatal exposure in the 2-generation reproduction study in rats, the reproductive/offspring toxicity NOAELs and LOAELs are well characterized and are used as endpoints for risk assessment for the appropriate population subgroups. Since there are no residual uncertainties that indicate the need for a special FQPA safety factor, the Special FQPA safety factor is 1X.

Dietary Exposure Acute and chronic dietary exposure and risk assessments were conducted. Food and water were considered in these somewhat refined assessments. Limited field trial data were available to assess the exposure from pre-harvest applications of pyrethrins; adequate data were available reflecting post-harvest and food-handling establishment applications. Percent of crop treated information were incorporated for some commodities. Exposures from pyrethrins in drinking water were modeled for both ground and surface water. Estimated risks for all subpopulations from acute and chronic exposures were generally well below the level of concern, with the exception of one scenario. Acute dietary exposures to pyrethrins for children 1-2 were at 100% of the population adjusted dose. This assessment is somewhat refined, but there is considerable uncertainty, given the minimum amount of field trial data. Additional percent crop treated information would be expected to reduce the estimated risks.

Residential Exposure Both residential handler scenarios and residential post-application scenarios were assessed. All of the handler scenarios have Margins of Exposure (MOEs) that exceed the target MOE; therefore, the handler risks are not of concern. The post application scenarios include mosquito abatement, turf treatment, indoor fogger use, pet treatment, space sprays, and compact metered release. Most of the MOEs estimated exceed the target MOE. The metered release MOEs of 40 to 780 for intermediate term exposures are less than the target MOE of 1000, and are of concern. There is considerable uncertainty for these estimates, so the Agency is requesting additional information about the products, including usage information and the droplet size of the spray.

Aggregate Exposures Food and water exposures were aggregated for acute (<1 day) exposures. Risk estimates for most sub-populations were well below the level of concern. Risk estimates for children (age 1-2) were just at or slightly exceeded the level of concern. Although a probabilistic assessment was conducted, the residue values used were high-end field trial values, and percent crop field trial data were available for a only limited number of crops. Therefore, HED considers this to be an upper-bound estimate, and the actual risk may be lower.

The aggregate assessment for short-term intervals included food, water, incidental oral, and inhalation exposures. The assessment was based on neurotoxic effects found in oral and inhalation studies. The

aggregate exposures for most sub-populations were well below our level of concern, with the exception of children, ages 1-6. The risk estimates for this population slightly exceeded the level of concern. However, these estimates are considered to be high end estimates for both the food and residential exposures, as described in the previous paragraph on food exposures. The residential assessments represent a high-end risk estimate as some of the label rates used, as described in the Master Label provided by the Pyrethrins Joint Venture, are higher than those found on most labels.

For intermediate and long-term exposures only food and water may be aggregated. The risk estimates are well below the level of concern, and again represent somewhat refined, but still high-end, exposures.

Occupational Exposures A variety of handler exposure scenarios were assessed including agricultural application, pesticide control operator applications, mosquito abatement application and veterinary/pet grooming. All of the short-term exposures assessed are not of risk concern. Most of the exposure scenarios assessed for intermediate-term exposures did not exceed the level of concern, with the exception of two mixer/loader agricultural scenarios and two pest control operator scenarios. The application of dust with bulb dusters and power dusters, a relevant and potentially significant scenario for occupational exposures, was not assessed due to the lack of adequate inhalation unit exposure data. The intermediate term occupational risks for agricultural handlers are conservative because pyrethrins are infrequently used on field crops and exposures of an intermediate duration (greater than 30 days in a row) are unlikely to occur. The intermediate term occupational risks for PCOs are conservative for crack and crevice treatments because the assumed area treated (1600 sf per building) is based upon the floor surface of the building rather than the cracks and crevices, which occupy a much smaller area.

Occupational post application inhalation exposures are anticipated primarily from metered release applications. The risk estimates for short term exposure is not of concern, however the estimates for intermediate (1-3 mos.) term exposures are of concern. The concerns about the high-end Master Label application rates used in the residential assessments also applies to the occupational assessments as well.

2.0 Ingredient Profile

Pyrethrins are botanical insecticides with mixed active ingredients present in commercially available extracts of the pyrethrum flower, largely *Chrysanthemum cinerariaefolium*. Such extracts, used for formulating the final product, contain 20-25% total pyrethrins, the main active constituents being pyrethrin 1and pyrethrin 2 plus smaller amounts of the related cinerins and jasmolins. Formulated products generally contain 0.25 - 0.5 % active ingredients.

2.1 Summary of Registered Uses

The Pyrethrin Joint Venture (PJV) is supporting the reregistration of pyrethrins. Uses of pyrethrins that are being supported by PJV include: (i) preharvest and postharvest uses on many agricultural crops; (ii) direct and indirect treatments of livestock animals and premises; (iii) treatments of commercial and industrial facilities and storage areas where raw and processed food/feed commodities are stored or processed; (iv) mosquito abatement areas including aquatic areas; (v) structural treatments; and (vi) treatment of domestic animals. The Master Label submitted by PJV, presented in Appendix 1, shows that there are at least 19 crop groups and several miscellaneous commodities that will be supported for reregistration.

On agricultural crops, pyrethrins may be applied preharvest or postharvest. Preharvest applications to field and orchard crops are allowed with a maximum of 10 treatments per growing season, and a single application rate of 0.05 lb ai/A, or 0.10 ppm ai in water when applied hydroponically. Preharvest applications to greenhouse crops are also allowed with a maximum of 10 treatments per growing season, and a single application rate of 0.05 lb ai/A when applied as a surface treatment or 0.00014 lb ai/1,000 cu. ft when applied as a space treatment. No preharvest intervals are established or proposed except for cotton which specifies a 14-day PHI.

Postharvest applications to vegetables, fruits, and nuts are allowed at the following maximum rates: (i) 0.01 lb ai/1,000 sq. ft for general surface treatment; (ii) 1.6×10^{-7} lb ai/ lb of fruit or vegetable (0.16 ppm) for direct surface application to fruits or tomatoes in baskets or hampers; (iii) 0.22 lb ai/1,000 sq. ft for crack and crevice treatment of bagged products; (iv) 0.00027 lb ai/1,000 cu. ft for space treatment of bagged products and sweet potatoes; and (v) 0.0001 lb ai/1,000 cu. ft for space treatment of fruits, vegetables, and copra.

The following formulation classes are presently registered for use: aerosol; combustible coil; dilutable concentrate; dust; emulsifiable concentrate; gel; impregnated packaging mat; microemulsion; microencapsulated (ready-to-use spray and liquid concentrate), ready-to-use liquid, pour-on (spot-on), pressurized dust, pressurized liquid, pressurized spray, shampoo, water-based concentrate, wettable powder, and towelette. The above formulations may be applied using ground and aerial equipment.

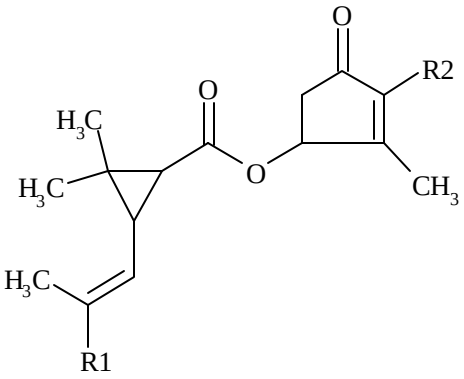
2.2 Structure and Nomenclature

Pyrethrins is the collective name of the insecticidal active ingredients present in pyrethrum extracts which are obtained from the dried and ground flowers of the pyrethrum plant, *Chrysanthemum cinerariaefolium*. The CAS Registry No. for the mixture is 8003-34-7. Currently, food/feed uses are only registered for products under PC code 069001, mixed esters of (+)-trans-chrysanthemic acid and (+)-pyrethroic acid. The nomenclature of the individual pyrethrins active ingredients is presented below in Table 1. The physicochemical properties of the refined pyrethrin extracts (TGAI) are listed in Table 2.

Throughout this document the individual compounds are referred to by the common names of the acid (in lower case e.g. pyrethrin, cinerin) followed by a number in Arabic (1 or 2). If common names are plural, but not followed by a numerical designation, then it refers to both 1 and 2 forms. If the term Pyrethrins is used, and followed by a numerical designation, than the term refers to all of the isomers of that number in the pyrethrum extract (e.g. Pyrethrins I includes pyrethrin I, cinerin I, and jasmolin I). Pyrethrum is also used as a term for insecticidal extract of the *Chrysanthemum cinerarieaefolium* plant, and is used in this document as a term to denote all six active ingredients collectively.

TABLE 2.1. Pyrethrin Nomenclature.

Chemical Structure



Pyrethrin I: R1 = CH_3; R2 = $CH_2CH=CHCH=CH_2$
Pyrethrin II: R1 = $COOCH_3$; R2 = $CH_2CH=CHCH=CH_2$
Cinerin I: R1 = CH_3; R2 = $CH_2CH=CH_3$
Cinerin II: R1 = $COOCH_3$; R2 = $CH_2CH=CH_3$
Jasmolin I: R1 = CH_3; R2 = $CH_2CH=CHCHCH_3$
Jasmolin II: R1 = $COOCH_3$; R2 = $CH_2CH=CHCHCH_3$

Common name	Pyrethrin 1
Molecular Formula	$C_{21}H_{28}O_3$
Molecular Weight	328.4
IUPAC name	(Z)-(S)-2-methyl-4-oxo-3-(penta-2,4-dienyl)cyclopent-2-enyl (1R,3R)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate
CAS name	(1S)-2-methyl-4-oxo-3-(2Z)-2,4-pentadienylcyclopenten-1-yl (1R,3R)-2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate
CAS #	121-21-1
Common name	Pyrethrin 2
Molecular Formula	$C_{22}H_{28}O_5$

Table 2.1 continued on following page

TABLE 2.1. Pyrethrin Nomenclature.	
Molecular Weight	372.4
IUPAC name	(Z)-(S)-2-methyl-4-oxo-3-(penta-2,4-dienyl)cyclopent-2-enyl (E)-(1R,3R)-3-(2-methoxycarbonylprop-1-enyl)-2,2-dimethylcyclopropane-carboxylate
CAS name	(1S)-2-methyl-4-oxo-3-(2Z)-2,4-pentadienyl-2-cyclopenten-1-yl (1R,3R)-3-[(1E)-3-methoxy-2-methyl-3-oxo-1-propenyl]-2,2-dimethylcyclo-propanecarboxylate
CAS #	121-29-9
Common name	Cinerin 1
Molecular Formula	$C_{20}H_{28}O_3$
Molecular Weight	316.4
IUPAC name	(Z)-(S)-3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl (1R,3R)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate
CAS name	(1S)-3-(2Z)-2-butenyl-2-methyl-4-oxo-2-cyclopenten-1-yl (1R,3R)-2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate
CAS #	25402-06-6
Common name	Cinerin 2
Molecular Formula	$C_{21}H_{28}O_5$
Molecular Weight	360.4
IUPAC name	(Z)-(S)-3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl (E)-(1R,3R)-3-(2-methoxycarbonylprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate
CAS name	(1S)-3-(2Z)-2-butenyl-2-methyl-4-oxo-2-cyclopenten-1-yl (1R,3R)-3-[(1E)-3-methoxy-2-methyl-3-oxo-1-propenyl]-2,2-dimethylcyclopropanecarboxylate
CAS #	121-20-0
Common name	Jasmolin 1
Molecular Formula	$C_{21}H_{30}O_3$
Molecular Weight	328.4
IUPAC name	(Z)-(S)-2-methyl-4-oxo-3-(pent-2-enyl)cyclopent-2-enyl (1R,3R)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate
CAS name	(1S)-2-methyl-4-oxo-3-(2Z)-2-pentenyl-2-cyclopenten-1-yl (1R,3R)-2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylate
CAS #	4466-14-2
Common name	Jasmolin 2
Molecular Formula	$C_{22}H_{30}O_5$
Molecular Weight	374.4
IUPAC name	(Z)-(S)-2-methyl-4-oxo-3-(pent-2-enyl)cyclopent-2-enyl (E)-(1R,3R)-3-(2-methoxycarbonylprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate

Table 2.1 continued on following page

TABLE 2.1. Pyrethrin Nomenclature.	
CAS name	(1S)-2-methyl-4-oxo-3-(2Z)-2-pentenyl-2-cyclopenten-1-yl (1R,3R)-3-[(1E)-3-methoxy-2-methyl-3-oxo-1-propenyl]-2,2-dimethylcyclopropanec arboxylate
CAS #	1172-63-0

2.3 Physical and Chemical Properties

TABLE 2.2. Physicochemical Properties of Refined Pyrethrins (TGAI).	
Parameter	Value
Boiling point	Pyrethrin 1 = 146-148 °C at 2 x 10^{-3} Torr Pyrethrin 2 = 196-198 °C at 7 x 10^{-3} Torr Cinerin 1 = 136-138 °C at 8 x 10^{-3} Torr Cinerin 2 = 182-184 °C at 1 x 10^{-3} Torr
pH	Not applicable because the TGAI is practically insoluble in water.
Density, bulk density, or specific gravity	0.982 g/mL at 20 °C Pyrethrin 1 = 1.5242 g/mL Pyrethrin 2 = 1.5355 g/mL
Water solubility	<10 ppm Pyrethrin 1 = 0.00002 g/100 mL at 20 °C Pyrethrin 2 = 0.00090 g/100 mL at 20 °C
Solvent solubility	Completely soluble in nonpolar organic solvents; <0.1% in ethylene glycol Soluble in alcohol, petroleum ether, and methylene chloride
Vapor pressure	Pyrethrin 1 = 2 x 10^{-5} mm Hg at 25 °C Pyrethrin 2 = 4 x 10^{-7} mm Hg at 25 °C
Dissociation constant, pK_a	Not applicable because pyrethrins do not dissociate
Octanol/water partition coefficient	Pyrethrin 1 = 5.90 pK_{OW} at 25 °C Pyrethrin 2 = 4.30 pK_{OW} at 25 °C
UV/visible absorption spectrum	Not available

3.0 Metabolism Assessment

3.1 Nature of the Residue in Foods

3.1.1. Description of Primary Crop Metabolism

The qualitative nature of the residue in plants is adequately understood based on acceptable metabolism studies conducted on three dissimilar crops: leaf lettuce, potatoes, and tomatoes. Studies have been conducted only with pyrethrin I, due to the difficulty incorporating a ^{14}C label into the other five active ingredients. It is assumed that the metabolism of all six active ingredients will be similar, due to the similarity in structures. However, this remains an uncertainty in this assessment.

The results show that pyrethrin 1is not readily translocated in the plants tested. Parent pyrethrin 1 was found in tomato fruit [13.18% Total Radioactive Residue (TRR)] and a negligible amount was found in potato tubers (0.75% TRR). For tomatoes and potatoes, most of the applied pyrethrin 1 or its metabolites remained in/on the foliage, and a small amount was translocated from the foliage to the fruit or root of the plant. The registrants state that this pattern is consistent with the expected behavior of pyrethrins, which are highly lipophilic compounds and, thus, would not be taken up efficiently by the plant following foliar application. Similarly, pyrethrin 1 was the major residue component identified in Day-0 lettuce samples which is expected because lettuce leaves were directly treated. The five identified metabolites are all products of cleavage of the ester bond. Numerous other metabolites were observed by HPLC. These identified metabolites, each present at <10 % of the Total Radioactive Residue (TRR), could be either cleaved or uncleaved.

A proposed metabolic pathway for pyrethrin 1 in plants is presented in Appendix 2 to this document. A table of major and minor residues found in the plant and livestock metabolism studies is presented in Appendix 3.

3.1.2 Description of Livestock Metabolism

The qualitative nature of the residue in ruminants and poultry is adequately understood based on acceptable metabolism studies reflecting both dermal and oral treatments. Both studies utilized [cyclopropyl-14C]pyrethrin as the test substance. They have been reviewed by HED (DP Barcodes D212488, et. al., 5/20/99, T. Morton; and D289826, 8/5/04, J. Deluzio) and deemed adequate to support reregistration requirements. In both studies, a moderate amount of cleavage of the ester was observed. Thus, in livestock, partial cleavage of pyrethrin 1 does occur. Uncleaved metabolites were also found, indicating that cleavage is only partial, not total.

The reviewed studies reported that excretion of radioactivity by both hens and goats was extremely rapid. For orally dosed hens, 89% of administered radioactivity was excreted within six hours of administration of the last dose. Goats excreted 75% of administered radioactivity within five hours of receiving the last dose.

These findings, according to the registrants, substantiate those of the study on metabolism of pyrethrin 1 in rats, that pyrethrins and their metabolites are rapidly eliminated following ingestion by mammals. For goats, the % TRR found in urine, feces, milk, and tissues was reported, so a distribution pattern can be obtained. Of total radioactivity in the four matrices, 97.8% was found in urine and feces, and only 2.2% was found in tissues and milk, confirming low transport to tissues and efficient elimination of pyrethrin 1 and its metabolites. Similar data were not given for hens, but the low absolute levels of radioactivity found in tissues and eggs suggest similar low transport to tissues and similarly efficient elimination.

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

No studies have been submitted that describe the nature or the magnitude of residues in rotational crops.

3.2 Environmental Degradation

The environmental fate data were developed for pyrethrin 1 as a representative chemical. All other pyrethrins are expected to have similar environmental fate properties. Parent pyrethrin 1 is not very persistent. When applied to soil, it is likely to remain near the surface and degrade relatively rapidly via photolysis (aqueous photolysis t½=11.8 hr; soil photolysis t½=<24 hr) and less rapidly via aerobic soil metabolism (t½ = 3.2 days). Parent pyrethrin is considered immobile (ASTM, 1996) because of the high Koc values (12,472 - 74,175) and there is an extremely small likelihood of its leaching to groundwater. Pyrethrins may be applied by air and surface water could become contaminated through spray drift or runoff events accompanied by erosion that occur shortly after application. In aquatic environments, pyrethrin is moderately persistent under aerobic aquatic metabolism (t½ = 10.5 days) and relatively persistent under anaerobic aquatic metabolism (t½ = 86.1 days). An evaluation of the structures of the degradates of pyrethrin show that they are the product of the rupture of the ester bridge of the parent, resulting in a carboxylic acid (chrysanthemic acid) and an alcohol (pyrethrolone). The resulting degradates have lost their pyrethroid activity. Chrysanthemic acid was formed in small amounts except under hydrolytic conditions at pH 9. Other major degradate observed, which was transient, was named (E)-isomer of pyrethrin I, in the aqueous photolysis study, but it was included in the expression of the half-life of the parent, resulting in a half-life of less than 1 day.

3.3 Rat Metabolism

Pyrethrin 1 and II structures undergo metabolism by oxidation at the alkyl side chains to yield several metabolites that are either excreted or conjugated and then excreted. Pyrethrin 1 is also hydrolyzed at the alcohol carboxylic acid ester linkage to yield the alcohol and acid, which may be oxidized at the alkyl side chains to make additional metabolites. Data from in vivo metabolic studies have been supported by in vitro studies. At least some in vitro data indicate that the jasmolins and cinerins are also metabolized by liver oxidase systems.

3.4 Toxicity Profile of Major Metabolites and Degradates

Although toxicity studies on the degradates were not provided, an evaluation of the structures indicate that they are the result of the rupture of the ester bridge of the parent, resulting in a carboxylic acid (chrysanthemic acid), and an alcohol (that subsequently are degraded to an acid as well). The resulting molecules have lost their neurotoxic activity; therefore, in this assessment, they were not considered of concern.

3.5 Summary of Residues for Tolerance Expression and Risk Assessment

3.5.1 Tabular Summary

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

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Pyrethrin 1, Pyrethrin 2, Jasmolin 1, Jasmolin 2, Cinerin 1, Cinerin 2	Pyrethrin 1, Jasmolin 1, Cinerin 1
	Rotational Crop	NS [1]	NS [1]
Livestock	Ruminant	Pyrethrin 1, Pyrethrin 2, Jasmolin 1, Jasmolin 2, Cinerin 1, Cinerin 2	Pyrethrin 1, Jasmolin 1, Cinerin 1
	Poultry		
Drinking Water		Pyrethrin 1, Pyrethrin 2, Jasmolin 1, Jasmolin 2, Cinerin 1, Cinerin 2	Not Applicable

[1]NS = No studies. No studies have been provided; therefore, no decision can be made at this time.

3.5.2 Rationale for Selection of Metabolites and Degradates

It is generally recognized that the neurotoxic qualities of pyrethroid insecticides require an intact ester. Major metabolites identified in the plant and animal metabolism studies, as well as environmental fate studies, are cleavage products of ester hydrolysis. Therefore, it is generally recognized that these metabolites are not of concern for the endpoints identified for the pyrethrins. Specific toxicity concerns have not been identified for the cleavage products themselves, and they are expected to be less toxic than the parent since they have lost their neurotoxic potential and are considerably more polar than the parent compounds.

4.0 Hazard Characterization/Assessment

4.1 Hazard and Dose-Response Characterization

Database Summary

Studies available and considered

- Acute: acute neurotoxicity
- Subchronic: 21-day dermal toxicity, subchronic inhalation toxicity
- Chronic: combined oral chronic toxicity/carcinogenicity (rat);
- Reproduction/Developmental: *oral:* developmental toxicity (rat and rabbit); 2-generation reproduction (rat)
- Other: mechanism study [7-, 14-, and 42-day exposures]

Acute - *oral:* developmental toxicity (rat and rabbit); acute neurotoxicity
Short-term - *oral*: developmental toxicity (rat and rabbit)/mechanistic data; *dermal*: developmental toxicity (rat and rabbit)/21-day dermal toxicity/mechanistic data; *inhalation*: subchronic inhalation toxicity (rat)
Intermediate/Subchronic - *inhalation*: subchronic inhalation toxicity (rat); *dermal*: 2-generation reproduction (rat)/21-day dermal toxicity/mechanistic data; *oral*: chronic toxicity (rat)/2-generation reproduction (rat)
Chronic - *inhalation*: subchronic inhalation (rat); *dermal*: 2-generation reproduction (rat)/21-day dermal toxicity; *oral*: chronic toxicity (rat)/2-generation reproduction (rat)

Mode of Action, Metabolism, Toxicokinetic Data
Pyrethrins [Pyrethrum] are a mixture of botanical pesticides, the active ingredients of which are **PYRETHRINS 1 and 2** [esters of pyrethrolone and chrysanthemic acid and pyrethroic acid], **CINERINS 1 and 2** [esters of cinerolone and chrysanthemic and pyrethroic acids], and **JASMOLIN 1 and 2** [esters of jasmolin and chrysanthemic and pyrethroic acids], collectively known as pyrethrins. Pyrethrum is considered an axonic poison. The axon of a nerve cell is vital in the transmission of nerve impulses from one cell body to other cells, and chemicals that affect this impulse transmission are referred to as axonic poisons. The fast knockdown of flying insects is the result of rapid muscular paralysis, making it appear to have its effect on the ganglia of the insect central nervous system. There is also evidence that its effects are on the neurons. Pyrethrins, along with pyrethroids, appear to affect the sodium channel.

Pyrethrin 1 is rapidly metabolized by cytochrome P-450-dependent microsomal oxidases in house flies and probably other insects. Pyrethrins structures undergo metabolism by oxidation at the alkyl side chains to yield several metabolites that are either excreted or are conjugated and then excreted. Pyrethrin 1 is also hydrolyzed at the alcohol carboxylic acid ester linkage to yield the alcohol and acid, which may be oxidized at the alkyl side chains to make additional metabolites. Since the jasmolins and cinerins do not have the dienyl moiety in the side chain, there would be fewer sites for oxidation than in the pyrethrins. Female rats

displayed a slightly longer half-life and higher peak levels in the blood, which took longer to attain than male rats. Both sexes excreted a slightly higher percentage of the administered dose *via* the feces than *via* the urine. Very little intact parent compound was found in the urine of male rats, but female rats displayed a significant amount in the urine. In both sexes, more of the parent compound was found in the feces, with the males displaying the greatest amount. Six metabolites were identified, and the main metabolite was chrysanthemum dicarboxylic acid, indicating hydrolysis of the parent compound at the ester linkage. Other identified metabolites indicated that the parent compound was oxidized at the side chains. There are at least 13 unknown metabolites.

With regard to the thyroid tumors observed in rats of both sexes, the mode of action data for pyrethrins are consistent with the mode of carcinogenic action that has been established for a number of pesticides that induce thyroid follicular cell tumors in rats. Rats are substantially more sensitive than humans to thyroid tumor formation and therefore, are not a good model for assessing carcinogenic potential of pyrethrins in humans (Hurley et al., 1998). This mode of action involves a reduction of circulating thyroid hormone, which activates homeostatic processes that increase thyroid stimulating hormone (TSH) release from the pituitary. TSH release stimulates the thyroid gland to increase thyroid hormone synthesis and release. Persistently elevated TSH levels will lead to thyroid follicular cell hypertrophy and hyperplasia, and with continuous stimulation, can lead to neoplasia.

Sufficiency of Data

The toxicological database, with the exception of a developmental neurotoxicity study and a comparative thyroid study, is adequate to support the reregistration of pyrethrins. Evidence of quantitative susceptibility was found following *in utero* and/or pre-/postnatal exposure in the 2-generation reproduction study in rats. However, except for the data needs described below, data are sufficient for important endpoints and dose-response evaluation for three species [rat, mouse, dog]. Data are sufficient for all exposure scenarios and for FQPA evaluation. Due to the finding of neuropathology in rats following acute exposure, a developmental neurotoxicity study is required. Due to concerns for the potential impact of pyrethrins exposure on the function of the thyroid, as evidenced by the increases in thyroid weights, changes in thyroxine UDP glycuronosyl-transferase activity, TSH, T3, and T4, and occurrence of thyroid tumors in rats noted in the pyrethrins database, a comparative thyroid study in adult and young animals is required. This study should include hormonal measurements for thyroid function. This request stems from concerns regarding the possible impact of perturbations of thyroid function on the development of the young.

Toxicological Effects

The critical effects are (1) neurobehavioral [rat, mouse] following acute, short-term, and chronic exposure, with neuropathological lesions following acute exposure; (2) thyroid [rat, dog] following chronic exposure; and (3) liver [rat, dog, mouse] following short- and long-term exposure. Following inhalation exposure, neurobehavioral effects were observed initially, and histopathological lesions of the lungs/respiratory tract were observed at all dose levels. The neurobehavioral effects and the mode of action are considered relevant to humans as the effects are observed in the rat and mouse, and the mode of action affects a basic function of the nervous system that is common to all animals.

There is suggestive evidence that pyrethrins are carcinogenic based on the weight-of-the-evidence considerations, which include the occurrence of benign liver tumors only in female rats. No treatment-related increase in tumors in male rats [other than thyroid adenomas] or mice of either sex was observed, and there is no concern for mutagenicity. The finding of thyroid tumors in rats of both sexes is not of concern for humans based on the mode of carcinogenic action data. It was classified as "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential". Pyrethrins show no significant developmental or reproductive effects in rats, although quantitative susceptibility was observed in the reproduction study where decreased pup body weight occurred at a dose level where no maternal effects were observed. Although one abortion and one full litter resorption were seen in the rabbit developmental toxicity study, relevance of these findings in ascribing evidence of developmental toxicity is equivocal since it is not uncommon for rabbits to abort/resorb their litters.

Dose-response
Studies demonstrating body-weight decrements [rat and rabbit], neurobehavioral effects [rat and rabbit], and thyroid effects [rat] were considered.

The oral Point of Departure [POD] for the acute RfD [general population, including infants and children] was based on an acute neurotoxicity study in rats. No appropriate single-dose endpoint was available specifically for the acute oral exposure of females 13-49 years old. The combined chronic toxicity/carcinogenicity study in rats was used as the basis for selecting the NOAEL for the chronic RfD. Also considered for this exposure scenario was the 2-generation reproduction study in rats. The chronic toxicity study was used because it provided the lowest NOAEL for an endpoint of concern [thyroid effects]. The rabbit developmental toxicity study was selected for the short-term incidental oral exposure scenario, and the 2-generation reproduction study in rats was selected for the intermediate-term incidental oral exposure scenario. Other studies considered for the latter scenario included the rabbit developmental toxicity study and a mechanistic study in rats. The selected study provides a POD that is protective of effects observed in the other studies.

Dermal risk assessments are not required due to negligible dermal absorption and dermal toxicity. There is an acceptable 21-day dermal toxicity study in rabbits in which no systemic or dermal toxicity was observed at the limit dose [1000 mg/kg/day]. Additionally, there is an acceptable human dermal penetration study available that demonstrates absorption of <1%.

The inhalation POD's were based on clinical signs and body-weight effects early [short-term] in the study and respiratory tract lesions observed at study termination [intermediate and long-term] in the 90-day inhalation toxicity study. The study was an appropriate route-specific study and was used for all exposure durations.

No quantification of cancer risk is required, based on the "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" classification.

The uncertainty factors used in determining the acute RfD exposure limits were: 10X for interspecies extrapolation; 10X for intraspecies extrapolation; and 3X for database uncertainty factor [UF_{DB}]. The uncertainty factors used in determining the chronic RfD exposure limits were: 10X for interspecies extrapolation and 10X for intraspecies extrapolation.

FQPA

No evidence of increased susceptibility of rats or rabbits was seen in developmental toxicity studies. Although there was evidence of increased quantitative susceptibility following *in utero* and/or pre-/postnatal exposure in the 2-generation reproduction study in rats, the reproductive/offspring toxicity NOAELs and LOAELs are well characterized and are used as endpoints for risk assessment for the appropriate population subgroups. Since there are no residual uncertainties that indicate the need for a special safety factor, the Special FQPA safety factor is 1X.

Table 4.1a Acute Toxicity Profile - **Pyrethrins**

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral [rat]	42008101?	LD_{50} = 1.40 g/kg LD_{50} = 2.14 g/kg (males) LD_{50} = 0.70 g/kg (females)	III III
		42599501	LD_{50} = 2370 mg/kg (males) LD_{50} = 1030 mg/kg (females) deaths preceded by tremors; females hyperactive	 III
		263780	LD_{50} = 3.81 g/kg (males) LD_{50} = 1.21 g/kg (females) rat	
870.1200	Acute dermal [rabbit]	41964801	LD_{50} >2000 mg/kg	III
870.1300	Acute inhalation [rat]	42008002	LC_{50} = 3.4 mg/L [887 mg/kg] LC_{50} = 3.9 mg/L (males) [997 mg/kg] LC_{50} = 2.5 mg/L (females) [672 mg/kg] tremors	III
870.2400	Acute eye irritation [rabbit]	41964802	produced conjunctional irritation in treated eyes of all 6 exposed rabbits; no conjunctional irritation observed in any eye by 72-hour reading. No corneal opacity or iritis.	III
870.2500	Acute dermal irritation	41964803	mild or slight skin irritant over 72 hours	IV
870.2600	Dermal sensitization	41964804	not a dermal sensitizer	negative

Table 4.1a Acute Toxicity Profile - **Pyrethrins**

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.6200	Acute Neurotoxicity [rat]	42925801	NOAEL = 20 mg/kg/day	-

Table 4.1b Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	MRID No. (year) Classification /Doses	Results
870.3100 90-Day oral toxicity [rodents]	no study located [range-finding study]	
870.3150 90-Day oral toxicity in nonrodents	no study located	
870.3200 21/28-Day dermal toxicity (rabbit)	42212601 (1992) acceptable/guideline 0, 100, 300, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day [highest dose tested] LOAEL = no effects observed
870.3250 90-Day dermal toxicity	no study located	
870.3465 90-Day inhalation toxicity (CD-Crl: (CD) BR rat)	42478201(1992) acceptable/guideline 0, 0.01, 0.03, 0.1, 0.35 mg/L [males 2.56, 7.67, 25.56, 89.46 mg/kg/day; females 2.69, 8.06, 26.88, 94.08 mg/lg/day]	NOAEL (systemic effects) = 0.03 mg/L/day LOAEL = 0.1 mg/L/day based on decreased body-weight gain [both sexes] and labored breathing and tremors during weeks 1-3 [females]. NOAEL (respiratory effects) = not attained LOAEL (respiratory effects) = 0.01 mg/L/day based on hypertrophy/hyperplasia [mucosal seromucous glands], pseudostratified ciliated/nonciliated columnar epithelial hyperkeratosis of the larynx [both sexes], goblet cell hyperplasia in the nasopharynx and nasoturbinates [males], and epithelial intracytoplasmic eosinophilic material in the nasoturbinates.
870.3700a Prenatal developmental in rodent (Charles River COBS CD rat)	40288202 (1987) acceptable/guideline 0, 5, 25, 75 mg/kg/day gestation days 6-15	**Maternal** NOAEL = 75 mg/kg/day [HDT] LOAEL = no effects. **Developmental** NOAEL = 75 mg/kg/day [HDT] LOAEL = no effects. no maternal or developmental toxicity was observed at 150 mg/kg/day in the range-finding study.
870.3700b Prenatal developmental in nonrodent (rabbit)	40288203 (1987) acceptable/guideline 0, 25, 100, 250 mg/kg/day gestation days 7-19	**Maternal** NOAEL = 25 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body-weight gain during the dosing period and clinical signs in one doe [excessive salivation, head arched backward, labored breathing]. **Developmental** NOAEL = 100 mg/kg/day LOAEL = 250 mg/kg/day, based on one abortion and total resorption of one litter of one doe.

Table 4.1b Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	MRID No. (year) Classification /Doses	Results
870.3800 Reproduction and fertility effects (Charles River COBS CD rats)	41327501 (1989) acceptable/guideline 0, 100, 1000, 3000 ppm 0, 6.4, 65, 196 mg/kg/day	**Parental/Systemic** NOAEL = 65 mg/kg/day LOAEL = 196 mg/kg/day based on decreased body weight in the F1 parental rats during the premating phase and in F1 females during gestation days 0 and 6 and lactation for the F2a and F2b pups. **Reproductive** NOAEL = 196 mg/kg/day [HDT] **Offspring** NOAEL = 6.4 mg/kg/day LOAEL = 65 mg/kg/day based on decreased F1b pup weights during lactation.
870.4100a Chronic toxicity rodents (Charles River CD rat)	MRID 41559501 (1990) acceptable/guideline 0, 100, 500, 2500 ppm M 0, 4.37, 42.9, 130 mg/kg/day F 0, 5.39, 55.5, 173 mg/kg/day	NOAEL = 4.37 mg/kg/day LOAEL = 42.9 mg/kg/day based an increased incidence of thyroid follicular cell hyperplasia in males. [see under 870.4200 below]
870.4100b Chronic toxicity nonrodent (dogs)	MRID 41496501 (1990) acceptable/guideline 0, 100, 500, 2500 ppm M 0, 2.57, 13.7, 66.3 mg/kg/day F 0, 2.8, 14.2 74.6 mg/kg/day (one year)	NOAEL = 13.7 mg/kg/day LOAEL = 66.4 mg/kg/day based on increased liver and weights [both sexes].
870.4200 Carcinogenicity (Charles River CD rats)	MRID 41559501 (1990) acceptable/guideline 0, 100, 1000, 3000 ppm M 0, 4.37, 42.9, 130 mg/kg/day F 0, 5.39, 55.5, 173 mg/kg/day	NOAEL = 4.37 mg/kg/day LOAEL = 42.9 mg/kg/day based on an increased incidence of thyroid follicular cell hyperplasia in males. **evidence of carcinogenicity: females displayed a treatment-related increase in hepatocellular adenomas at the high-dose level [5/60, 8%] compared to both control groups [0/60 and 1/60], and the incidence was outside the historical control range [0%-6%]; both sexes displayed a treatment-related increase in thyroid follicular cell adenomas and/or carcinomas**
870.4300 Carcinogenicity mice	41559401 (1990) acceptable/guideline 100, 2500, 5000 ppm M 13.8, 346, 686 mg/kg/day F 16.6, 413, 834 mg/kg/day	NOAEL = 100 ppm [13.8/16.6 mg/kg/day] LOAEL = 1000 ppm [346/413 mg/kg/day based on increased liver weights in both sexes and microscopic pathology in the liver [vacuolar fatty change] in males. **no evidence of carcinogenicity**
Gene Mutation - Ames assay 870.5265	41344701 (19\\) acceptable/guideline 0, 292, 585, 877, 2924, 5848, 8772 µg/plate	no evidence of mutagenicity in strains TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation

Table 4.1b continued on the following page

Table 4.1b Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	MRID No. (year) Classification /Doses	Results
Cytogenetics - CHO chromosomal aberrations 870.5375	41344601 (19\\) acceptable/guideline w/S9 - 0.01, 0.02, 0.04, 0.08 µL/mL w/out S9 - 0.04, 0.08, 0.16, 0.32 µL/mL	no evidence of increased chromosomal aberrations with and without metabolic activation.
Cytogenetics - CHO chromosomal aberrations 870.5375	43987001 (19\\) acceptable/guideline 6.25, 12.5, 25, 50, 100, 150 µg/mL 10, 25, 40, 55, 70, 85, 100 µg/mL [repeat]	no evidence of induction of chromosomal aberrations in CHO cells either with or without metabolic activation at dose levels up to and including excessive cytotoxicity.
Other Effects - UDS 870.5550	41344501 (19\\) acceptable/guideline 0, 0.03, 0.10, 0.30, 0.60, 1.0, 3.0 µL/mL	pyrethrum extract did not induce unscheduled DNA synthesis
870.6200a Acute neurotoxicity screening battery (Charles River CD rat)	42925801 (1993) acceptable/guideline M 40, 125, 400 mg/kg F 20, 63, 200 mg/kg	NOAEL = 20 mg/kg/day LOAEL = 63 mg/kg/day based on tremors in females. Males at 125 mg/kg displayed decreased motor activity. Neuropathological findings at HDT [both sexes]
870.6200b Subchronic neurotoxicity screening battery	no study available	
870.6300 Developmental neurotoxicity	no study available	
870.7485 Metabolism and pharmacokinetics (Sprague-Dawley rat)	43554304/43884101plus literature publications (19\\) single dose: 10 (both sexes), 50 mg/kg (females), 100 (males) mg/kg repeat dose 10 mg/kg/day (14 days)	Pyrethrin 1 and II structures undergo metabolism by oxidation at the alkyl side chains to yield several metabolites that are either excreted or conjugated and then excreted. Pyrethrin 1 is also hydrolyzed at the alcohol carboxylic acid ester linkage to yield the alcohol and acid, which may be oxidized at the alkyl side chains to make additional metabolites. Data from *in vivo* metabolic studies have been supported by *in vitro* studies. At least some *in vitro* data indicate that the jasmolins and cinerins are also metabolized by liver oxidase systems.
870.7600 Dermal penetration	46382501 (2004) 12.5 µg/cm^2 (males) dermal dose 4.19 µg/kg (males) oral dose	absorption : 0.22±0.05% of administered dose

Table 4.1b continued on the following page

Table 4.1b Subchronic, Chronic and Other Toxicity Profile		
Guideline No./ Study Type	MRID No. (year) Classification /Doses	Results
Special studies (Sprague-Dawley [Crl:CD®(SD)IGS BR] rats)	45889802 (2002) M 0, 8000 ppm 7 days [0, 300 mg/kg/day] 14 days [0, 420 mg/kg/day] 42 days [0, 434 mg/kg/day] F 0, 100, 3000, 8000 ppm 7 days [0, 6.76, 163, 263 mg/kg/day] 14 days [0, 7.23, 203, 466 mg/kg/day] 42 days [0, 6.6, 199, 499 mg/kg/day]	increased liver microsomal enzyme activity, increased thyroid weight, changes in thyroid function [decreased T3/T4, increased TSH], follicular cell hypertrophy
Special studies (Sprague-Dawley [Crl:CD®(SD)IGS BR] rats)	45889803 (2002) M 0, 8000 ppm F 0, 100, 3000, 8000 ppm	increased enzyme activities following exposure to pyrethrins at 8000 ppm [both sexes] and females at 3000 ppm fo 7-ethoxy resorufin O-deethylase, 7-pentoxyresorufin O-dependentylase, testosterone 7α-hydroxylase activity, testosterone 16β-hydroxylase, testosterone 6β-hydroxylase, and thyroxine UDPglycuronosyltransferase

4.2 FQPA HAZARD CONSIDERATIONS

4.2.1. Adequacy of the Toxicity Data Base

The toxicology database for pyrethrins includes the following studies for assessing the need for a Special FQPA Safety Factor.

- rat developmental toxicity study (acceptable)
- rabbit developmental toxicity study (acceptable)
- two-generation reproduction study in rats (acceptable)

4.2.2 Evidence of Neurotoxicity

There is a concern for neurotoxicity resulting from exposure to pyrethrins, based on (1) tremors in females, decreased motor activity in males, and neuropathology in both sexes in the acute neurotoxicity study; (2) clinical signs [excessive salivation and head arched backward] in one female rabbit following exposure during gestation; and (3) tremors in female rats in the subchronic inhalation study. In the range-finding, developmental toxicity studies in rats and rabbits, tremors/convulsions were observed in those that died on test. In the mouse [90-day] range-finding study, tremors and increased/decreased activity were observed at dose levels that also resulted in mortality. As stated previously pyrethrins are axonic poisons.

4.2.3 Developmental Toxicity Studies

EXECUTIVE SUMMARY: In a developmental toxicity study [MRID 40288202], female Charles River COBS CD rats [25/group] were administered pyrethrum extract [57.574%] *via* gavage at dose levels of 0 [0.5% methyl cellulose], 5 mg/kg/day, 25 mg/kg/day, and 75 mg/kg/day from gestation day 6 through gestation day 15 [two low-dose dams were not dosed on day 6].

There were no deaths. One high-dose female delivered her litter on day 19, one day prior to scheduled delivery. There were no treatment-related effects on clinical signs, and body-weight gain was comparable among the groups. Food consumption information was not provided.

There were no abortions, and the pregnancy rate was not adversely affected. The numbers of corpora lutea, implantations, and live fetuses were comparable among the groups. There was one dead fetus [control]. There was a slight increase in resorptions [early] with increasing dose [19, 23, 28, and 30], and both pre- [7.8% *vs* 16.6%] and post-implantation [5.7% *vs* 8.6%] losses were highest at the high-dose level compared to the control. Gravid uterine weights were comparable among the groups. Fetal body weight was not adversely affected, and the sex ratio was comparable among the groups. There was a dose-related increase [5, 7, and 10 with increasing dose *vs* 0 in the control] in the incidence of 14th rudimentary rib(s), but the incidence in each case was within the historical control data submitted with the study. There was no apparent effect on the incidence of any malformation, and external, visceral, and skeletal development was not adversely affected.

The maternal toxicity NOAEL is 75 mg/kg/day, the highest dose tested. The NOAEL for developmental toxicity is 75 mg/kg/day, the highest dose tested.

The results of this study should be considered with those of the range-finding study in determining the acceptability of the study based on the guidelines. In the rat range-finding study [MRID 40603701], dose levels of 0, 37.5, 75, 150, 300, and 600 mg pyrethrins /kg/day were administered to 5 assumed pregnant Sprague-Dawley derived Charles-River COBS CD rats/group *via* gavage on gestation days 6 through 15. Deaths occurred in the three highest dose groups [2, 3, 2 with increasing dose]. The two highest dose groups were terminated [day 6]. The rats that died displayed tremors and convulsions prior to death. Two dams dosed at 75 mg/kg/day displayed tremors and/or convulsions [days 6 or 7] and four of the dams at 150 mg/kg/day displayed tremors and/or convulsions. No treatment-related effects were observed on body weight/gain in the remaining three treatment groups [37.5, 75, and 150 mg/kg/day]. No effects were reported on the mean number of viable fetuses, mean post-implantation loss, and mean numbers of implantations or corpora lutea. Based on these data, dose levels of 5, 25, and 75 mg/kg/day were selected for the definitive study. The previous review considered 75 mg/kg/day to be, at best, marginally acceptable. Although no maternal toxicity was demonstrated in the definitive study, it was concluded that no scientific or regulatory purpose would be served by requiring another study in the rat. It is to be noted that there was no dose-response for death; i.e., 2 deaths occurred at both the150 and 600 mg/kg/day dose levels while 3 deaths occurred at 300 mg/kg/day. Additionally, the two highest dose levels were terminated early, due to excessive toxicity, but the dams in the 150 mg/kg/day dose group also displayed the same signs of toxicity but were not terminated [continued on test].

Based on the available data, this guideline developmental toxicity study is classified **Acceptable/Guideline**, and it satisfies the guideline [OPPTS 870.3700; §83-3(a)] for a developmental toxicity study in the rodent.

EXECUTIVE SUMMARY: In a developmental toxicity study [MRID 40288203], female New Zealand White SPF rabbits [16/group] were administered pyrethrum extract [57.574%] *via* gavage at dose levels of 0 [0.5% methylcellulose], 25 mg/kg/day, 100 mg/kg/day, and 250 mg/kg/day from gestation day 7 through gestation day 19. Does were artificially inseminated [8 donor males; semen from one male was used to inseminate an equal number of females in each group]. The does were sacrificed on gestation day 29, and their pups were delivered.

There were no deaths. Clinical signs of toxicity [excessive salivation, head arched backward, and labored breathing] were observed at the high-dose level [2-3 does; gestation day 18 or 19] and in one mid-dose doe [gestation day 19]. During the first week of dosing [gestation days (GD) 7-13] and over the entire dosing period [GD 7-19], the high-dose does displayed a negative body-weight gain. At the mid-dose level, there was a dose-related decrease in body-weight gain throughout the dosing period [GD 7-13 (53% of control); GD 7-19 (64% of control)]. Overall body-weight gain [days 0-29] was comparable among the groups. Food consumption information was not provided.

There was one abortion at the high dose [GD 28], and one high-dose doe had a totally resorbed litter [4 early resorptions]. The pregnancy rate was comparable among the groups. The numbers of corpora lutea, implantations, live fetuses, and resorptions were comparable among the groups, as were pre- and post-implantation losses. Gravid uterine weights were comparable among the groups. Fetal body weight was not adversely affected, and the sex ratio was comparable among the groups. There was no apparent effect on the incidence of any malformation, and external, visceral, and skeletal development were not adversely affected.

The maternal toxicity NOAEL is 25 mg/kg/day, based on decreased body-weight gain during the dosing period and clinical signs in one doe [excessive salivation, head arched backward] at the maternal toxicity LOAEL of 100 mg/kg/day. The NOAEL for developmental toxicity is 100 mg/kg/day, based on one abortion and total resorption of one litter of one doe at the LOAEL of 250 mg/kg/day.

In determining the acceptability of this study, the results of this study should be considered with those of the range-finding study. In the rabbit range-finding study [MRID 40603702], dose levels of 0, 37.5, 75, 150, 300, and 600 mg/kg/day were administered to 5 pregnant New Zealand White, SPF, rabbits/group *via* gavage on gestation days 7 through 19. Two of the high-dose does died, and all of the does in this group displayed tremors and/or convulsions (in some cases). During the treatment period, does in the 300 mg/kg/day [11%] and 600 mg/kg/day [19%] dose groups displayed body-weight loss. Increased post-implantation loss was observed at 150 [16.7%], 300 [12.5%], and 600 [44.4%] mg/kg/day compared to the control [2.9%]. Based on these data, dose levels of 25, 100, and 250 mg/kg/day were selected for the definitive study.

This developmental toxicity study is classified **Acceptable/Guideline**, and it satisfies the guideline [OPPTS 870.3700; §83-3(b)] requirement for a developmental toxicity study in the rabbit.

4.2.4 Reproductive Toxicity Study

EXECUTIVE SUMMARY: In a 2-generation reproduction study [MRID 41327501], Charles River COBS CD rats [28/sex/group] were administered pyrethrum extract [57.574%] *via* the diet at dose levels of 0, 100 ppm [6.4 mg/kg/day],1000 ppm [65 mg/kg/day], and 3000 ppm [196 mg/kg/day]. Rats in the F0 generation were maintained on the test diet for 77 days prior to mating [≈17 weeks old]. The F1 rats were feed the diets for 70 days [15 weeks old] prior to mating.

There were no treatment-related deaths or clinical signs of toxicity. Body weight was not adversely affected during the pre-mating [dosing] period of the F0 rats [both sexes], but the high-dose F0 females displayed a decrease in body-weight gain during the period between matings [study week 20 (50% of control), 22 (43% of control), 23 (43% of control), and 24 (16% of control)]. The high-dose F0 females also displayed decreased body-weight gains during F1a lactation period [net weight loss (-3 grams) *vs* positive weight gain in the control (6 grams)]. Decreased body weights were observed in the high-dose F1 rats [males 89%-93%/females 93%-98% of control] during the pre-mating period, and body-weight gains over the weeks 5-16 pre-mating period were slightly lower than control at the mid- [males 95%/females 92% of control] and high- [males 94%/females 92% of control] dose levels. The F1 high-dose males displayed a statistically-significantly lower body weight at week 5, the beginning of the dosing period [89% of control], and throughout the pre-mating period while the high-dose F1 females attained statistical significance [93%-94% of control] only at the end of the pre-mating period [weeks 15-16]. Body-weight gain over the 10-week pre-mating period was lower in F1 rats of both sexes at the high-dose level compared with the controls, with females displaying the greater deficit [males 78%-94%/females 67%-92%% of control]. Food consumption was comparable among the F0 rats of both sexes during the pre-mating period. Food consumption of the F1 rats was slightly lower at the high-dose level, mainly during the first few weeks of dosing. Food consumption during both lactation periods of F0 females was comparable among the groups. F1 females displayed decrease food consumption during lactation for F2a [high dose] and F2b [mid- and high-dose levels] litters. Food efficiency was comparable among the groups for both generations.

There were no significant differences among the groups in either the mating [93%-100%] or fertility [52%-86%] indices in either generations. Gestation length was comparable among the groups for both generations and both litters of each generation. Copulatory interval for the F0 parents was increased slightly compared to the control at the mid- [F1a mating: 139%/F1b mating: 121% of control] and high- [F1a mating: 148%/F1b mating: 127% of control] dose levels [dose-related]. During the F1 matings for both litters, the mid- and high-dose copulatory intervals continued to be increased compared to the control, but the low-dose group displayed the longest copulatory interval [204% (F2a litters)/170% of control (F2b litters)].

There was no apparent, treatment-related, effect on the live-born index, litter size, or sex ratio. There was an increase in the number of dead F2b pups at birth at the high-dose level; however, this increase can be attributed to one litter of 16 stillborn pups. Pup survival throughout lactation was comparable among the groups for both generations/both litters. Body weights of pups at the high-dose level [both sexes] were decreased throughout lactation [all litters], with the magnitude of the deficit increasing with time [79%-95% of control]. Pups at the mid-dose level [F1b and F2a females] displayed slight decreases in body weight [93%-95% of control]. Body-weight gains of the pups were lower at the mid- [males 93%-96%/females 93%-95% of control] and high-dose [males 93%-95%/females 78%-87% of control] levels during lactation [days 0-21].

The parental systemic toxicity NOAEL is 1000 ppm [65 mg/kg/day], based on decreased body weight in the F1 parental rats during the premating phase and in F1 females during gestation days 0 and 6 and lactation for the F2a and F2b pups at the parental systemic toxicity LOAEL of 3000 ppm [196 mg/kg/day]. The NOAEL for reproductive toxicity is 196 mg/kg/day, the highest dose tested. The NOAEL for offspring toxicity is 100 ppm [6.4 mg/kg/day], based on decreased F1b pup weights during lactation at the offspring toxicity LOAEL of 1000 ppm [65 mg/kg/day].

This 2-generation reproduction study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.3800; §83-4] for a reproduction/fertility effects study in the rodent.

4.2.5 Additional Information from Literature Sources

No other information was located in the literature for pyrethrins that would be applicable to the FQPA assessment.

4.2.6 Pre-and/or Postnatal Toxicity

There is a concern for pre- and/or postnatal toxicity resulting from exposure to pyrethrins.

4.2.6.1 Determination of Susceptibility

There is no evidence of increased susceptibility [qualitative and quantitative] following *in utero* exposure to pyrethrins in either the rat or rabbit developmental toxicity study. There is evidence of increased susceptibility [quantitative] following *in utero* and/or pre-/postnatal exposure in the 2-generation reproduction study in rats [decreased F1b pup weights during lactation at the NOAEL for the parental rats].

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

There is a low degree of concern for the effects observed [decreased F1 pup body weight] in the **acceptable** 2-generation reproduction study at a dose level that had no apparent adverse effect on the parental animals. There is a clear NOAEL [6.4 mg/kg/day] for the offspring effect [decreased pup body

weight at LOAEL of 65 mg/kg/day]. There were no fetal effects observed in the developmental toxicity study in rats at dose levels up to 75 mg/kg/day. One abortion and one full litter resorption were seen in the rabbit developmental toxicity study at the highest dose tested [250 mg/kg/day]. The relevance of these findings in ascribing evidence of developmental toxicity is considered equivocal since it is not uncommon for rabbits to abort/resorb their litters. Furthermore, the NOAEL from the reproduction study, or more protective NOAELs, were used for risk assessment. There are no residual concerns.

4.3 Recommendation for a Developmental Neurotoxicity Study

4.3.1 Evidence that supports requiring a Developmental Neurotoxicity study

Pyrethrum is considered an axonic poison. There is also evidence that its effects are on the neurons. Pyrethrins, along with pyrethroids, appear to affect sodium channel function by binding to a unique site on the channel that is distinct from the five well-characterized neurotoxin recognition sites but is allosterically coupled to three of these sites [Soderlund, 1995]. In the acute neurotoxicity study, tremors, salivation, exaggerated or no startle response, decreased grip strength, and decreased rearing were observed on the day of dosing, and neuropathological lesions were observed in both sexes. In the rabbit developmental toxicity study, excessive salivation and head arched backward and labored breathing were observed during the dosing period. In the 90-day inhalation study, tremors and hyperactivity were observed during the first week of exposure. In a metabolism study in rats, twitching, spasms, and tremors were observed 1-5 hours after the first dose of 4 consecutive doses of 400 mg/kg pyrethrin 1 in DMSO given at 12-hour intervals, *The developmental neurotoxicity study is an upper tier study which would only be required if effects observed (e.g. lesions of the CNS) in the acute and 90-day neurotoxicity studies indicate concerns for potential increased sensitivity of the infant or neonate.* Based on the finding of neuropathy in the acute neurotoxicity study in rats, a developmental neurotoxicity study is required.

4.3.2 Evidence that supports not requiring a Developmental Neurotoxicity study

Developmental toxicity was not observed in the rat at 75 mg/kg/day [highest dose tested]. The NOAEL for offspring in the 2-generation reproduction study is 6.4 mg/kg/day [LOAEL is 65 mg/kg/day, based on decreased pup body weight during lactation]. The apparent neurotoxic effects occur at relatively high dose levels; *e.g*., at 200 mg/kg (neuropathy and clinical signs) and 63 mg/kg (clinical signs) following acute exposure of adult rats, at 100 mg/kg/day following exposure to female rabbits during gestation days 7-19, and at 27 mg/kg/day (clinical signs) in female mice during the first week of inhalation exposure.

Evidence Supporting Requiring DNT pyrethrins considered an axonic poison; neurotoxic clinical signs and neuropathology observed following oral and inhalation exposure		
study	neurotoxic clinical signs	neuropathology

acute neurotoxicity study	tremors, salivation, exaggerated or no startle response, decreased grip strength, increased motor activity, decreased rearings at 63 and 200 mg/kg	focal/multifocal myelin/axonal degeneration in sciatic, peroneal, or tibial nerves at 200 mg/kg (females)/400 mg/kg (males)
rabbit developmental toxicity study	excessive salivation, head arched backward at 100 mg/kg/day	no assessment performed
90-day inhalation study	tremors, hyperactivity at 27 mg/kg/day [initially/first week]	not observed at HDT 90-94 mg/kg/day
metabolism study	twitching, spasms, tremors at 400 mg/kg [one dose]	no assessment performed
Evidence Supporting NOT Requiring DNT neuropathology observed only at 200 mg/kg (females)/400 mg/kg {males); LOAEL for neuropathology was 63 mg/kg (females)/125 mg/kg (males).		

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

A dose analysis was conducted in order to determine the need for and size of a database uncertainty factor [UF_{DB}] in the absence of a submitted developmental neurotoxicity study (DNT) for pyrethrins. Assuming the doses tested in the required DNT will be similar to those in the 2-generation reproduction study [there is no subchronic neurotoxicity study available in the pyrethrin database], the doses will be 6.4, 65, and 196 mg/kg/day. If we assume that a clear NOAEL for offspring effects will be achieved in the DNT [in this case we will assume 6.4 mg/kg/day is the NOAEL], and we compare the assumed NOAEL from the DNT to the doses selected for risk assessment, then the scenarios in the following table will be applicable:

Endpoint [1]	Dose Selected, mg/kg/day	Assumed NOAEL of DNT, mg/kg/day	Conclusion
Acute Dietary	20	6.4	The DNT NOAEL is lower than the dose selected for risk assessment and a UF_{DB} of 3X is required.
Chronic Dietary	4.4	6.4	The DNT NOAEL is in the same range as the dose selected for risk assessment and no UF_{DB} is required.
Short-Term Incidental Oral	20	6.4	The DNT NOAEL is lower than the dose selected for risk assessment and a UF_{DB} of 3X is required

Endpoint [1]	Dose Selected, mg/kg/day	Assumed NOAEL of DNT, mg/kg/day	Conclusion
Intermediate-Term Incidental Oral	6.4	6.4	The DNT NOAEL is equal to the dose selected for risk assessment and no UF_{DB} is required.
Short-Term Inhalation	7.7	6.4	The DNT NOAEL is in the same range as the dose selected for risk assessment and no UF_{DB} is required.
Intermediate-, and Long-Term Inhalation	0.26	6.4	The DNT NOAEL is greater than the dose selected for risk assessment and no UF_{DB} is required.
[1] The shaded rows indicate endpoints where a database uncertainty factor should be applied.			

4.4 Hazard Identification and Toxicity Endpoint Selection

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

An appropriate endpoint specific to females of child-bearing age was not available in the database. No effects were observed at the highest dose tested in rats and rabbits.

4.4.2 Acute Reference Dose (aRfD) - General Population (including Infants and Children)

Study Proposed: acute neurotoxicity study - rat OPPTS 870.6200

MRID No.: 42825801

EXECUTIVE SUMMARY: In an acute oral neurotoxicity study [MRID 42925801], Charles River CD rats (15/sex/dose) were orally gavaged once with pyrethrins [57.467%] at doses of 0 (corn oil), 40 (males)/20 (females), 125 (males)/63 (females), or 400 (males)/200 (females) mg/kg. Neurobehavioral evaluations, consisting of Functional Observational Battery (FOB) and motor activity, were conducted at Day -1 (prestudy), Day 1 (3 hrs postdosing, peak time of effect) and Days 7 and 14. At terminal sacrifice (Day 15), animals were perfused and selected regions of the nervous system were assessed histologically.

Five high-dose males and two high-dose females died on the day of dosing. Clinical signs and neurobehavioral evaluation revealed treatment-related changes at the high-dose only and only on the day of dosing. The findings included tremors [13 males and 7 females], urogenital wetness [1 male and 5 females], and salivation [3 females]. During the Day 1 FOB evaluations, increased incidences of fine tremors (3 high-dose males; 2 mid-dose females and 7 high-dose females), coarse tremors (10/13 high-males and 7/10 high-dose females {numerator is cage incidence, denominator is arena incidence}), exaggerated startle response (9 high-dose males and 6 high-dose females), no startle response (one high-dose female), decreased grip

strength (hind-limb high-dose males; fore-limb high-dose females), and increased body temperature (high-dose both sexes) were observed. During the motor activity assessment, decreased rearing was observed in males at the mid- and high-dose levels and in the high-dose females. Fine movements were decreased in the mid-dose males and increased in both sexes at the high-dose level. Decreased ambulation was observed in both sexes at the high-dose level and in the mid-dose males, although there was no dose response in males *per se*. Treatment-related neuropathological findings [minimal focal or multifocal myelin/axonal degeneration in sciatic, peroneal or tibial nerves] were present at the high-dose level in both sexes.

The NOAEL for neurotoxicity is 20 mg/kg, based on tremors in females at the LOAEL of 63 mg/kg. At 125 mg/kg/day, which is the LOAEL for males, males displayed decreased motor activity [decreased rearing and fine movements]. At the highest dose tested [males 400 mg/kg; females 200 mg/kg], deaths, coarse tremors, exaggerated startle response, increased body temperature, decreased grip strength, anogenital wetness and salivation; increased motor activity [total and fine movement] but decreased ambulation and rearing; and neuropathology [minimal focal or multifocal myelin/axonal degeneration in sciatic, peroneal or tibial nerves] were observed.

This acute neurotoxicity study in the rat is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.6200] for an acute neurotoxicity study in the rat. A separate DER was not prepared for the range-finding study; time of peak effect and difference in sensitivity between the sexes were identified.

Dose and Endpoint for Establishing cRfD: **NOAEL = 20 mg/kg/day**, based on tremors in females at the LOAEL of 63 mg/kg/day..

Uncertainty Factor(s): 300X [10 interspecies; 10X intraspecies; 3X database uncertainty factor]

Comments about Study/Endpoint/Uncertainty Factor: The route and duration [one dose] of exposure are appropriate for selection of the acute dietary endpoint for the general population. The NOAEL is supported by the rabbit developmental toxicity study in which the maternal toxicity NOAEL is 25 g/kg/day, based on decreased body-weight gain during the dosing period and clinical signs in one doe [excessive salivation, head arched backward (gestation day 19)] at the maternal toxicity LOAEL of 100 mg/kg/day. A database uncertainty factor of 3X is proposed due to the lack of a developmental neurotoxicity study.

$$\textbf{Acute RfD} = \frac{20 \text{ mg/kg/day}}{300} = \textbf{0.07 mg/kg/day}$$

4.4.3 Chronic Reference Dose (cRfD)

Study proposed: chronic toxicity/carcinogenicity - rat OPPTS 870.4300

EXECUTIVE SUMMARY: In a chronic toxicity/carcinogenicity study [MRID 41559501], 60 Charles River CD rats/sex/dose were administered pyrethrum extract [57.574 %w/w] *via* the diet at concentrations of 0 ppm, 0 ppm (two control groups), 100 ppm [males 4.37 mg/kg/day/females 5.39 mg/kg/day], 1000 ppm [males 42.9 mg/kg/day/females 55.5 mg/kg/day] and 3000 ppm [males 130 mg/kg/day/females 173 mg/kg/day] for 104 weeks.

There was no adverse effect of treatment on survival and no apparent treatment-related clinical signs of toxicity. There was a slight reduction in body weight [≈92%-93% of control] throughout the study in males at the high-dose level compared to one of the two control groups. High-dose females displayed a greater decrease in body weight [82%-89% of control; 87%-98% of control] compared to one of the control groups. Mid-dose females displayed decreased body weight at 26 weeks and 52 weeks compared to one of the control groups. Body-weight gain was lower in the high-dose males [e.g., weeks 0-26: 86%-88% of control, weeks 0-52: 87%-88% of control] throughout the first year of the study. Females at the high-dose level displayed a greater body-weight gain deficit than the males throughout most of the study [weeks 0-26: 76%-82% of control; weeks 0-52: 75%-76% of control]. At the mid-dose level, females displayed a decrease in body-weight gain periodically during the study compared to one of the controls [weeks 0-26: 87% of control; weeks 0-52: 90% of control]. During the first 13 weeks of the study, decreased body-weight gains were observed in the mid-dose females [93% and 88% of control] and in the high-dose males [89% and 88% of control] and females [84% and 80% of control]. Food consumption was decreased at the high-dose level for both sexes and at the mid-dose level for females, mainly during the first part of the study.

There were no apparent, treatment-related changes in the hematology or urinalysis parameters monitored. There were treatment-related increases in both aspartate aminotransferase and alanine aminotransferase in males at the high-dose level throughout the study and at study termination. A similar increase in these liver enzymes was not observed in females.

At the high-dose level, both sexes displayed decreased adrenal weights [absolute (females) and relative-to-brain (both sexes)]. Increased liver weights were observed in males at the low- and high-dose levels [relative-to-body] and in females at the high-dose level [relative-to-body weight]. *It is to be noted that the thyroid was not weighed.*

In the liver, accentuated lobulation was observed in males at a higher incidence in all treatment groups [no dose response] than in either control, but this macroscopic lesion is not considered to be toxicologically significant. A similar increase in accentuated lobulation of the liver was not observed in females. Microscopically, spongiosis hepatis was significantly increased in males at the high-dose level [35% *vs* 17%-18% in controls]. Females at the mid- [40%] and high-dose [37%] levels displayed a significant increase in the incidence of bile duct hyperplasia [12% and 17% in controls].

There was a slight [statistically significant] increase in follicular cell adenomas and combined adenomas/carcinomas and hyperplasia in males at the mid- and high-dose levels, and the incidence of follicular cell adenomas was significantly increased in females at the high-dose level compared to the controls. Females at the high-dose level displayed an increase in the incidence of hepatocellular adenomas.

Theca cell tumors were observed in the high-dose females only. A reevaluation of the pathology data [TXR # 013354] changed the classification of ovarian theca cell tumors to stromal hyperplasia, which is not considered to progress to cancer.

High-dose males displayed a slight increase in the incidence of parathyroid adenomas [4/56] compared with the controls [1/53 and 0/55] and other treatment groups [0/56 and 0/57]. Following the reevaluation of the parathyroids [TXR # 013354], the parathyroid tumors are not considered treatment-related, based on the facts that only males showed a significant increasing trend for adenomas but the increase was not significant in the pair-wise comparison, and the incidence [3/56, 5%] was within the historical control range [1.47%-6.98%].

There was an increased incidence of keratoacanthoma in males at the high-dose level compared to both control groups. A reevaluation of the pathology data [TXR # 013354] changed the classification of several lesions, and it was concluded that although the tumor incidence in the high-dose males was significant by trend and pair-wise comparison, the finding was not biologically significant; the incidence was within the historical control range; these tumors are commonly observed in rats; and the tumor incidence was only of borderline significance.

The systemic toxicity NOAEL is 100 ppm [males 4.37 mg/kg/day; females 5.39 mg/kg/day], based on an increased incidence of thyroid follicular cell hyperplasia in males at the systemic LOAEL of 1000 ppm [males 42.9 mg/kg/day; females 55.5 mg/kg/day]. At the high-dose level, males displayed a significant increase in aspartate aminotransferase and alanine aminotransferase throughout the study compared to the controls and other treatment groups, females displayed an increased incidence of thyroid follicular cell hyperplasia [statistical significance not attained], and both sexes displayed a significant increase in relative liver weight.

Females displayed a treatment-related increase in the incidence of hepatocellular adenomas at the high-dose level [5/60, 8%] compared to both control groups [0/60 and 1/60], and the incidence was outside the historical control range [0%-6%]. Both sexes displayed a treatment-related increase in the incidence of thyroid follicular cell adenomas and/or carcinomas

This guideline chronic toxicity/carcinogenicity study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870.4300; §83-5] for a chronic toxicity/ carcinogenicity study in the rat. The NOAEL/LOAEL are the same as in the original DER, but the LOAEL endpoint differs from the original DER. In the original review, the increased incidence of accentuated lobulation of the liver in males was an endpoint on which the original LEL was set. However, the HED RfD Committee [TXR # 011579]

recommended a revision upwards [from 4.37 to 42.9 mg/kg/day] in the NOAEL/ [from 42.9 to 130 mg/kg/day] in the LOAEL for males, discounting this lesion in the liver. In the current review, the LOAEL is based on the increased incidence of thyroid follicular cell hyperplasia observed at the mid-dose [42.0 mg/kg/day] level in males. Both sexes at the high-dose level displayed an increased incidence of thyroid follicular cell hyperplasia. Therefore, the current NOAEL/LOAEL differs from that recommended by the HED RfD Committee.

Dose and Endpoint for Establishing cRfD: **NOAEL = 100 ppm [males 4.37 mg/kg/day; females 5.39 mg/kg/day], based on an increased incidence of thyroid follicular cell hyperplasia in males at the systemic LOAEL of 1000 ppm [males 42.9 mg/kg/day; females 55.5 mg/kg/day].**

Uncertainty Factor(s): 100X [10 interspecies; 10X intraspecies]

Comments about Study/Endpoint/Uncertainty Factor: The route and duration of exposure are appropriate for selection of the chronic dietary endpoint. This study was not selected previously by the RfD/Peer Review Committee for the endpoint/dose for the RfD [TXR # 011579] due to the revision of the NOAEL from 4.37 to 42.9 mg/kg/day and deficiencies in the histopathological examination of tissues. Subsequently, the CPRC evaluated additional data submitted to address the deficiencies, and the study was classified Acceptable [TXR No. 0013077]. ***Previously, the RfD Committee selected the 2-generation reproduction study with a NOAEL of 100 ppm [6.4 mg/kg/day], based on decreased F1b pup weights during lactation at the reproductive toxicity LOAEL of 1000 ppm [65 mg/kg/day]***. The rat chronic oral toxicity study provides a slightly lower NOAEL [on a mg/kg/day basis] than the previously-selected study, but the NOAELs/LOAELs on a ppm basis are the same [100 ppm/1000 ppm] and the studies can be considered co-critical. The chronic rat study was selected since the endpoint [thyroid hyperplasia] is based on findings in a target organ of concern. A database uncertainty factor is not required since the results of the developmental neurotoxicity study are not expected to impact this risk assessment.

$$\textbf{Chronic RfD} = \frac{4.4 \text{ mg/kg/day}}{100} = \textbf{0.04 mg/kg/day}$$

4.4.4 Incidental Oral Exposure (Short-and Intermediate Term)

4.4.4.1 Incidental Oral Exposure: Short-Term (1-30 days)

Study Proposed: acute neurotoxicity study - rat OPPTS 870.6200

MRID No.: 42825801

EXECUTIVE SUMMARY: see under Acute RfD.

Dose and Endpoint for Risk Assessment: **NOAEL** = 20 mg/kg/day, based on tremors in females at the

LOAEL of 63 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factor: The route and duration of exposure are appropriate for selection of the short-term incidental oral endpoint. A database uncertainty factor of 3X is proposed due to the lack of a developmental neurotoxicity study.

4.4.4.2 Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

Study Proposed: 2-generation reproduction study - rat OPPTS 870.3800

MRID No.: 41327501

EXECUTIVE SUMMARY: In a 2-generation reproduction study [MRID 41327501], Charles River COBS CD rats [28/sex/group] were administered pyrethrum extract [57.574%] *via* the diet at dose levels of 0, 100 ppm [6.4 mg/kg/day],1000 ppm [65 mg/kg/day], and 3000 ppm [196 mg/kg/day]. Rats in the F0 generation were maintained on the test diet for 77 days prior to mating [≈17 weeks old]. The F1 rats were feed the diets for 70 days [15 weeks old] prior to mating.

There were no treatment-related deaths or clinical signs of toxicity. Body weight was not adversely affected during the pre-mating [dosing] period of the F0 rats [both sexes], but the high-dose F0 females displayed a decrease in body-weight gain during the period between matings [study week 20 (50% of control), 22 (43% of control), 23 (43% of control), and 24 (16% of control)]. The high-dose F0 females also displayed decreased body-weight gains during F1a lactation period [net weight loss (-3 grams) *vs* positive weight gain in the control (6 grams)]. Decreased body weights were observed in the high-dose F1 rats [males 89%-93%/females 93%-98% of control] during the pre-mating period, and body-weight gains over the weeks 5-16 pre-mating period were slightly lower than control at the mid- [males 95%/females 92% of control] and high- [males 94%/females 92% of control] dose levels. The F1 high-dose males displayed a statistically-significantly lower body weight at week 5, the beginning of the dosing period [89% of control], and throughout the pre-mating period while the high-dose F1 females attained statistical significance [93%-94% of control] only at the end of the pre-mating period [weeks 15-16]. Body-weight gain over the 10-week pre-mating period was lower in F1 rats of both sexes at the high-dose level compared with the controls, with females displaying the greater deficit [males 78%-94%/females 67%-92%% of control]. Food consumption was comparable among the F0 rats of both sexes during the pre-mating period. Food consumption of the F1 rats was slightly lower at the high-dose level, mainly during the first few weeks of dosing. Food consumption during both lactation periods of F0 females was comparable among the groups. F1 females displayed decrease food consumption during lactation for F2a [high dose] and F2b [mid- and high-dose levels] litters. Food efficiency was comparable among the groups for both generations.

There were no significant differences among the groups in either the mating [93%-100%] or fertility [52%-86%] indices in either generations. Gestation length was comparable among the groups for both generations and both litters of each generation. Copulatory interval for the F0 parents was increased slightly compared

to the control at the mid- [F1a mating: 139%/F1b mating: 121% of control] and high- [F1a mating: 148%/F1b mating: 127% of control] dose levels [dose-related]. During the F1 matings for both litters, the mid- and high-dose copulatory intervals continued to be increased compared to the control, but the low-dose group displayed the longest copulatory interval [204% (F2a litters)/170% of control (F2b litters)].

There was no apparent, treatment-related, effect on the live-born index, litter size, or sex ratio. There was an increase in the number of dead F2b pups at birth at the high-dose level; however, this increase can be attributed to one litter of 16 stillborn pups. Pup survival throughout lactation was comparable among the groups for both generations/both litters. Body weights of pups at the high-dose level [both sexes] were decreased throughout lactation [all litters], with the magnitude of the deficit increasing with time [79%-95% of control]. Pups at the mid-dose level [F1b and F2a females] displayed slight decreases in body weight [93%-95% of control]. Body-weight gains of the pups were lower at the mid- [males 93%-96%/females 93%-95% of control] and high-dose [males 93%-95%/females 78%-87% of control] levels during lactation [days 0-21].

The parental systemic toxicity NOAEL is 1000 ppm [65 mg/kg/day], based on decreased body weight in the F1 parental rats during the premating phase and in F1 females during gestation days 0 and 6 and lactation for the F2a and F2b pups at the parental systemic toxicity LOAEL of 3000 ppm [196 mg/kg/day]. The NOAEL for reproductive toxicity is 196 mg/kg/day, the highest dose tested. The NOAEL for offspring toxicity is 100 ppm [6.4 mg/kg/day], based on decreased F1b pup weights during lactation at the offspring toxicity LOAEL of 1000 ppm [65 mg/kg/day].

This 2-generation reproduction study is classified **Acceptable/Guideline**, and it satisfies the guideline [OPPTS 870.3800; §83-4] for a reproduction/fertility effects study in the rodent. The NOAEL and LOAEL for parental systemic toxicity differ from those in the original DER but agree with the recommendation of the RfD/Peer Review Committee [TXR # 011579] that these be revised upward from 6.4 mg/kg/day and 65 mg/kg/day to 65 mg/kg/day and 196 mg/lg/day, respectively.

Dose and Endpoint for Establishing cRfD: **NOAEL = 6.4 mg/kg/day, based on decreased F1b pup weights during lactation at the offspring toxicity LOAEL of 1000 ppm [65 mg/kg/day].**

Uncertainty Factor(s): 100X [10 interspecies; 10X intraspecies]

Comments about Study/Endpoint/Uncertainty Factor: Other studies considered include the rabbit developmental toxicity study, in which the maternal toxicity NOAEL is 25 mg/kg/day, based on decreased body-weight gain during the dosing period and clinical signs in one doe [excessive salivation, head arched backward, labored breathing] the LOAEL of 100 mg/kg/day. The NOAEL for enzyme induction [ALT, AST] in the oral chronic rat toxicity study for the 6-month period is 42.9 mg/kg/day [LOAEL 130 mg/kg/day]. In a mechanistic study of 7 days, 14 days and 42 days, the NOAEL for P450 enzyme induction was 100 ppm [6.6-7.3 mg/kg/day; females]. The selected study provides a value that is more protective. A database uncertainty factor is not required since the results of the

developmental neurotoxicity study are not expected to impact this risk assessment.

4.4.5 Dermal Absorption

Dermal Absorption Factor: 0.22%, based on an acceptable human dermal penetration study that demonstrates an absorption value of 0.22%.

4.4.6 Dermal Exposure: (Short, Intermediate, and Long Term)

Dermal risk assessments are not required since no endpoint was identified following repeated [21 days] dermal exposure to rabbits at the limit dose, and there is negligible dermal absorption.

4.4.7 Inhalation Exposure (Short, Intermediate, and Long Term)

4.4.7.1 Inhalation Exposure: Short -Term (1- 30 days)

Study Proposed: subchronic inhalation study - rat OPPTS 870.3465

MRID No.: 42478201

EXECUTIVE SUMMARY: In a subchronic inhalation toxicity study [MRID 42478201],15 CD-Crl: (CD) BR Sprague-Dawley rats/sex/group were administered pyrethrum extract [57.574% pyrethrins] *via* inhalation [whole- body exposure chamber, 1000 liter glass volume] daily [6 hours/day, 5 days/week] for 13 weeks at concentrations of 0, 0.01, 0.03, 0.1, or 0.35 mg/L [males: 0, 2.56, 7.67, 25.56, or 89.46 mg/kg/day; females:0, 2.69, 8.06, 26.88, or 94.08 mg/kg/day, respectively].

One high-dose male died on day 15. Prior to death, this rat displayed labored breathing. There were no other treatment-related deaths. Tremors were observed in 2 mid-high dose females and 9 high-dose females during the first week only. Labored breathing was observed in 4 mid-high and 6 high-dose females during the first week of exposure and in 3 mid-high and 2 high-dose females during the third week. Six high-dose males displayed labored breathing during the first week, with the effect persisting in one male until study termination. Other treatment-related clinical signs observed mainly at the two highest dose levels included matted hair coats and dried yellow material on the face. In-chamber clinical observations observed mainly at the high-dose level included secretory signs, labored respiration, tremors, hyperactivity, and matted coat. Body weights were significantly decreased in females at the two highest dose levels by week 3 [95% and 94% of control, with increasing dose], and the deficit continued throughout the study with the magnitude of the difference increasing with time [week 13: 93% and 91% of control with increasing dose]. Males displayed a slight [non-significant] decrease in body weight [95% of control] at the two highest dose levels throughout the study. Body-weight gains were significantly lower during week 1 in males at the two highest dose levels [mid-high 81%/high 83% of control] and at week 3 at the mid-high dose level [83% of control]. Males at these two dose levels continued to display a slight [non-significant] deficit in body-weight gain throughout the study [week 13

91% of control]. Mid-high [84%-90% of control] and high-dose [81%-86% of control] females displayed a significant, dose-related, decrease in body-weight gain throughout most of the study. Food consumption was comparable among the groups for both sexes.

Slight decreases [93%-96% of control] in hematology parameters [hemoglobin, hematocrit, RBCs] were observed in both sexes at the high-dose level following 13 weeks of exposure, and males at all dose levels displayed a significant but small decrease in RBC. Both sexes at the high-dose level displayed increased liver weights. There was a dose-related increase in relative brain and kidney weights in females at the mid-high and high-dose levels, and both sexes displayed increased relative kidney, lung, and liver weights at the high-dose level. Microscopic lesions were noted in the respiratory tissues at all dose levels and included hypertrophy/hyperplasia in the ventral diverticulum and ventral seromucosal glands of the larynx mucosa, metaplasia/hyperplasia in the ventral diverticulum and ventral seromucous glands in the larynx mucosa, and metaplastic epithelial hyperkeratosis in the mucosa of the larynx of both sexes; goblet cell hyperplasia in the epithelial mucosa of the nasopharynx in males; and goblet cell hyperplasia and intracytoplasmic eosinophilic material in the nasoturbinates of both sexes. At higher concentrations, goblet cell hyperplasia in the epithelial mucosa of the nasopharynx of females, hyperplasia and hyperkeratosis in the nonkeratinized stratified squamous epithelium of the larynx in both sexes, subacute/chronic inflammation and squamous cell hyperplasia in the nasoturbinates of both sexes, hypertrophy/hyperplasia in the epithelium of the terminal bronchioles of the lungs in both sexes, edema and congestion in the lungs of males, and increased severity of subacute/chronic inflammation and alveolar/intraalveolar macrophages in the lungs of both sexes were observed. The severity of most of the lesions increased with dose.

A NOAEL for respiratory lesions was not attained. At the LOAEL (lowest dose tested) [0.01 mg/L/day; males 2.56 mg/kg/day; females 2.69 mg/kg/day], metaplasia/hyperplasia of the seromucous glands of the larynx mucosa [both sexes], hypertrophy/hyperplasia of the seromucous glands of the larynx mucosa [both sexes], goblet cell hyperplasia in the nasopharynx and nasoturbinates [males], and epithelial intracytoplasmic eosinophilic material in the nasoturbinates were observed. At 0.35 mg/L/day (highest dose tested) [males 89.46 mg/kg/day; females 94.08 mg/kg/day], chronic inflammation, squamous cell hyperplasia of the nasoturbinates [both sexes], and decreased RBC parameters [hemoglobin, hematocrit, and erythrocytes] in both sexes were observed.

The systemic NOAEL is 0.03 mL/kg/day [7.67 mg/kg/day; females 8.06 mg/kg/day], based on tremors, labored breathing, hyperactivity, secretory signs, matted coat, decreased body weight and body-weight gain at the systemic LOAEL of 0.1 mL/kg/day [males 25.56 mg/kg/day; females 26.88 mg/kg/day].

This guideline subchronic inhalation toxicity study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [§82-4; 870.3465] for a subchronic inhalation toxicity study.

Dose/Endpoint for Risk Assessment: **systemic NOAEL = 0.03 mg/L/day [7.67/8.06 mg/kg/day]**, based on tremors, labored breathing, hyperactivity, secretory signs, matted coat, decreased body weight and body-weight gain at the systemic LOAEL of 0.1 mL/kg/day [males 25.56 mg/kg/day; females 26.88 mg/kg/day].

Comments about Study/Endpoint/Uncertainty Factor(s): The route of exposure is appropriate. Effects [tremors, labored breathing, hyperactivity, decreased body weights] were observed only during the first few weeks [weeks 1-3] of the study in females, but continued throughout the study in one male. Interspecies [10X] and intraspecies [10X] uncertainty factors should be applied.

4.4.7.2 Inhalation Exposure: Intermediate-Term (1- 6 Months)

Study Proposed: subchronic inhalation study - rats OPPTS 870.3465

MRID No.: 42478201

EXECUTIVE SUMMARY: See under Short-Term Inhalation Exposure.

Dose/Endpoint for Risk Assessment: **portal-of-entry LOAEL = 0.01 mg/L/day [2.57 mg/kg/day]**, based on hypertrophy/ hyperplasia of the mucosal seromucous glands, pseudostratified ciliated/nonciliated columnar epithelial hyperkeratosis of the larynx [both sexes], goblet cell hyperplasia in the nasopharynx and nasoturbinates [males], and epithelial intracytoplasmic eosinophilic material in the nasoturbinates. At the highest dose tested [0.35 mg/L/day], chronic inflammation and squamous cell hyperplasia of the nasoturbinates [both sexes] were observed.

Comments about Study/Endpoint/Uncertainty Factor(s): Because no NOAEL for respiratory tract lesions was identified, a 10X uncertainty factor should be applied to the LOAEL, as well as interspecies (10X) and intraspecies (10X) uncertainty factors.

4.4.7.3 Inhalation Exposure: Long-Term (> 6 Months)

Study Proposed: subchronic inhalation study - rat OPPTS 870.3465

MRID No.: 42478201

EXECUTIVE SUMMARY: See under Short-Term Inhalation Exposure.

Dose/Endpoint for Risk Assessment: **LOAEL = 0.01 mg/L/day [2.57 mg/kg/day]**, based on hypertrophy/ hyperplasia of the mucosal seromucous glands, pseudostratified ciliated/nonciliated columnar epithelial hyperkeratosis of the larynx [both sexes], goblet cell hyperplasia in the nasopharynx and nasoturbinates [males], and epithelial intracytoplasmic eosinophilic material in the nasoturbinates.

NOTE: In the initial review of this study [TXR # 0011068], the study was referred to the HED Science Analysis Branch for a policy assessment for inhalation studies not demonstrating a NO(A)EL for hyperplasia, hypertrophy and/or metaplastic responses in the respiratory tract due to treatment. In a subsequent memo [TXR # 0051792], the original reviewer requested the registrant to consult with the Agency [1994] as to the need for a carcinogenicity study *via* the inhalation route of exposure. No SAB review was located. In the CARC document [TXR # 013354], under the Structure Activity Relationship section it states that "Some pyrethroids such as permethrin and cypermethrin have been indicated to cause **lung** and/or liver **tumors** in mice." In the mouse carcinogenicity study on pyrethrins, there was an increased incidence of lung carcinomas in mid- [5%] and high- [6%] dose males *vs* 0% in control males, but the CARC concluded that these were not treatment-related, based on the fact that the incidences were within the testing facility's historical control range [0%-8%]. However, there was no discussion as to whether a long-term inhalation toxicity study is required.

Comments about Study/Endpoint: The route of exposure is appropriate. Effects [tremors, labored breathing, hyperactivity, decreased body weights] were observed during the first few weeks of the study but continued throughout the study in one male. Although the study duration was only 90 days, the NOAEL used for the chronic RfD [NOAEL 6.4 mg/kg/day or 4.4 (rat)] is ≈2.5X higher than the LOAEL of the inhalation study [2.57 /2.56mg/kg] and is, therefore, not appropriate for this route of exposure-duration risk assessment. Because no NOAEL for respiratory tract lesions was identified, a 10X uncertainty factor should be applied to the LOAEL, as well as interspecies (10X) and intraspecies (10X) uncertainty factors.

4.4.8 Margins of Exposure

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

Route of Exposure	Duration of Exposure		
	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational Exposure			
Dermal	NR	NR	NR
Inhalation	100	1000	1000
Residential (non-dietary) Exposure			
Incidental Oral	300	N/A	N/A
Dermal	NR	N/A	N/A
Inhalation	100	N/A	N/A

NR = Not Required; N/A = Not Applicable

For occupational intermediate-term and long-term inhalation exposure risk assessments, a MOE of 1000 is required. The MOE is based on 10x for intraspecies variation, 10x for interspecies extrapolation, and 10x for lack of a NOAEL. For residential incidental oral exposures, an MOE of 300 is required for incidental oral exposures, based on 10x for intraspecies variation, 10x for interspecies extrapolation, and 3x for database uncertainty factor (oral), due to the lack of a developmental neurotoxicity study. The (hazard-based) special FQPA safety factor is 1X.

4.4.9 Recommendation for Aggregate Exposure Risk Assessments

As per FQPA (1996), when there are potential residential exposures to the pesticide, an aggregate risk assessment must consider exposures from three major sources: oral, dermal, and inhalation exposures. No endpoint was identified for dermal exposure, so dermal exposures need not be considered in the aggregate assessment. Endpoints related to neurotoxicity were selected for short-term (1-30 days) via the oral and inhalation routes, so they may be aggregated. The endpoints selected for intermediate- and long-term exposures are different for oral and inhalation routes, so an aggregate assessment for these exposure intervals cannot be done.

4.4.10 Classification of Carcinogenic Potential

In accordance with the EPA *Draft Guidelines for Carcinogen Risk Assessment* (July, 1999), the Committee classified pyrethrins as **"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"** based on the following weight-of-the-evidence considerations:

(i) The occurrence of benign liver tumors only and only in female Crl:CD®(SD)IGS BR rats.
(ii) There was no treatment-related increase in liver tumors in male Crl:CD®(SD)IGS BR rats.

(iii) There was no treatment-related increase in tumors in either sex of Charles River CD mice.
(iv) There is no concern for mutagenicity.

With regard to the **thyroid tumors**, the mode of action data for pyrethrins are consistent with the mode of carcinogenic action that has been established for a number of pesticides that induce thyroid follicular cell tumors in rats (Hurley et al., 1998). This mode of action involves a reduction of circulating thyroid hormone, which activates homeostatic processes that increase thyroid stimulating hormone (TSH) release from the pituitary. TSH release stimulates the thyroid gland to increase thyroid hormone synthesis and release. Persistently elevated TSH levels will lead to thyroid follicular cell hypertrophy and hyperplasia. Effects are reversible on removal of the TSH stimulus, at least early in the process. However, continuous stimulation of the thyroid by TSH can lead to neoplasia. Most antithyroid pesticides operate at an extrathyroidal site by increasing hepatic metabolism and excretion of thyroid hormone (e.g., Thiazopyr). However, a few pesticides (e.g, Amitrole) have been shown to operate at an intrathryoidal site (e.g., interference with thyroid hormone synthesis *via* inhibition of thyroid peroxidase).

Non-mutagenic chemicals that produce thyroid follicular cell tumors in rats by prolonged TSH stimulation are not likely to be carcinogenic to humans. Humans respond as do experimental animals to disturbances in thyroid function from various antithyroid stimuli, such as iodide deficiency, partial thyroidectomy and goitrogenic chemicals; *i.e*., when circulating thyroid hormone levels go down, the TSH level rises, which in turn leads to thyroid hypertrophy and hyperplasia (goiter). Cellular and biochemical studies, however, provide compelling evidence that rats are substantially more sensitive than humans to the development of thyroid follicular cell tumors in response to thyroid hormone imbalance (IARC, 2001, Meek et al., 2003, EPA,1998; Dohler et al., 1979). There are a number of quantitative differences between rats and humans that explain this increased sensitivity of the rat. The rat has a much shorter thyroid hormone half-life than humans; for example, thyroxin (T4) half-life in the rat is ≈12 hours compared to 5-9 days in the human (Dohler et al., 1979). The longer half-life in humans is likely related to the presence of a high-affinity binding globulin for thyroxin that is absent in the rat. Binding of thyroid hormone to this globulin would account for slower metabolic degradation and clearance. Additionally, there is a larger thyroid hormone reserve in the human compared to the rat. The rat thyroid gland is more active than the human thyroid gland, as evidenced by increased turnover rate and increased hepatic clearance of thyroid hormones (T3, T4) in the rat compared to the human. Additionally, the constitutive TSH levels are approximately 25 times higher in rats than in humans, reflecting the increased activity of the thyroid-pituitary axis in rats (Dohler et al, 1979; McClain 1992). Further, rats appear to be very susceptible to thyroid neoplasia secondary to hypothyroidism. Modest changes in thyroid hormone homeostasis may promote tumor formation in rats. In contrast, data in humans suggest that prolonged TSH stimulation of the thyroid gland is unlikely to induce malignant changes (Curran and DeGroot, 1991). This conclusion is also supported by the lack of evidence that patients with Graves disease, where an autoantibody stimulates the TSH receptor, have an increased risk for thyroid cancer (Mazzaferri, 2000).

Table 4.3 Endpoints and Doses To Be Used in The Risk Assessments			
Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49 years of age)	NOAEL = mg/kg/day UF = **Acute RfD** = mg/kg/day	FQPA SF = 1X **aPAD** = acute RfD / FQPA SF = mg/kg/day	**no appropriate endpoint for this exposure scenario was identified**
Acute Dietary (General population including infants and children)	NOAEL = 20 mg/kg/day UF = 300 **Acute RfD** = 0.07 mg/kg/day	FQPA SF = 1X aPAD = acute RfD (0.07) / FQPA SF (1) = 0.07 mg/kg/day	**acute neurotoxicity study in rats** LOAEL = 63 mg/kg/day based on tremors in females
Chronic Dietary (All populations)	NOAEL= 4.37 mg/kg/day UF =100 **Chronic RfD** = 0.044 mg/kg/day	FQPA SF = 1X **cPAD** = chronic RfD (0.044) / FQPA SF (1) = 0.044 mg/kg/day	**rat chronic toxicity study** LOAEL = 42.9 mg/kg/day based on increased incidence of thyroid follicular cell hyperplasia in males
Short-Term Incidental Oral (1-30 days)	NOAEL= 20 mg/kg/day	**Residential** LOC for MOE =300 **Occupational** = NA	**acute neurotoxicity study in rats** LOAEL = 63 mg/kg/day based on tremors in females
Intermediate-Term Incidental Oral (1-6 months)	NOAEL = 6.4 mg/kg/day	**Residential** LOC for MOE = 100 **Occupational** = NA	**2-generation reproduction study - rat** LOAEL = 65 mg/kg/day based on decreased F1b pup body weight/body-weight gain during lactation
Short-Term Inhalation (1 to 30 days)	NOAEL= 0.03 mL/kg/day [7.67 mg/kg/day]	**Residential** LOC for MOE = 100 **Occupational** LOC for MOE = 100	**rat subchronic inhalation toxicity study** LOAEL = 25.56 mg/kg/day based on tremors, labored breathing, hyperactivity, secretory signs, matted coat, decreased body weight/body-weight gain
Intermediate-Term Inhalation (1 to 6 months)	LOAEL = 0.01 mL/kg/day (2.56 mg/kg/day)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 1000	**subchronic inhalation toxicity - rat** LOAEL = 2.56 mg/kg/day based on respiratory tract lesions

Table 4.3 Endpoints and Doses To Be Used in The Risk Assessments			
Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Long-Term Inhalation (>6 months)	LOAEL = 0.01 mL/kg/day (2.56 mg/kg/day)	**Residential** LOC for MOE = 1000 **Occupational** LOC for MOE = 1000	**rat subchronic inhalation toxicity study** LOAEL = 2.56 mg/kg/day based on respiratory tract lesions
Cancer (oral, dermal, inhalation)	**Classification**: **"Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"**		

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

NOTE: The Special FQPA Safety Factor described above **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.

4.5 Special FQPA Safety Factor

Based upon the aforementioned data [4.2], it is recommended that the hazard-based special FQPA safety factor [10X] be removed [1X] since there are no residual uncertainties for pre- and/or post natal toxicity.

4.6 Endocrine disruption

There is evidence that pyrethrins is associated with endocrine disruption. Direct measurements of serum thyroid hormones [T3, T4, and TSH], as well as histopathological alterations in the thyroid [follicular cell hypertrophy, follicular cell hyperplasia, follicular cell adenomas and/or carcinomas] indicate endocrine disruption.

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

FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, pyrethrins may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

5.0 Public Health Data

5.1 Incident Reports

An incident report has been prepared for pyrethrins (J. Blondell, D309023, 1/06/05). Because pyrethrins are often used with a synergist such as piperonyl butoxide (PBO), it was difficult to determine if the symptoms were due to pyrethrin alone. In the Incident Data System, only one case involving pyrethrum alone was reported. This incident involved 8 employees in Washington State who developed unspecified symptoms after repacking pyrethrum powder into smaller containers. Poison Control Center Data (1993-2001) indicated that there were nearly 10,000 reported pyrethrum exposures; however, most of these exposures were from pyrethrins in head lice shampoos. During 1993-1998, 48% of these exposures involved shampoos and during 1999-2001, 99% of the exposures involved shampoos. Pyrethrins have also been suspected of causing allergic reactions, particularly in persons sensitive to ragweed, and for this reason the incident report recommends that the labels on products used in enclosed spaces include the following warning statement:

> "*Avoid contact with skin or eyes. Susceptible individuals may experience irritant or allergic-type reactions. Persons with asthma or ragweed allergy may experience difficulty breathing and should avoid use in enclosed spaces and consult their physician prior to use.*"

6.0 Exposure Characterization/Assessment

6.1 Dietary Exposure/Risk Pathway

Residues in food and the dietary exposure analyses are described in the following memoranda: 1) J. Deluzio, 12/13/04, DP Barcode: D309021; 2) J. Deluzio, 10/12/04, DP Barcode: D295748; and 3) J. Deluzio, 12/20/04, DP Barcode: D295749.

6.1.1 Residue Profile

Residues of the pyrethrins tend to stay on the plant surfaces, with little translocation to the root and other

parts of the plant. This is consistent with other lipophilic compounds. Surface residues are vulnerable to photolysis. The aerobic soil metabolism half life is approximately 3 days, indicating that residues break down rather quickly.

Pyrethrins are used in many types of indoor setting where food may be present, such as warehouses, grain storage areas, restaurants, and food manufacturing plants. Generally, the pyrethrins break down more slowly than in the outdoors where the residues are prone to photolysis.

When applied to livestock, or when livestock consume feed bearing residues of pyrethrins, little breakdown of the parent compound is observed in fatty matrices, such has fat, milk fat, egg yolk, and poultry skin. In plants, livestock, and the environment, the breakdown products of the pyrethrins are of less toxicological concern than the parent compound, so only the six active ingredients of pyrethrum are considered in the dietary assessment.

Pyrethrins may be determined using FDA Multiresidue methods. Pyrethrins are completely recovered (>80% recovery) using FDA multiresidue protocol Sections 302 (Protocol D), 303 (Protocol E), and 304 (Protocol F). The registrant used a GC/ECD method (EN-CAS Method ENC-14/93 and/or Pharmaco LSR) in the analysis of samples collected from the magnitude of the residue and storage stability studies. This method has not been subjected to an independent method validation or validation by the EPA laboratories. An adequate analytical method is available for enforcing pyrethrin tolerances in animal commodities. A GLC method with electron capture detection is listed in PAM, Vol. II (Section 180.128) as Method I. The method can determine residues of each pyrethrins I ester (pyrethrin 1, cinerin 1, and jasmolin 1); however, the analysis of pyrethrins residues are based upon pyrethrins I because it is the most easily detected ester of pyrethrins.

Insufficient crop field trial studies reflecting pre-harvest uses of pyrethrins have been submitted to support the existing uses. The data that are available indicate that residues of pyrethrins I components (pyrethrin 1, cinerin 1, and jasmolin 1) were less than the data-collection method LOQ (<0.02 ppm) in/on the following representative commodities after treatments with an EC formulation at 1.0x the maximum preharvest use rate: (i) root and tuber vegetables (carrots, potatoes, radish roots, and sugar beet roots); (ii) fruiting vegetables (peppers and tomatoes); and (iii) citrus fruits (grapefruit and oranges). Residues of pyrethrins I components were, however, detectable in/on the following treated commodities: (i) leaves of root and tuber vegetables (up to 1.02 ppm in/on radish tops); (ii) leafy vegetables (up to 0.55 ppm in/on spinach); (iii) Brassica (cole) leafy vegetables (up to 0.49 ppm in/on mustard greens); (iv) legume vegetables (up to 0.072 ppm in/on succulent bean pods); (v) foliage of legume vegetables (up to 0.45 ppm in/on succulent pea vines); (vi) cucurbit vegetables (up to 0.023 ppm in/on cantaloupes); and (vii) berries (up to 0.055 ppm in/on blueberries). In addition, detectable residues of pyrethrins I were reported for the following miscellaneous commodities: (i) cranberries (up to 0.030 ppm); (ii) grapes (up to 0.096 ppm); and (iii) strawberries (up to 0.068 ppm). HED is requesting that additional field trial be submitted by the PJV (J. Deluzio, 10/12/04, D295748).

Adequate data depicting the magnitude of residues of pyrethrins in food-handling establishments and food storage areas are available. These data indicate that the established tolerance of 1 ppm will not be exceeded in representative food commodities that had been covered during space, contact, and intermittent spray aerosol treatments using representative SC/L and PrL formulations.

6.1.2 Water Exposure

The drinking water exposure was performed using the environmental fate characteristics of representative chemical, pyrethrin 1, for which the environmental fate database was developed. All other pyrethrins are expected to have similar environmental fate characteristics; therefore, the Estimated Drinking Water Concentrations (EDWCs) are considered suitable representative values for all the pyrethrins. The mosquito adulticide uses of the pyrethrins were not considered in this drinking water assessment. The calculations were based on the agricultural uses only, which have a higher application rate. Since it is possible that pyrethrins may be applied directly over bodies of water, the EDWC calculations are considered conservative. The values in Table 6.1 generally represent upper-bound estimates of the concentrations that might be found in surface water and groundwater due to the use of pyrethrin on multiple crops by aerial spraying (S. Dutta, 8/19/04, DP Barcode D295750).

Table 6.1. Summary of Estimated Surface and Ground Water Concentrations for Pyrethrins.

Exposure Duration	Water Source	
	Surface Water Conc., ppb [a]	Ground Water Conc., ppb [b]
Acute	4.078	0.003
Chronic (non-cancer)	0.21	0.003

[a] From the Tier I FIRST - Index Reservoir model. Input parameters are based on 10 applications at the agricultural use rate of 0.05 lb ai/A and a re-application interval of 1 day.
[b] From the SCI-GROW model assuming a maximum seasonal use rate of 0.5 lb ai/A, a K_{oc} of 12,400 ml/g, and a half-life of 3.2 days.

FIRST (FQPA Index Reservoir Screening Tool) is a screening model designed to estimate the pesticide concentrations found in surface water for use in drinking water assessments. It provides high-end values on the concentrations that might be found in a small drinking water reservoir due to the use of pesticide. Like GENEEC, the model previously used for Tier I screening level, FIRST is a single-event model (one run-off event), but can account for spray drift from multiple applications. FIRST takes into consideration the so called Index Drinking Water Reservoir by representing a larger field and reservoir than the standard GENEEC scenario. The FIRST scenario includes a 427 acres field immediately adjacent to a 13 acres reservoir, 9 feet deep, with continuous flow (two turnovers per year). The reservoir receives a spray drift event from each application plus one runoff event. The runoff event moves a maximum of 8% of the applied pesticide into the reservoir. This amount can be reduced due to degradation on field and the effect of binding to soil. Spray drift is equal to 6.4% of the applied concentration from the ground

spray application and 16% for aerial applications.

FIRST also makes adjustments for the percent crop area. While FIRST assumes that the entire watershed would not be treated, the use of a PCA is still a screen because it represents the highest percentage of crop cover of any large watershed in the US, and it assumes that the entire crop is being treated. Various other conservative assumptions of FIRST include the use of a small drinking water reservoir surrounded by a runoff-prone watershed, the use of the maximum use rate, no buffer zone, and a single large rainfall.

SCIGROW (Screening Concentration in Ground Water) provides a groundwater screening exposure value to be used in determining the potential risk to human health from drinking water contaminated with the pesticide. Since the SCIGROW concentrations are likely to be approached in only a very small percentage of drinking water sources, i.e., highly vulnerable aquifers, it is not appropriate to use SCIGROW for national or regional exposure estimates.

SCIGROW estimates likely groundwater concentrations if the pesticide is used at the maximum allowable rate in areas where groundwater is exceptionally vulnerable to contamination. In most cases, a large majority of the use area will have groundwater that is less vulnerable to contamination than the areas used to derive the SCIGROW estimate.

6.1.3 Acute and Chronic Dietary Exposure and Risk

Both chronic and acute dietary (food and water) exposure assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 2.03), which uses food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994 to 1996 and 1998. The analyses were performed to support the tolerance reassessment eligibility decision for 19 crop groups and several miscellaneous commodities. There are no monitoring data available for pyrethrins.; therefore, the dietary exposure analyses were conducted using current tolerance values, Codex Maximum Residue Limits (MRLs), field trial data, and translated data. DEEM 7.81 processing factors were used in this assessment.

Acute Dietary Exposure Results and Characterization

An acute probabilistic assessment was conducted. Residue distribution files were developed if sufficient field data were provided. Along with these files, current tolerances, Codex MRLs, translated data, and percent of crop treated data (%CT) were used to generate an estimate of the acute dietary exposure. The results of the analysis are presented in Table 6.2. Note that these analyses include exposure to dietary food **and** water. The risk estimates for the US population and all population subgroups generally do not exceed HED's level of concern. **The exposure estimate for the U. S. population is 54% of the acute Population Adjusted Dose (aPAD) and 100% of the aPAD for children (1-2 yrs old) at the 99.9th percentile of exposure.** The most significant contributors to the children's exposure estimates are pineapple, dried oat-babyfood, and banana. The processing factors and percent crop

treated information represent upper bound estimates. The exposure assessments may be refined with the submission of additional field trial data, percent crop treated estimates for additional commodities, and processing studies.

Chronic Dietary Exposure Results and Characterization

A somewhat refined assessment was conducted to assess the chronic dietary exposure to pyrethrins. Current tolerances, field trial data, translated data, default processing factors, percent crop treated (%CT), and an upper bound estimate for the chronic drinking water concentration were used. The HAFT (highest average field trial) of 0.23 ppm from a spray food handling study was used for all food-handling establishment uses of pyrethrins. Results of the exposure and risk analyses are presented in Table 6.2. HED concludes that for all supported commodities, the chronic dietary exposure estimates did not exceed the Health Effects Division's (HED) level of concern for the U. S. population and all population subgroups. **The exposure estimate for the US population is 11% of the chronic Population Adjusted Dose (%cPAD) and 32 % for the highest exposed population, children (1-2 years of age).**

Table 6.2 Summary of Dietary Exposure and Risk for Pyrethrins

Population Subgroup [a]	Acute Dietary (99.9th Percentile)			Chronic Dietary [b]		
	aPAD, mg/kg/day	Exposure, mg/kg/day [b]	% aPAD	cPAD, mg/kg/day	Exposure, mg/kg/day	% cPAD
General U.S. Population	0.07	0.038	54	0.04	0.0044	11
All Infants (< 1 yr)	0.07	0.068	97	0.04	0.0088	22
Children 1-2 yrs	**0.07**	**0.070**	**100**	**0.04**	**0.013**	**32**
Children 3-5 yrs	0.07	0.051	73	0.04	0.011	27
Children 6-12 yrs	0.07	0.034	49	0.04	0.0068	17
Youth 13-19 yrs	0.07	0.025	35	0.04	0.0036	9
Adults 20-49 yrs	0.07	0.031	43	0.04	0.0035	9
Adults 50+ yrs	0.07	0.019	27	0.04	0.0031	8
Females 13-49 yrs	0.07	0.027	38	0.04	0.0031	8

[a] The values for the population with the highest risk for each type of risk assessment are bolded.

[b] No cancer endpoint has been identified at this time; therefore, no cancer dietary risk assessment has been conducted.

Cancer Dietary Exposure Results and Characterization

For pyrethrin, there is suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential; therefore, no cancer dietary risk assessment was conducted.

6.2 Residential (Non-Occupational) Exposure/Risk Pathway

The residential exposure and risk assessment is more extensively described in a memorandum by Lloyd and Dole (DP Barcode: D315957; 4/22/2005).

Based on the master label, ten residential exposure scenarios have been assessed for this RED. Only inhalation and incidental ingestion exposure assessments have been conducted for the residential scenarios. Dermal exposures were not assessed because significant toxicity from dermal exposure is not expected, and therefore, no dose or endpoints were selected for dermal exposure. Short term exposures are assessed all handler and post-application exposure scenarios.

6.2.1 Residential Uses

6.2.1.1. Residential Exposure Scenarios

The residential exposure assessment includes both handler and post-application exposure scenarios. The term handler applies to individuals, including homeowners, who mix, load, and apply the pesticide product. The term post-application describes individuals who are exposed to pesticides after entering areas previously treated with pesticides. Only short-term exposures were assessed for most scenarios because the pyrethrins are used only on an intermittent basis and the residues disperse quickly. Intermediate-term exposures were assess for indoor metered release scenarios.

Based on information provided in the Pyrethrins Master Label regarding current registrant supported uses, HED assessed the following residential exposure scenarios for the pyrethrins RED.

Handler Exposure Scenarios

1) Aerosol can application - indoor surface spray
2) Load/apply dusts - indoor surface treatment and home gardens
3) Mix/load/apply liquids with LP handwand - indoor surface spray and crack and crevice application
4) Mix/load/apply liquids with trigger sprayer - indoor surface spray and crack and crevice application
5) Mix/load/apply liquids with hose-end sprayer - Lawns

Post Application Exposure Scenarios

1) Inhalation exposure from aerial application of mosquito adulticide
2) Inhalation exposure from truck mounted ULV application of mosquito adulticide
3) Toddler incidental oral ingestion of residue from treated turf
4) Toddler incidental oral ingestion of residues deposited on carpet
5) Toddler incidental oral ingestion of residues deposited on vinyl flooring
6) Toddler incidental oral ingestion of residues on pets
7) Inhalation exposure to aerosol spray during and after space spray application
8) Inhalation exposure from compact metered release systems

6.2.1.2 Residential Exposure Data and Assumptions

Application Parameters

Application rates for all of the exposure scenarios assessed are based on information provided in the Pyrethrins Master Label. The Pyrethrins Master Label lists all of the uses that the Pyrethrins Joint Venture members are supporting. Therefore, it is important all labels be revised to reflect the supported uses and maximum allowable application rates provided in the Master Label. However, the application rate for the compact metered release scenario is based upon the Purge II label (EPA Reg No. 9441-161), which is a typical product that is used in the compact aerosol dispenser units.

Handler Exposure Data

Data from the PHED or ORETF data bases were used to assess residential handler exposures. Default application assumptions regarding areas treated or amounts applied for residential handler scenarios are documented in the HED Science Advisory Committee on Exposure SOP 12: Recommended Revisions To The Standard Operating Procedures For Residential Exposure Assessment (2/22/2001).

Post Application Exposure Data

HED Residential Exposure SOPs

The default factors used for the assessment are taken from the Exposure Science Advisory Committee SOP 12. SOP 12 provides values to assess post application inhalation and non-dietary ingestion exposure to lawn care pesticides, and indoor broadcast and crack and crevice treatments.

Non-Dietary Exposure Task Force Exposure Data

Primary assumptions for assessing post-application exposure to use of foggers and aerosols in indoor residential settings were based on data provided by the Non-Dietary Exposure Task Force (NDETF). The NDETF was formed in 1996 from members of the Pyrethrin Joint Venture (PJV) and Piperonyl Butoxide Task Force II (PBTFII), Task Forces set up in the 1980s by producers, formulators, and marketers of the AIs to respond to reregistration needs. NDETF includes; Bayer CropSciences, Botanical Resources Australia, Endura S.p.A, McLaughlin Gormley King Company, Pyrethrum Board of Kenya, Prentiss Inc., S.C. Johnson and Son, Inc., and Valent BioSciences Corporation. NDETF's

purpose is to produce scientifically sound data on non-dietary exposures to pyrethrin, the pyrethroids, piperonyl butoxide, and MGK-264.

The NDETF conducted studies to examine the deposition of residues from total release foggers. The studies conducted with formulations of pyrethrin/piperonyl butoxide and permethrin/Pyrethrins were submitted to EPA in January 2004. The studies simulated the use of a fogger and aerosol products indoors to provide data on air dispersion and deposition on surfaces (walls, floor). Carpet and vinyl were selected as the flooring surfaces of interest because of their different physical and chemical properties and because they represent a significant amount of the floor coverings used in homes in North America. While the focus of the NDETF efforts was on total release foggers, a study was also conducted to determine both dispersion (air levels) and deposition (on flooring) of pyrethrin/piperonyl butoxide resulting from the use of a hand held aerosol spray can. Potential direct exposure of the user was also measured. Air sampling from the breathing zone of the applicator and analysis of residues on cotton gloves was performed. A more detailed evaluation of the NDETF Study data used for the pyrethrins residential exposure assessment is provided in separate review (D302120, B. Daiss, 5/11/04).

Spray Drift Task Force Exposure Data

HED used the AgDRIFT model to calculate airborne concentrations from aerial ULV applications. The model was developed by the Spray Drift Task Force, a coalition of pesticide registrants whose primary objective was to develop a comprehensive data base of off-target spray drift information along with an appropriate modeling system. The model has been peer reviewed by EPA's Science Advisory Panel and has been used in previous mosquito adulticide exposure assessments (e.g. carbaryl, malathion). AgDRIFT predicts the motion of spray material released from an aircraft, including the mean position of the material and the variance about the mean resulting from turbulent fluctuations. The model provides information on what percentage of the application volume remains aloft and what percentage of the resulting droplets is deposited on surfaces in the treated area and downwind. AgDRIFT allows for estimation of air concentration in breathing zones and residues deposited on turf. For this assessment, however, only breathing zone concentrations were estimated using AgDRIFT because dermal exposure is not a route of concern for pyrethrins, and estimates of turf deposition used for assessing incidental ingestion were based more conservatively on direct application of pyrethrins to turf grass. Turf grass application involves a higher application rate and a more direct application pathway.

Exposure Assumptions

General Assumptions

- Average body weight of an adult is 70 kg
- Average body weight of a toddler is 15 kg
- Exposure is assessed on day of application (i.e., day zero)
- The application rates were taken from the Pyrethrins Master Label

Residential Handler Assumptions

- 0.5 acres (22,000 square feet) is treated per day with garden hose-end sprayer
- average home treated with space spray or crack and crevice treatment has 1600 square feet of surface area
- 1000 square feet of garden is treated per day with a dust applicator
- One aerosol can is used per day for indoor surface sprays
- Each aerosol can contains 16 oz. of product and contains 0.25 percent pyrethrin by weight.

Mosquito Abatement Assumptions

Aerial Applications

- fixed wing aircraft release height is 100 feet
- rotary aircraft release height is 30 feet
- average droplet size is 50 microns (per label and/or Public Health Pesticide Applicator Manual (25-50 microns)
- wind speed is 2 mph (per label and/or Applicator Manual (<10 mph)
- temperature is 86°F (per label and/or pesticide Applicator Manual (50-95°F)

Truck Mounted ULV Spray Application

- a dilution factor of 0.01 is applied to the airborne concentration at the maximum application rate (i.e., 1% of product released is available for exposure)
- breathing zone airborne concentration is estimated to be approximately 4-6 ft above the ground
- adult breathing rate is 1.0 m^3 per hour; child breathing rate is 0.7 m^3 per hour (NAFTA breathing rates for light activity)
- exposure duration is < 2 hours

Turf and Indoor Surface Treatment Post Application Exposure Assumptions

- estimated turf transferable residue is assumed to be 5% of the maximum application rate
- indoor surface residue is 0.98 µg/cm^2 based on NDETF study data and a maximum application rate of 0.00033 lbs ai/1000 ft^3 for indoor foggers
- hand transfer efficiency is 8% for carpet; 11% for vinyl based on NDETF data
- saliva extraction factor is 50 percent
- surface portion of hand put in mouth is 20 cm^2
- hand-to-mouth exposure frequency is 20 times per hour
- Exposure duration is 2 hours

Toddler Object to Mouth Scenario

- object to mouth transfer efficiency is equal to 20% of the application rate
- ingestion rate of residues from mouthing turf or a small object is 25 cm^2

Toddler Incidental Soil Ingestion Scenario

- soil ingestion rate is 100 mg/day
- fraction of ai available in uppermost cm of soil (fraction/cm) is 100 percent based on soil incorporation into top 1 cm of soil after application

Pet Treatment Post Application Assumptions

- one half of a 16 oz spray container is used to treat each animal
- transferable residue from a treated pet is assumed to be 20% of the maximum application rate for sprays
- surface area of a treated (30 lb) dog is 6000 cm^2 (EPA 1993 Wildlife Exposure Factors Handbook - carbaryl)
- saliva extraction factor is 50 percent
- surface portion of hand put in mouth is 20 cm^2
- frequency of hand-to-mouth events is one per day (frequency modified to reflect transferable residue assumption which is based on a 5 minute heavy rubbing/petting technique that would lead to significantly higher hand concentrations than would result from a single contact)

Space Spray Application Exposure Assumptions

- Inhalation during and after aerosol space spray application
- the master label rate of 0.00033 lb ai/1000 ft^3 is applied
- adult breathing rate is 1.0 m^3 per hour and child breathing rate is 0.7 m^3 per hour. These values are from SOP#12 and are recommended for scenarios of a few hours in duration.
- exposure duration is <2 hours

Compact Metered Release Exposure Assumption

- The application rate is based upon the Clean Air Purge II Label (EPA Reg. No. 9441-161_. This product contains 1% pyrethrins by weight in a 232 gram container. One container will apply 3000 sprays per month at 15 minute intervals and is sufficient for a 6000 ft^3 interior space.
- The amount of pyrethrins applied per spray is 0.77 mg based upon the application of 77 mg of product containing 1% pyrethrins.
- The dispenser unit is used in a generic house as defined in the Multi-Chamber Concentration and Exposure Model Version 1.2 (MCCEM). This house has an interior volume of 14440 cubic feet and hourly air change rates of 0.18 in summer and 0.45 in the fall and spring.
- Multiple unit(s) are installed for a whole house treatment at a rate of one unit per 6000 ft^3 and the initial concentration is 0.0045 m^3.
- A single unit is installed in the kitchen for the kitchen only treatment. The kitchen is assumed to internal volume of 1060 ft^3, which is a standard value from MCCEM. The initial concentration is 0.025 mg/m^3 in the kitchen.
- The breathing rate is 13.3 m^3/day for adults and 8.7 m^3/day for children. These values are from SOP#12 and are recommended for scenarios of a few days in duration. They are a daily average and account for time spent at rest or in sedentary activities.
- For the kitchen only treatment it is assumed that 10% of the exposure period would be spent in the rest of the house.

Data Used for Assessing Post Application Exposures

Substance and scenario specific data from the NDETF study was used to determine deposition of piperonyl butoxide on vinyl and carpet flooring following use of a total release indoor fogger. NDETF

data were also used to determine transfer of piperonyl butoxide residues from fogger treated vinyl and carpet flooring to the hands of a playing toddler. A more detailed evaluation of the NDETF Study data used for the piperonyl butoxide residential exposure assessment is provided in separate review (D302120, B. Daiss, 5/11/04).

Post-fogger release floor concentration was assumed to be 0.98 µg/cm^2. This is based on data from NDETF Study Volume 2, Post-Application Deposition Measurements for Pyrethrins & Piperonyl Butoxide Following Use of a Total Release Indoor Fogger. The measured mean floor concentration was 2.25 µg/cm^2 following fogger application at the rate of 0.00076 lb ai per 1000 ft^3. The measured deposition was adjusted to reflect a maximum application rate of 0.00033 lb ai per 1000 ft^3. HED used the mean measured deposition which excluded the concentration on the floor center coupon because the coupon under the total release canister appeared to be an outlying data point. The maximum pyrethrin concentration measured on the coupon under the total release canister was 121 µg/cm^2. The next highest concentration was 6.68 µg/cm^2 on a coupon at a distance of two feet from the canister. This deposition pattern was not repeated in findings from NDETF Study Volume 23, Post-Application Deposition Measurements for Pyrethrins & Piperonyl Butoxide Following Use of a Total Release Indoor Fogger. The mean floor concentration including the floor center coupon was 5.79 µg/cm^2.

Transfer of piperonyl butoxide from fogger treated carpet was assumed to be 8% of deposition based on data from Volume 29 of the NDETF Study, Measurement of Transfer of Pyrethrin and Piperonyl Butoxide Residues from Vinyl and Carpet Flooring Treated with a Fogger Formulation to DSS Wetted Hands Following a Single Hand Press. Transfer of pyrethrins from fogger treated vinyl flooring was assumed to be 11% of deposition based on data from Volume 13 of the NDETF Study, Measurement of Transfer of Pyrethrin and Piperonyl Butoxide Residues from Vinyl and Carpet Flooring Treated with a Fogger Formulation to DSS Wetted Hands Following a Single Hand Press.

Indoor air concentration for the period during and after aerosol space spray application was assumed to be 0.13 mg per cubic meter (mg/m^3) based on data from Volume 18 of the NDETF Study, "Measurement of Air Concentration, Dermal Exposure, and Deposition of Pyrethrin and Piperonyl Butoxide Following the Use of an Aerosol Spray". The measured two hour time weighted average air concentration at the 5 foot level (air samples were also collected at the one foot level) was 0.019 µg/L (0.19 mg/m^3) following aerosol application of 9.3 grams of a 0.5% pyrethrin formulation. This application was made to a simulated residential room that had an interior volume of 2048 ft^3. The theoretical concentration is 1.6 mg ai/m^3 (0.000051 lb ai/1000 ft^3) based upon the above parameters and assuming no deposition (the room was not ventilated during the two time periods). The measured air concentration of 0.019 mg/m^3 was then adjusted by a factor of 6.6 to reflect the master application rate of 0.00033 lb ai/1000 ft^3.

Inhalation following release of a total release aerosol fogger was not modeled separately because the master label application rates for the foggers are the same as the space sprays. The space spray application involves more direct and immediate exposure. The fogger labels typically require that the

room be closed and vacated during release of the fogger, that the room be kept closed for a period of 1-2 hours, and that the room be opened and aired for a period of time (e.g. 30 minutes, 1 hour) prior to re-occupancy.

The approach for estimating air concentrations from truck-mounted ULV spray applications is based on the SOP for residential exposure assessment for inhalation exposure from use of an outdoor space spray for pest control. The approach was modified to assume that 1% of the highest application rate for a truck mounted ULV sprayer is available in the breathing zone of the resident. It is assumed that the full application rates for a truck-mounted ULV sprayer (with a one percent dilution factor) is available in the breathing zone of the residential bystander, i.e., an application rate expressed as lbs. ai/ft^2, is converted into a concentration expressed in a per cubic foot (ft^3) basis.

The indoor concentrations resulting from the use of the compact metered release units in homes was modeled using MCCEM. Single chamber modeling was used to determine the air concentrations that would result from a whole house installation of multiple compact units. Multi-zone modeling was used to determine the air concentrations that would result from the installation of a compact unit in a single room in a house, such as the kitchen. In both cases the emissions source was defined in the data entry screen of MCCEM as one emission that lasts for a minute and which occurs every fifteen minutes. The emission rates were 111 mg/hr for one minute for the whole house scenario and 46 mg/hr for one minute for the kitchen only scenario (MCCEM requires that the emission be expressed as units per hour). Graphs of the output from the MCCEM runs are included as Appendix 6. These graphs indicate that the concentration increased steadily for the first few hours and that steady state concentrations were reached in 12 to 60 hours depending upon the number of zones and the air exchange rate. Because the units run continuously for thirty days before the cartridge needs to be changed, it is assumed that exposures could occur at steady state concentrations, therefore, the steady state concentrations were used for exposure assessment. More information on MCCEM may be found at the EPA website http://www.epa.gov/opptintr/exposure/docs/mccem.htm.

6.2.1.3. Residential Exposure and Risk Estimates

Most residential handler and post application scenarios were assessed as short term exposures because pyrethrins are used only on an intermittent basis and the residues disperse or degrade rapidly. However, the compact metered release sprays are packaged to release product regularly for a 30-day period and may be immediately replaced, resulting in intermediate-term exposures. Exposure and risk estimates for the scenarios are summarized in Table 6.3 below and the calculations provided in Appendix 4. All of the short-term scenarios have MOEs that exceed the target MOE, therefore the risks are not of concern.

The exposure estimates for this assessment are based on maximum application rates as provided in the master label. In some cases, it appears that the master label rates are higher than typical label rates. The application rate of 0.00033 lb ai/1000 ft^3 for the space spray scenario was based upon the master label and it is assumed that the product labels would conform to this rate. Many of the product labels have

statements such as "apply for 5 to 10 seconds to an average size room" which would prevent excessive application. Some labels have statements, however, such as "apply until the room is filled with a fine mist", which are less specific. In the latter case, it is conceivable that an entire can could be used and the resulting air concentration would exceed the master label rate. If, for example, an entire 16 ounce can of 0.5% pyrethrin product were used in a small residence, such as a 500 ft^2 studio apartment, the resulting concentration would be 0.00125 lbs ai/1000 ft^3 which is 3.8 times the master label rate.

The risks for the metered release scenarios are conservative because it was assumed that the aerosols would remain airborne until they were removed by ventilation and the effect of aerosol settling was not considered. Aerosol settling could be a major factor depending upon the aerosol size and rate of evaporation. Information regarding the aerosol size and evaporation rate could be used to refine the risks, particularly for the residential scenarios where the ventilation removal rate is probably slower than the settling rate.

The master label indicates that the metered release system application rate of 0.000476 lb ai/1000 ft^3/day can be used in domestic dwellings and indoor sites. Commercially available aerosol dispensers that appear to be intended for the residential areas apply much less than the master label rate. These dispensers apply aerosols from 6.4 oz cans at 15 minute intervals and each can will deliver approximately 3000 applications in a month to a 6000 ft^3 space. The application rate for these dispensers is approximately 0.000028 lb ai/1000 ft^3/day if continuous operation is assumed. This rate is 17 times less than the master label rate.

The SOP default residential unit exposures selected for each scenario were based on central-tendency values from PHED. Summary descriptions of these data are provided in Table 12 of Appendix 4. The mean exposure data from the NDETF study used to estimate exposures from indoor fogger release are comprehensive and should accurately represent likely exposures from total release foggers.

Table 6.3 Summary of Residential Risks

Scenario	Exposed Population	Exposure Route	Short Term MOE [a]	Intermediate Term MOE [b]
Residential Handler Exposures				
Aerosol Can Application - Indoor Surface Treatment	Adults	Inhalation	170,000	N/A [c]
Load/Apply Dusts - Indoor Surface Treatment			9,700	N/A [c]
Load/Apply Dusts - Home Gardens			790,000	N/A [c]
Low Pressure Handwands - Indoor Surface Spray			200,000	N/A [c]
Low Pressure Handwands - Indoor Crack and Crevice			51,000	N/A [c]
Trigger Sprayer - Home Gardens			4,000,000	N/A [c]

Table 6.3 Summary of Residential Risks				
Scenario	Exposed Population	Exposure Route	Short Term MOE [a]	Intermediate Term MOE [b]
Trigger Sprayer - Indoor Crack and Crevice			12,000	N/A [c]
Hose End Sprayer - Lawn Application			720,000	N/A [c]
Post Application Exposures Following Mosquito Abatement Applications				
Aerial Application	Children	Inhalation	24,000	N/A [c]
	Adults		89,000	N/A [c]
Truck Application	Children	Inhalation	2,400	N/A [c]
	Adults		8,900	N/A [c]
Toddlers Playing on Treated Turf				
Hand to Mouth	Children	Incidental Oral	13,000	N/A [c]
Object to Mouth			2,100	N/A [c]
Soil Ingestion			150,000	N/A [c]
Aggregate of Above			1,800	N/A [c]
Toddlers Playing on Floors after Fogger Treatment				
Carpet Floors	Children	Incidental Oral	9,500	N/A [c]
Vinyl Floor			6,900	N/A [c]
Pet Treatment Post Application Exposures				
Playing with Treated Pets	Children	Incidental Oral	240,000	N/A [c]
Post Application Exposure Following Space Spray Applications				
Aerosol Spray	Children	Inhalation	640	N/A [c]

Table 6.3 continued on following page

Table 6.3 Summary of Residential Risks				
Scenario	Exposed Population	Exposure Route	Short Term MOE [a]	Intermediate Term MOE [b]
	Adult		2,100	N/A [c]
Post Application Exposure Following Metered Release				
Single Chamber MCCEM Modeling of Whole House Metered Release at 0.18 air changes per hour (ACH)	Children	Inhalation	120	40
	Adult		370	130
Single Chamber MCCEM Modeling of Whole House Metered Release at 0.45 ACH	Children	Inhalation	290	100
	Adult		890	310
Two Zone MCCEM Modeling of Kitchen Only Metered Release at 0.18 ACH	Children	Inhalation	310	100
	Adult		940	310
Two Zone MCCEM Modeling of Kitchen Only Metered Release at 0.45 ACH	Children	Inhalation	740	240
	Adult		2,200	740

[a.] Target short term MOEs are 100 for inhalation exposures and 300 for incidental oral exposures.
[b.] The target intermediate term MOE is 1000 for inhalation exposures.
[C.] N/A = Not applicable for this exposure scenario.

6.3 Other

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

7.0 Aggregate Risk Assessments and Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard

(e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

No endpoint was identified for dermal exposure to the pyrethrins, so dermal exposures need not be considered in the aggregate assessment.

7.1 Acute Aggregate Risk

Only food and water are generally aggregated for acute (one-day) exposures to pesticides. The probabilistic dietary assessment that includes both food and water exposures may be found in section 6.1.3 of this document. The exposure estimate for the US population is 54% of the acute Population Adjusted Dose (aPAD) and 100% of the aPAD for children (1-2 yrs old) at the 99.9th percentile of exposure. HED is generally not concerned unless the exposure substantially exceeds 100% of the aPAD. The sensitivity analysis shows that the most significant contributors to the children's exposure estimates are pineapple, dried oat-babyfood, and banana. The processing factors and percent crop treated information represent upper bound estimates. The exposure assessments may be refined with the submission of additional field trial data, percent crop treated estimates for additional commodities, and processing studies.

7.2 Short-Term Aggregate Risk

Incidental oral and inhalation exposures may be expected as a result of the residential use of pyrethrins. Endpoints relating to neurotoxicity were selected for the both the oral and inhalation routes so the risks may be aggregated. An aggregate risk index approach must be used since the target MOEs are different for the different exposure routes.

Exposures via the oral route may be expected from food, water, and incidental oral exposures in the home. Average food and water exposure values were used, as described in section 6.1. Incidental oral exposures may result from children playing on treated turf and ingesting soil or inserting their hands in their mouths during or after playing on treated turf. Pyrethrins may be used as a space spray, so children may be exposed by touching treated surfaces and inserting their hands in their mouths. Pyrethrins may also be directly applied to pets, so children may be exposed by putting their hands in their month after petting. The highest exposure via the incidental oral route resulted from toddlers re-entering treated lawns, so this scenario was used in the aggregate assessment.

Exposures via the inhalation route may be expected from many sources. People may be exposed after pyrethrins are applied as part of mosquito abatement programs. Pyrethrins may be used inside the home as foggers or sprays; the adult applying the product, or adults and children entering the treated area after use may be exposed to pyrethrin. The highest exposure via the inhalation route was from the space spray, so this scenario was used in the short-term aggregate assessment.

The aggregate risk index (ARI) method was used to estimate the risk from aggregated oral and inhalation exposures, and results are found in Table 7.2. HED is generally not concerned if the ARI_{agg} exceeds 1. The ARI_{agg} is 0.93 for children, while the ARI_{agg} exceeds one for all other populations.

The calculated exposure values for food and water were high-end estimates. Percent crop treated data were not available for all commodities. High-end field trial data were generally used, because sufficient data were not available for all commodities such that an average residue value could be used. Summary descriptions of these data are provided in Table 12 of Appendix 4. The mean exposure data from the NDETF study used to estimate exposures from indoor fogger release were comprehensive and should accurately represent likely exposures from total release foggers.

Although the ARI_{agg} for children slightly exceeds HED's level of concern, it is considered to be a high-end estimate and the actual risk is likely to be much lower.

7.3 Intermediate-Term Aggregate Risk

The endpoints selected for the oral and inhalation routes of exposure cannot be aggregated as a systemic endpoint was selected for oral exposures and a local effect was selected for the inhalation exposures. Incidental oral exposures are not expected for this interval, so aggregation with dietary exposures are not required.

7.4 Long-Term Aggregate Risk

The endpoints selected for the oral and inhalation routes of exposure cannot be aggregated as the a systemic endpoint was selected for oral exposures and a local effect was selected for the inhalation exposures. Incidental oral exposures are not expected for this interval, so aggregation with dietary exposures are not required.

A somewhat refined chronic dietary (food and water) assessment was previously described in section 6.1 of this document. The exposure estimate for the US population is 11% of the chronic Population Adjusted Dose (%cPAD) and 32 % for the highest exposed population, children (1-2 years of age). The processing factors and percent crop treated information represent upper bound estimates. The exposure assessments may be refined with the submission of additional field trial data, percent crop treated estimates for additional commodities, and processing studies.

7.5 Cancer Risk

No quantification of cancer risk is required, based on the "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" classification.

8.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to pyrethrum and any other substances and the pyrethrum does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that pyrethrum has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Table 7.2. **Short-Term Aggregate Risk Calculations**								
Population	**Food + Water Exposure**	**Incidental Oral Exposure**	**Total Incidental Oral + Food + Water Exposure**	**MOE Food + Water+ Incidental Oral**	**ARI Food + Water+ Incidental Oral**	**MOE Inhalation**	**ARI Inhalation[1]**	**Aggregate ARI[2]**
Adult Male	0.0037	0	0.0037	5405	18	370	3.7	3.1
Adult Female	0.0034	0	0.0034	5850	19	370	3.7	3.1
Child	0.011	0.005	0.016	1250	4.2	120	1.2	0.93
Non-hisp/non-white/ non-black *(Highest Exposed Adult Subpop*)	0.0069	0	0.0069	2900	9.7	370	3.7	2.7

[1]$ARI = [MOE_{CALCULATED\ (i.e.,\ FOOD,\ WATER,\ DERMAL,\ INHALATION,\ ORAL)} \div MOE_{ACCEPTABLE}]$ (Note: Target ARI = 1)

[2]$\text{Aggregate ARI} = \dfrac{1}{\frac{1}{ARI_{FOOD+WATER+ORAL}} + \frac{1}{ARI_{INHALATION}}}$

9.0 Occupational Exposure/Risk Pathway

The occupational exposure and risk assessment is more extensively described in a memorandum by Lloyd and Dole (DP Barcode: D315957; 4/21/2005).

9.1 Occupational Risk

9.1.1 Occupational Scenarios

Based on the Master Label, thirty occupational exposure scenarios have been assessed for this RED. Only inhalation exposures have been assessed for each of the occupational scenarios. Dermal exposures were not assessed because no dose or endpoints were selected for dermal exposure. Short and intermediate/long term exposures are expected/assessed for occupational exposure scenarios based on use patterns.

The term handler applies to individuals who mix, load, and apply the pesticide product. Based primarily on information provided in the Pyrethrins Master Label regarding current registrant supported uses, HED assessed the following scenarios for agricultural, professional pest control operator, and mosquito control applications for the pyrethrins RED. Application of dust with shaker can, bulb duster and power duster, a relevant and potentially significant exposure scenario was not assessed due to lack of dust-specific or adequate surrogate data on inhalation exposure associated with this activity.

<u>Agricultural Handler Scenarios</u>

1) Mix/Load liquids for aerial application or chemigation to field crops
2) Mix/Load liquids for ground-boom application to field crops
3) Mix/Load liquids for airblast application to field crops
4) Mix/Load wettable powders for aerial application or chemigation to field crops
5) Mix/Load wettable powders for ground-boom application to field crops
6) Mix/Load wettable powders for airblast application to field crops
7) Aerial application of liquids to field crops
8) Ground boom application to field crops
9) Airblast application to field crops
10) Mix/Load/Apply liquids with high pressure (HP) hand wand to greenhouses
11) Mix/Load/Apply liquids with backpack sprayer or low pressure (LP) handwand to greenhouses
12) Mix/Load/Apply wettable powder with backpack sprayer or LP hand wand to greenhouses
13) Mix/Load/Apply liquids with backpack sprayer or LP hand wand to agricultural premises and equipment
14) Flag aerial spray application

Pesticide Control Operator Scenarios

1) Mix/Load/Apply liquids with LP handwand - indoor surface spray or crack or crevice treatment;
2) Mix/Load/Apply WP with LP handwand - indoor surface spray or crack or crevice treatment;
3) Mix/Load/Apply liquids with turfgun - turf;
4) Mix/Load/Apply WP with turfgun - turf;
5) Mix/Load/Apply liquids with back pack sprayer or LP handwand to stored grain
6) Mix/Load/Apply liquids with HP handwand to stored grain
7) Mix/Load/Apply liquids with LP handwand to stored produce
8) Aerosol spray application - indoor surface spray

Mosquito Abatement Scenarios

1) Mix/Load liquids for aerial application
2) Mix/Load liquids for ULV truck mounted spray application
3) Aerial application
4) Apply liquids with truck mounted ULV sprayer (airblast sprayer unit exposure used as surrogate)
5) Mix/Load/Apply liquids with back pack sprayer

Animal Groomer and Veterinary Technician Scenarios

1) Aerosol can application

9.1.2. Occupational Handler Exposure Data and Assumptions

9.1.2.1. Application Parameters and Exposure Data

Application Parameters

Application rates for all of the exposure scenarios assessed are based on information provided in the Pyrethrins Master Label. The Master Label was submitted to the Agency by the Pyrethrins Joint Venture, care of the Consumer Specialty Products Association. The Pyrethrins Master Label lists all of the uses that the Pyrethrins Joint Venture members are supporting. Therefore, it is important all labels be revised to reflect the supported uses and maximum allowable application rates provided in the Master Label.

Exposure Data

HED Occupational Exposure SOPs

It is the policy of the HED to use data from the Pesticide Handlers Exposure Database (PHED) or Occupational and Residential Exposure Task Force (ORETF) data to assess handler exposures for regulatory actions when chemical-specific monitoring data or other handler-specific data are not available. PHED was designed by a task force of representatives from the US. EPA, Health Canada, the California Department of Pesticide Regulation, and members of the American Crop Protection Association. PHED is a software system consisting of two parts; 1) a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions, and 2) a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates). The ORETF completed four studies which were designed to provide representative, or generic surrogate exposure data for pesticide handler risk assessment. The studies were designed by the Task Force, which included input from representatives of the crop protection field, regulatory agencies, and commercial applicators. The studies monitored professionals applying granular formulation by push spreader and various formulations by pressurized hose-end handgun or spray gun; and volunteers representing non-professional consumers applying granular formulation by push spreader and liquid formulations by garden hose-end sprays. Overall, the four ORETF studies were well-conducted and the data for all scenarios is considered of better quality and quantity than what is currently contained in PHED. Default application assumptions regarding areas treated or amounts applied for agriculture and mosquito abatement handler exposure scenarios are documented in the HED Science Advisory Committee on Exposures SOP 9, Standard Values for Daily Acres Treated in Agriculture (7/5/2000).

National Pest Management Association Survey

Information on how pest control operators use pesticide products was obtained from a survey conducted by the National Pest Management Association (NPMA). NPMA sponsored a Pest Control Operators (PCO) Product Use and Usage Information Survey. Using a retrospective telephone survey method, the enumerator (Dr. Richard Patterson of the University of Florida) contacted 148 PCO firms and was able to complete 67 surveys. The survey was national in scope and included 12-23 responses from each of four regions. The survey collected information on where PCOs apply their products, product brands that are used for wood destroying insects and general pest control, and the amount of time PCOs spend on application, travel, equipment set up, mixing/loading products, administrative and other activities.

OPP's Biological and Economic Analysis Division (BEAD) conducted a review of the NPMA survey. BEAD drew the following conclusions regarding the robustness and validity of the survey data. Given that there are approximately 19,000 PCO firms in the U.S., it is highly unlikely that a sample size of 67 represents a statistically valid sample. The use of a retrospective survey methodology may have

introduced errors in the data. Pesticide survey firms like Doane use a prospective survey instrument sent to growers in advance thus allowing them to keep detailed accounts of their pesticide usage in real time throughout the year. Despite its small size and retrospective methodology, however, the information collected is far more robust than BEAD typically gets when asking questions of this nature. BEAD typically contacts 1-5 PCOs and asks chemical specific questions which may bias the responses if PCOs value the chemical under review. (D. Brassard, date)

9.1.2.2. Exposure Assumptions

The following assumptions were used in estimating risks to occupational handlers from exposure to pyrethrins:

1) Average body weight of an adult handler is 70 kg
2) Exposure duration is short-term and intermediate/long term for agricultural handlers, PCOs and mosquito control applicators
3) Baseline inhalation exposure (no respiratory protection)
4) The application rates are from the master label and are listed in Table 3 above
5) The values for areas treated or amounts used per day were generally taken from ExpoSAC Policy #9 except as noted. These values are listed below:

6) aerial applications

- 350 acres per day for typical acreage field crops; 1200 for high acreage field crops (e.g., corn, rice, wheat)
- 7500 acres per day for mosquito control adulticide applications

groundboom applications

- 80 acres treated per day for field crops
- 40 acres treated per day for golf course turf

airblast applications

- 40 acres treated per day for agricultural applications
- ULV truck mounted sprayer - 3000 acres treated per day for mosquito control (airblast used as surrogate)

animal groomers and veterinary technicians

- 8 animals are treated per day
- one-half of a 16 oz. spray container used to treat each animal

high pressure handwand application

- 10 acres treated or 1000 gallons of spray solution used per day

backpack spray or a low pressure handwand sprayer applications

- 2 acres treated or 40 gallons of spray solution used per day for agricultural and/or mosquito control applications
- 5 grain storage bins treated per day with cross-sectional area of 1000 square feet per bin
- 5 food produce storage warehouses treated per day, area treated per warehouse is 10,000 square feet

pest control operator applications

- a maximum of 7 commercial buildings or residential homes treated per day for general pest control management activities
- average area treated per building is 1600 square feet for surface spray and crack and crevice treatment and 12800 cubic feet for space spray application (EPA Exposure Factors Handbook)

The assumptions used for veterinary and grain storage treatments are not included in the Occupational Exposure SOPs but represent values that have been used by the Agency in previous assessments (e.g., carbaryl, cyfluthrin).

- Assumptions used for daily area treated for produce storage warehouses are based on best professional judgement.

- Assumptions used for general pest control applicators are based data from the NPMA survey. Based on BEADs review of the NPMA survey, PCOs conducting general pest control activities would treat an average of between 6 and 7 buildings per day, assuming an 8-hour work day. According to the EPA Exposure Factors Handbook, a central tendency estimate of the average residential house is 369 m^3 (12800 ft^3). Given a typical ceiling height of 8 feet, the typical house has about 1,600 ft^2 of surface area. Given that NPMA survey data indicate that PCOs spend approximately the same amount of time applying general pest control formulations to residential and commercial buildings (68 minutes for residential buildings, 70 minutes for day care buildings, and 79 minutes for commercial/institutional buildings), it is assumed that approximately the same area is treated for residential and commercial structures.

- Airblast application unit exposure data was used to assess exposure resulting from truck mounted ULV application of mosquito adulticide. In the absence of more equipment specific data, airblast unit exposure data is thought to provide reasonable surrogate exposure information based on the similarity of the two application methods and has been used for this purpose in previous HED occupational exposure assessments (e.g., carbaryl).

9.1.3. Occupational Handler Exposure and Risk Estimates

The target MOEs are 100 for short term exposure and 1000 for intermediate/long term exposures. Exposure and risk estimates for the handler scenarios are summarized below, and detailed information may be found in Appendix 4.

All of the short term MOEs are above the target MOE of 100 and therefore the short term risks are not of concern. Two of the agricultural handler scenarios and two of the PCO handler scenarios are of concern for intermediate term exposures with MOEs that are less than the target MOE of 1000. The scenarios of concern are listed below:

- Mix/Load wettable powders for aerial application or chemigation to field crops with an application rate of 0.05 lb ai/acre. The MOE is 69 for high acre crops and 240 for typical acre crops.

- Mix/Load/Apply WP with LP handwand to greenhouses with an application rate of 0.15 lb ai/acre. The MOE is 240.

- Mix/Load/Apply WP with LP handwand for surface treatments with an application rate of 0.056 lb ai/1000 ft^2. The MOE is 260 assuming 11,200 square feet (7 buildings) treated per day.

- Mix/Load/Apply wettable powders with LP handwand for crack and crevice treatment at an application rate of 0.22 lb ai/1000 ft^2. The MOE is 66 assuming 11,200 square feet (7 buildings) treated per day and 460 assuming 1600 square feet (one building) treated per day.

It was also assumed, based on the master label, that products for all applications are supported/available in multiple forms i.e., liquids, dust, and wettable powders. However, given that the majority of pyrethrin products are available as liquid formulations, scenarios involving handling and application of liquid formulations are likely to be more representative of actual exposure.

The intermediate term occupational risks for agricultural handlers are conservative because pyrethrins are infrequently used on field crops and exposures of an intermediate duration (greater than 30 days in a row) are unlikely to occur. According the SLUA report, the percent crop treated values for field crops are generally less than 2.5 percent. The intermediate term occupational risks for PCO are conservative for crack and crevice treatments because the assumed area treated (1600 ft2 per building) is based upon the floor surface of the building rather than the cracks and crevices, which occupy a much smaller area.

The SOP default occupational and residential unit exposures selected for each scenario were based on central-tendency values from PHED. Summary descriptions of these data are provided in Table 12 of Appendix 4. The mean exposure data from the NDETF study used to estimate exposures from indoor fogger release are comprehensive and should accurately represent likely exposures from total release foggers.

Uncertainties identified by BEAD regarding the NPMA survey data used to determine potential exposures to PCO should also be noted. Regarding the robustness and validity of the NPMA survey data BEAD drew the following conclusions. Given that there are approximately 19,000 PCO firms in the U.S., it is highly unlikely that a sample size of 67 represents a statistically valid sample. The use of a retrospective survey methodology may have introduced errors in the data. Pesticide survey firms like Doane use a prospective survey instrument sent to growers in advance thus allowing them to keep detailed accounts of their pesticide usage in real time throughout the year. Despite its small size and retrospective methodology, however, the information collected is more robust than BEAD typically gets

when asking questions of this nature. BEAD typically contacts 1-5 PCOs and asks chemical specific questions which may bias the responses if PCOS value the chemical under review.

For pest control operator and mosquito abatement scenarios, assuming full day application rates for each application method may significantly overestimate total exposure. Based on data on usage of likely pyrethrins containing pesticides presented in the NPMA survey, this assumption would result in significant overestimate of exposure for PCOs. Similarly, assuming continuous usage of pyrethrins containing pesticides for mosquito abatement applications may also overestimate total exposure based on personal communication with mosquito control district officials regarding current usage of these products. However, pyrethrins are used to control a large number and a wide variety of pests and labels do not restrict or preclude repeated applications or long term use. Given the potential for multiple applications and long-term use for occupational handlers, inclusion of a repeated use/long-term exposure scenario for pest control operators and mosquito abatement is considered reasonable.

Application of dust with shaker can, bulb duster and power duster, a relevant and potentially significant exposure scenario for both residential and occupational exposures, was not assessed due to lack of dust-specific or adequate surrogate data on inhalation exposure associated with this activity. Use of existing applicator data for surrogate exposure assumptions would likely underestimate potential risk

9.2 Occupational Post Application Exposure and Risk

According to the master label, pyrethrins are used as space sprays in a wide variety of indoor areas such as barns, greenhouses, food storage areas, food processing areas, restaurants and residences. For many of the applications there are restrictions such as 'Do not allow unprotected persons to enter until treated area has been thoroughly ventilated' which minimize post application exposures. The label does not have a specific ventilation requirement for metered release applications but it does prohibit the placement of the metering device within 8 feet of exposed food, dishes, utensils and food handling or preparation areas.

Given the above use characteristics, occupational post application inhalation exposures are anticipated primarily from metered release applications. To assess these exposures, a scenario that involves the metered release into a dairy barn was evaluated because pyrethrins are commonly used in dairy barns and because the ventilation characteristics of dairy barns are relatively well defined.

9.2.1. Exposure Data Sources, Assumptions and Calculation Methods

Data Sources

No exposure data was available to assess post application exposures.

Assumptions

- The following assumptions were made regarding occupational post application exposures in dairy barns with metered release systems:
- The metered release rate of 0.00476 lb ai/1000 cubic feet (cf) was used to assess exposures. It was divided by six to account for one metered release every four hours.
- Two metered releases would occur during an eight hour work day.
- The interior volume is 500 cf per cow and is based upon 50 square feet per cow times a ceiling height of 10 feet.
- The ventilation rate is 50 cubic feet per minute (CFM) per cow. This value is from extension recommendations for dairy barn design.
- A typical dairy barn would contain 100 cows with an interior volume of 50,000 cf and a ventilation rate of 5000 CFM or six air changes per hour.
- The breathing rate was assumed to be 1.0 cubic meter per hour (1 m^3/hr).

Calculation Methodology for Post Application Exposures

The post application inhalation exposures were calculated using a rate of purging formula taken from the ACGIH Manual of Industrial Ventilation, 22nd Edition (This formula is also in the EPA MCCEM). This formula accounts for the decrease in airborne concentrations that result from the mechanical ventilation of an interior space. This formula was used to calculate exposures at one minute intervals for 480 minutes (eight hours) following a metered release. The 480 one minute air concentrations were then averaged to yield an 8 hour average air concentration, which was multiplied by the breathing rate of 1.0 m^3/hr to yield the daily exposure. The exposure in mg/day was then divided by the body weight to yield a daily dose in mg/kg/day. The algorithms for these calculations are detailed in Table 5 of Appendix 4.

9.2.2 Post Application Exposure and Risk Estimates

The exposure and risk estimates for inhalation exposures in dairy barns are detailed in Table 5 of Appendix 4 and the MCCEM output is included in Appendix 6. The MOE for short term exposure is 1200, which exceeds the target MOE of 100 and is not of concern. The MOE for intermediate term exposure is 400, which does not exceed the target MOE of 1000 and is of concern. These MOEs are representative of a space that is ventilated at the rate of six air changes per hour and the MOEs would be lower in areas that receive less ventilation.

10.0 Data Needs and Label Requirements

10.1 Toxicology

- A developmental neurotoxicity study is required.

- A comparative thyroid study is required.

10.2 Residue Chemistry

- An ILV for the proposed single analyte regulatory method (as opposed multiresidue methods) is required for the determination of pyrethrin residues of concern in/on plant commodities.

- Storage stability data for representative commodities of oilseeds, nonoily grains, and root crops.

- Storage stability data for the processed commodities of representative oilseeds (cottonseed or peanut) and grains (preferably field corn or wheat). In addition, storage stability data on dried fruits (preferably raisins or prunes) to confirm whether residues of pyrethrins I decline on other dried processed fruits.

- Magnitude of Residue Studies to support uses of pyrethrins on foods stored in multi-walled paper or cloth bags.

- Magnitude of the residue studies reflecting preharvest uses on representative commodities of all crop groups and miscellaneous commodities which are being supported for reregistration.

- Magnitude of the residue studies reflecting postharvest uses for all crops (except potato and sweet potato) which are being supported for reregistration.

- Magnitude of Residue Studies to support the uses on tobacco.

- Processing studies on apple, barley, cacao bean, coconut, coffee, corn (field), cotton, fig, flax, oat, peanut, pineapple, plum, rice, rye, safflower, sorghum, soybean, sugarcane, sunflower, tea, and wheat.

- A confined rotational crop study.

10.3 Occupational and Residential Exposure

There are no occupational/residential exposure studies outstanding at this time.

References

Hurley et al (1998) Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. *Environ. Health Perspect*. 106(8): 437-445.

Soderlund, D. M. and D. C. Knipple. 1995. Actions of insecticides on sodium channels: multiple target sites and site-specific resistance. In: "Molecular Action of Insecticides on Ion Channels" (J. M. Clark, Ed.), American Chemical Society, Washington, DC, pp. 97-108.

Appendix 1. Master Label for Uses of Pyrethrins Supported in Reregistration by the Pyrethrins Joint Venture

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.

Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Agricultural				
Preharvest Application to Field, Orchard, and Greenhouse Crops				
Crop Group 1: Root and Tuber Vegetables [including Arracacha; Arrowroot; Artichoke, Chinese; Artichoke, Jerusalem; Beet, garden, Beet, sugar; Burdock, edible; Canna edible; Carrot; Cassava; Celeriac; Chayote; Chervil, turnip-rooted; Chicory; Chufa; Dandelion; Dasheen; Ginger; Ginseng; Horseradish; Leren; Parsley, turnip-rooted; Parsnip; Potato; Radish; Radish, Oriental; Rutabaga; Salsify; Salsify, black; Salsify, Spanish; Skirret; Sweet Potato; Tanier; Taro; Turmeric; Turnip; Yam bean; and Yam, true]				
Application to outdoor growing crops	0.050 lb/A	10	0 [1]	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 2: Leaves of Root and Tuber Vegetables [including Beet, garden; Beet, sugar; Burdock, edible; Carrot; Cassava; Chervil, turnip-rooted; Chicory; Dasheen; Parsnip; Radish; Radish, Oriental; Rutabaga; Salsify, black; Tanier; Taro; Turnip; and Yam, true]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 3: Bulb Vegetables [including Garlic; Garlic, great headed; Leek; Onion, dry bulb; Onion, green; Onion, potato; Onion, tree; Onion, welsh; and Shallot]				

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.

Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 4: Leafy Vegetables (Except Brassica Vegetables) [including Amaranth, leafy; Arugula; Cardoon; Celery; Celery, Chinese; Celtuce; Chervil; Chrysanthemum, edible-leaved; Chrysanthemum, garland; Corn salad; Cress, garden; Cress, upland; Dandelion; Dock; Endive; Fennel, Florence; Kale, sea; Lettuce, head; Lettuce, leaf; Orach; Parsley; Purslane, garden; Purslane, winter; Radicchio; Rhubarb; Spinach; Spinach, Chinese; Spinach, New Zealand; Spinach, vine; Swiss chard; and Tampala]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 5: Brassica (Cole) Leafy Vegetables [including Broccoli; Broccoli, Chinese; Broccoli raab; Brussels sprouts; Cabbage; Cabbage, Chinese, Bok choy; Cabbage, Chinese, mustard; Cabbage, Chinese, napa; Cauliflower; Collards; Kale; Kohlrabi; Mustard greens; Mustard spinach; and Rape greens]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.

Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 6: Legume Vegetables (Succulent or Dried) [including Bean (adzuki, broad, dry, kidney, lablab, lima, moth, mung, navy, pink, pinto, rice, runner, snap, tepary, urd, wax, yardlong); Catjang; Chickpea; Cowpea; Guar; Gum, edible; Jackbean; Lentil; Lupin, grain; Pea (blackeyed, crowder, dry, dwarf, edible-pod, English, field, garden, green, pigeon, snow, southern, succulent, sugar snap); Soybean; and Swordbean]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 7: Foliage of Legume Vegetables [including Bean (dry, lima, snap); cowpea; Lupin, grain; Pea (field and pigeon); Soybean]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 8: Fruiting Vegetables (Except Cucurbits) [including Chili; Eggplant; Groundcherry; Pepino; Pepper (bell, nonbell, nonbell sweet); Tomatillo; Tomato]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.

Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 9: Cucurbit Vegetables [including Balsam apple; Balsam pear; Cantaloupe; Chayote; Cucumber; Cucumber, Chinese; Gherkin, West Indian; Gourd, edible; Melon; Melon, citron; Muskmelon; Pumpkin; Squash; Squash, summer; Squash, winter; Watermelon; Waxgourd, Chinese]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 10: Citrus Fruits (Citrus spp., Fortunella spp.) [including Calamondin; Citron, citrus; Citrus; Citrus hybrids; Grapefruit; Kumquat; Lemon; Lime; Mandarin, satsuma; Orange, sour; Orange, sweet; Pummelo; Tangelo; Tangerine]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 11: Pome Fruits [including Apple; Crabapple; Loquat; Mayhaw; Pear; Oriental Pear; and Quince]				

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Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 12: Stone Fruits [including Apricot; Cherry, sweet; Cherry, tart; Nectarine; Peach; Plum; Plum, chickasaw; Plum, damson; Plum, Japanese; and Plum, prune]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 13: Berries [including Blackberry, Blueberry; Currant; Elderberry; Gooseberry; Huckleberry; Loganberry; and Raspberry (black and red)]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 14: Tree Nuts [including Almond; Beech nut; Brazil nut; Butternut; Cashew; Chestnut; Chinquapin; Filbert; Hickory nut; Macadamia nut; Pecan; Pistachio; Walnut, black; and Walnut, English]				

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Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 15: Cereal Grains [including Barley; Buckwheat; Corn (field, pod, pop, and sweet); Millet; Millet, pearl; Millet, proso; Oat; Rice; Rice, wild; Rye; Sorghum, grain; Teosinte; Triticale; Wheat; Wheat, vavilovi; Wheat, wild einkorn; and Wheat, wild emmer]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 16: Forage, Fodder, and Straw of Cereal Grains [including Barley; Corn (field, pod, pop, and sweet); Millet; Millet, pearl; Millet, proso; Oat; Rice; Rice, wild; Rye; Sorghum (forage and grain); Teosinte; Triticale; Wheat; Wheat, vavilovi; Wheat, wild einkorn; and Wheat, wild emmer]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.				
Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Crop Group 17: Grass Forage, Fodder, and Hay [including Alkali sacaton; Alkaligrass; Arizona cottontop; Bahiagrass; Beachgrass; Bentgrass; Bentgrass, spike; Bermudagrass; Blowoutgrass; Bluegrass; Bluegrass, silky; Bluestem australian; Bluestem, big; Bluestem, Caucasian; Bluestem, Diaz; Bluestem, little; Bluestem, sand; Bluestem, silver; Bluestem, south African; Bluestem, yellow; Bristlegrass, plains; Bromegrass; Broomsedge; Buffalograss; Buffelgrass; Canarygrass, annual; Canarygrass, reed; Caribgrass; Carpetgrass; Carpetgrass, broadleaf; Centipedegrass; Cordgrass, marsh hay; Crabgrass; Curly mesquite; Dallisgrass; Dropseed, pine; Dropseed, sand; Dropseed, tall; Fescue; Fingergrass, feather; Foxtail, creeping; Foxtail, meadow; Gamagrass, eastern; Grass; Grass, galleta; Grass, gama; Grass, muhly; Grass, pasture; Grass, St. Augustine; Grass, wildrye; Grass, zoysia; Hairgrass tufted; Hardinggrass; Indiangrass; Junegrass; Limpograss; Lovegrass; Maidencane; Mannagrass; Millet, foxtail; Millet, Japanese; Molassesgrass; Napiergrass; Needlegrass; Oat, sand; Oat, slender; Oat, wild; Oatgrass; Oatgrass, tall; Oniongrass; Orchardgrass; Pangolagrass; Panicgrass; Paspalum; Polargrass; Quackgrass; Redtop; Reedgrass; Rhodesgrass; Rhodesgrass, multiflower false; Ricegrass, indian; Ryegrass, Italian; Ryegrass, perennial; Sandreed, prairie; Sixweeks threeawn; Sloughgrass; Smilograss; Sorghum, forage; Spikeoat; Sprangletop, green; Squirreltail; Sudangrass; Sunolgrass; Tanglehead; Timothy; Timothy, alpine; Trisetum, spike; Vaseygrass; Veldtgrass, perennial; Velvetgrass; Wheatgrass; Wheatgrass, bluebunch; Wheatgrass, crested; Wheatgrass, fairway; Wheatgrass, intermediate; Wheatgrass, pubescent; Wheatgrass, Siberian; Wheatgrass, slender; Wheatgrass, streambank; Wheatgrass, tall; Wheatgrass, thickspike; Wheatgrass, western; and Windmillgrass, hooded]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 18: Nongrass Animal Feeds (Forage, Hay, Straw, and Hay) [including Alfalfa; Arrowleaf balsamroot; Burclover; Clover; Clover, alsike; Clover, alyce; Clover, arrowleaf; Clover, ball; Clover, berseem; Clover, bigflower; Clover, crimson; Clover, hop; Clover, lappa; Clover, persian; Clover, red; Clover, rose; Clover, seaside; Clover, strawberry; Clover, striate; Clover, sub; Clover, sweet; Clover, true; Clover, white; Clover, whitetip; Crownvetch; Kudzu; Lespedeza; Lupine; Lupine, forage; Lupine, sweet; Mustard; Sainfoin; Trefoil; Velvetbean; Vetch; and Vetch, milk]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.				
Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Crop Group 19: Herbs and Spices [Including Allspice; Angelica; Anise; Anise hyssop (mint); Anise, star; Annatto; Balm; Basil; Borage; Burnet; Camomile; Caper; Caraway; Caraway, black; Cardamom; Cardamon amomum; Cassia; Catnip; Celery, seed; Chervil; Chive; Chive, Chinese; Cinnamon; Clary; Clove; Coriander; Costmary; Cilantro (False coriander); Cumin; Curry; Dill; Dillweed; Fennel; Fennel, florence; Fenugreek; Grains of paradise; Horehound; Juniper berry; Lavender; Lemongrass; Lovage; Mace; Marigold, pot; Marjoram (Oregano); Mustard; Nasturtium; Nutmeg; Parsley; Pennyroyal; Pepper, black; Pepper, white; Poppy; Rosemary; Rue; Saffron; Sage; Savory, summer; Savory, winter; Sweet bay; Tansy; Tarragon; Thyme; Vanilla; Wintergreen; Woodruff; and Wormwood]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Miscellaneous Fruit, Subtropical/Tropical [including Acerola; Atemoya, Avocado; Banana; Carob bean; Cherimoya; Date; Durian; Feijoa; Fig; Guava; Kiwifruit; Lychee; Mango; Papaya; Passionfruit; Persimmon; Pineapple; Pomegranate; Rambutan; and Starfruit (Carambola)]				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.				
Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Vegetable, Oriental [including Artichoke, Chinese; Balsam pear (bitter melon); Bean, mung; Bean, yardlong; Broccoli, Chinese; Cabbage, Chinese, bok choy; Cabbage, Chinese, mustard; Cabbage, Chinese, napa; Coriander (Cilantro); Dasheen; Ginger; Ginseng; Melon, citron; Radish, oriental; Spinach, Chinese; and Waxgourd, Chinese] Note: Individual crops listed above belong to various crop groups previously listed.				
Application to outdoor growing crops	0.050 lb/A	10	0	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Miscellaneous Commodities: Asparagus; Coffee; Cotton; Cranberry; Grape; Jojoba; Okra; Safflower; Strawberry; Sugarcane; Sunflower; and Tea				
Application to outdoor growing crops	0.050 lb/A	10	14 (cotton seed) 0 (all other crops)	Do not reapply within 3 days except under extreme pest pressure. Aerial applications: do not apply less than 2 gal. of diluted solution/A to field crops or less than 10 gal. of diluted solution/A to orchard crops.
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Postharvest Application to Vegetables, Fruit, and Nuts				

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.				
Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Food/Feed Storage Areas -Full: Postharvest Application to Apple, Blackberry, Blueberry, Boysenberry, Cherry, Crabapple, Currant, Dewberry, Fig, Gooseberry, Grape, Guava, Loganberry, Mango, Muskmelon, Orange, Peach, Pear, Pea, Pineapple, Plum, Potato, Raspberry, or Tomato in baskets, on trucks, in processing plants, in hampers, or in temporary storage areas (including raw stock stacked in yards) Copra (processed) in baskets, on trucks, in processing plants, in hampers, or in temporary storage areas (including raw stock stacked in the yard) Postharvest application to Almonds, Peanuts, and Walnuts (English/black) in bulk or bags				
Surface - General	0.01 lb/1,000 sq. ft	Not specified (NS)	NA [2]	Do not apply more than 1 time per day. Do not reapply within 7 days.
Surface - Direct application to fruits or tomatoes in baskets or hampers	1.6×10^{-7} lb/ lb of fruit or vegetable (0.16 ppm)	NS	NA	
Space - Bagged products and sweet potatoes	0.00027 lb/1,000 cu. ft	NS	NA	Do not apply more than 10 times to sweet potatoes.
Space - Fruits, vegetables, and copra	0.0001 lb/1,000 cu. ft	NS	NA	.
Postharvest Application to Stored Grain and Seed				
Direct application to bulk grain and seed	0.10 lb/1,000 bushels grain	NS	NA	See below for rate in ounces pyrethrins per 100 lb grain or seed.
- Barley	0.0033 oz/cwt			
- Beans	0.0027 oz/cwt			
- Beans, lima	0.0029 oz/cwt			
- Birdseed	0.0032 oz/cwt			
- Buckwheat	0.0033 oz/cwt			
- Cocoa beans	0.0037 oz/cwt			
- Corn	0.0029 oz/cwt			
- Cottonseed	0.0057 oz/cwt			
- Flax	0.0029 oz/cwt			
- Grain sorghum	0.0029 oz/cwt			
- Oats	0.0050 oz/cwt			

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.				
Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
- Pea (field)	0.0027 oz/cwt			
- Rice	0.0036 oz/cwt			
- Rye	0.0029 oz/cwt			
- Wheat: club, common, durham	0.0027 oz/cwt			
- Wheat: emmer, spelt	0.0040 oz/cwt			
Direct Application to Animals				
Cattle (Beef/Range/Feeder and Dairy); Hogs/Pig/Swine; Goats (Meat and Dairy); Kids; Sheep; Lamb; Rabbits; Game Animals (including Beefalo, Buffalo, Deer, Exotics such as European red deer, Llamas, Moose, Elk); Livestock (including Donkeys, Horses, Ponies, Mules); and Poultry				
Direct application to livestock - Dust	1.0%	NA	NA	Do not apply more than 1 time per day. Do not reapply within 1 day. Do not apply microencapsulated products to lactating or food animals.
Direct application to livestock - Solution	0.035 lb/gal	NA	NA	
Direct application to livestock - Towelette	0.2%	NA	NA	
Direct application to livestock - Spot-on or Pour-on	1.0%	NA	NA	
Direct application to poultry - Solution	0.01%	NA	NA	
Direct application to poultry - Dust	0.9%	NA	NA	
Application to Agricultural Premises and Equipment - Indoor, Animals Present				

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.

Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Greenhouses (empty) Agricultural/Farm Structures/Buildings and Equipment: Animal houses; Calf hutches; Calving pens and parlors; Dairies; Dairy farms; Goat houses; Livestock housing structures; Loafing sheds; Poultry houses; Poultry operations; Rabbit houses; Rabbit hutches; Stables; Swine houses. Barns/Barnyards/Auction Barns: Barns (Beef, Cattle, Dairy, Horse, Hog, and Livestock) Dairy Farm Milking Stalls/Parlors: Milk houses; Milking parlors Dairy Farm Milk Storage Rooms/Houses/Sheds: Milk rooms Dairy Farm Milk Handling Facilities/Equipment: Milk handling equipment Dairy Farm Milking Equipment: Milking equipment Seed Houses/Stores/Storage Areas/Warehouses: Stored seed warehouses; Seed warehouse bins; Granaries; Seed storage sites; Seed bins; Stable bins; Stored seed warehouses Silos and Mushroom houses				
Surface - General	0.06 lb/ 1,000 sq. ft	NA	NA	Remove or cover exposed food and water before application. When used in dairy barns or facilities: close milk bulk tank lids to prevent contamination from spray and from dead or falling insects. Remove or cover milking utensils before application. Wash teats of animals before milking. Do not apply more than 1 time per day. Do not reapply within 1 day.
Surface - Crack and crevice or spot	0.22 lb/ 1,000 sq. ft	NA	NA	
Space - General	0.0008 lb/ 1,000 cu. ft	NA	NA	
Space - Metered release	0.005 lb/ 1,000 cu. ft/ day	NA	NA	Do not place metering device directly over or within 8 feet of exposed feeds, dishes, milking utensils, and feed handling or preparation areas.
Domestic Home and Garden				
Garden and Greenhouse Crops (See Agricultural; Preharvest Application to Field, Orchard, and Greenhouse Crops)				
Application to outdoor growing crops	0.050 lb/A	10	0 [1]	Do not reapply within 3 days except under extreme pest pressure. In case of extreme pest pressure do not reapply within 24 hours.

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.				
Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Application to hydroponically grown crops	0.10 ppm in water	10	0	
Surface application to greenhouse grown crop	0.0012 lb/1,000 sq. ft or 0.050 lb/A	10	0	
Space application to greenhouse grown crop	0.00014 lb/1,000 cu. ft	10	0	
Commercial/Industrial/Institutional Establishments - Indoor				
Surface - General	0.056 lb/ 1,000 sq. ft	NA	NA	Remove or cover exposed food and water before application. Remove or cover dishes, utensils, food processing equipment, and food preparation surfaces, or wash them thoroughly before use. Do not apply more than 1 time per day. Do not reapply within 1 day.
Surface - Crack and crevice or spot	0.22 lb/ 1,000 sq. ft	NA	NA	
Surface - Crack and crevice or spot [in the presence of food or feed in multi-wall or cloth bags]	0.22 lb/ 1,000 sq. ft	NA	NA	
Space - General	0.00033 lb/ 1,000 cu. ft	NA	NA	
Space - Metered release	0.005 lb/ 1,000 cu. ft/ day	NA	NA	Do not place metering device directly over or within 8 feet of exposed foods, dishes, utensils, food processing equipment, and food handling or preparation areas.
Eating Establishments -Indoor				
Eating Establishments (Food Contact) [Equipment/Utensils; Food Handling Areas; Food Serving Areas]: Cafeterias; Restaurants; Mess halls				

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.

Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Surface - General	0.056 lb/ 1,000 sq. ft	NA	NA	Remove or cover exposed food and water before application. Remove or cover dishes, utensils, food processing equipment, and food preparation surfaces, or wash them thoroughly before use. Do not apply more than 1 time per day. Do not reapply within 1 day. Except in Federally inspected meat and poultry plants, food processing operations may continue when the product is applied as a general surface spray with care and in accordance with the directions and precautions on the label, at a maximum rate of 0.011 lb pyrethrins per 1,000 sq. ft.
Surface - Crack and crevice or spot	0.22 lb/ 1,000 sq. ft	NA	NA	Remove or cover exposed food and water before application. Remove or cover dishes, utensils, food processing equipment, and food preparation surfaces, or wash them thoroughly before use. Do not apply more than 1 time per day. Do not reapply within 1 day. Except in Federally inspected meat and poultry plants, food processing operations may continue when the product is applied as a crack and crevice treatment with care and in accordance with the directions and precautions on the label, at a maximum rate of 0.22 lb pyrethrins per 1,000 sq. ft.
Surface - Crack and crevice or spot [in the presence of food or feed in multi-wall or cloth bags]	0.22 lb/ 1,000 sq. ft	NA	NA	
Space - General	0.00033 lb/ 1,000 cu. ft	NA	NA	Do not make space spray applications when facility is in operation. During space spray operations, cover or remove food. During space spray operations, cover food processing surfaces or clean after treatment with a suitable detergent and rinse with potable water before use. Do not apply more than 1 time per day. Do not reapply within 1 day.

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.

Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Space - Metered release	0.005 lb/ 1,000 cu. ft/ day	NA	NA	Do not place metering device directly over or within 8 feet of exposed foods, dishes, utensils, food processing equipment, and food handling or preparation areas.
Food Handling and Processing Establishments - Indoor				
Food Handling and Processing Plant Premises and Equipment (Food Contact): Bakeries; Bottling plants; Beverage plants; Canneries; Conveying Equipment; Dried fruit processing plants; Feed areas of commercial buildings; Food areas of commercial buildings; Food processing plants; Fruit packing sheds; Mushroom processing plants; Peanut processing plants; Processing areas of dried food products; Tobacco processing plants; Wineries Meat Processing Plant Premises and Equipment (Food Contact): Conveying equipment; Edible product areas of official establishments operating under the meat; poultry; shell egg grading and egg products inspection operations; Meat packing plants; Poultry processing plants; Rabbit processing plants; USDA inspected meat and poultry plants Dairies/Cheese Processing Plant Premises and Equipment (Food Contact): Dairies Egg Processing Plants Tobacco Processing Plants Feed Mills/Feed Processing Plants: Conveying equipment; Feed processing and handling sites; Flour mills; Grain mills; Mills; Milling operations; Roll housing and hoppers; Stored grain mills; Rice mills Feed/Food Treatment - Storage/Processing/Handling Equipment: Conveying equipment; Grain handling equipment				

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.

Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Surface - General	0.056 lb/ 1,000 sq. ft	NA	NA	Remove or cover exposed food and water before application. Remove or cover dishes, utensils, food processing equipment, and food preparation surfaces, or wash them thoroughly before use. Do not apply more than 1 time per day. Do not reapply within 1 day. Except in Federally inspected meat and poultry plants, food processing operations may continue when the product is applied as a general surface spray with care and in accordance with the directions and precautions on the label, at a maximum rate of 0.011 lb pyrethrins per 1,000 sq. ft.
Surface - Crack and crevice or spot	0.22 lb/ 1,000 sq. ft	NA	NA	Remove or cover exposed food and water before application. Remove or cover dishes, utensils, food processing equipment, and food preparation surfaces, or wash them thoroughly before use. Do not apply more than 1 time per day. Do not reapply within 1 day. Except in Federally inspected meat and poultry plants, food processing operations may continue when the product is applied as a crack and crevice treatment with care and in accordance with the directions and precautions on the label, at a maximum rate of 0.22 lb pyrethrins per 1,000 sq. ft.
Surface - Crack and crevice or spot [in the presence of food or feed in multi-wall or cloth bags]	0.22 lb/ 1,000 sq. ft	NA	NA	
Space - General	0.00033 lb/ 1,000 cu. ft	NA	NA	Do not make space spray applications when facility is in operation. During space spray operations, cover or remove food. During space spray operations, cover food processing surfaces or clean after treatment with a suitable detergent and rinse with potable water before use. Do not apply more than 1 time per day. Do not reapply within 1 day.

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.				
Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Space - Metered release	0.005 lb/ 1,000 cu. ft/ day	NA	NA	Do not place metering device directly over or within 3, 10, or 17 feet of exposed foods, dishes, utensils, food processing equipment, and food handling or preparation areas.
Retail and Storage - Indoor				
Commercial Storage/Warehouses Premises: Brandy storage warehouses; Dried fruit warehouses; Elevators; Food storage areas; Freight containers; Peanut storage warehouses; Spirit storage; Storage areas; Storage areas of dried food products; Stored seed warehouses; Warehouses; Wine storage warehouses; Tobacco warehouses Food Stores/Markets/Supermarkets Premises and Equipment: Food marketing - storage- distribution; Grocery and convenience stores; Stores; Supermarkets; Conveying equipment; Freight containers; Stored product areas Food/Feed Storage Areas-Full: Stored product areas				
Surface - General	0.056 lb/ 1,000 sq. ft	NA	NA	Remove or cover exposed food and water before application. Remove or cover dishes, utensils, food processing equipment, and food preparation surfaces, or wash them thoroughly before use. Do not apply more than 1 time per day. Do not reapply within 1 day. Except in Federally inspected meat and poultry plants, food processing operations may continue when the product is applied as a general surface spray with care and in accordance with the directions and precautions on the label, at a maximum rate of 0.011 lb pyrethrins per 1,000 sq. ft.

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.				
Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Surface - Crack and crevice or spot	0.22 lb/ 1,000 sq. ft	NA	NA	Remove or cover exposed food and water before application. Remove or cover dishes, utensils, food processing equipment, and food preparation surfaces, or wash them thoroughly before use. Do not apply more than 1 time per day. Do not reapply within 1 day. Except in Federally inspected meat and poultry plants, food processing operations may continue when the product is applied as a crack and crevice treatment with care and in accordance with the directions and precautions on the label, at a maximum rate of 0.22 lb pyrethrins per 1,000 sq. ft.
Surface - Crack and crevice or spot [in the presence of food or feed in multi-wall or cloth bags]	0.22 lb/ 1,000 sq. ft	NA	NA	
Space - General	0.00033 lb/ 1,000 cu. ft	NA	NA	Do not make space spray applications when facility is in operation. During space spray operations, cover or remove food. During space spray operations, cover food processing surfaces or clean after treatment with a suitable detergent and rinse with potable water before use. Do not apply more than 1 time per day. Do not reapply within 1 day.
Space - Metered release	0.005 lb/ 1,000 cu. ft/ day	NA	NA	Do not place metering device directly over or within 8 feet of exposed foods, dishes, utensils, food processing equipment, and food handling or preparation areas.
Transportation				
Commercial Transportation Facilities and Shipping Containers - Feed/Food - Empty: Grain transportation containers (truck beds; planes; box cars; cargo ship holds)				

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.

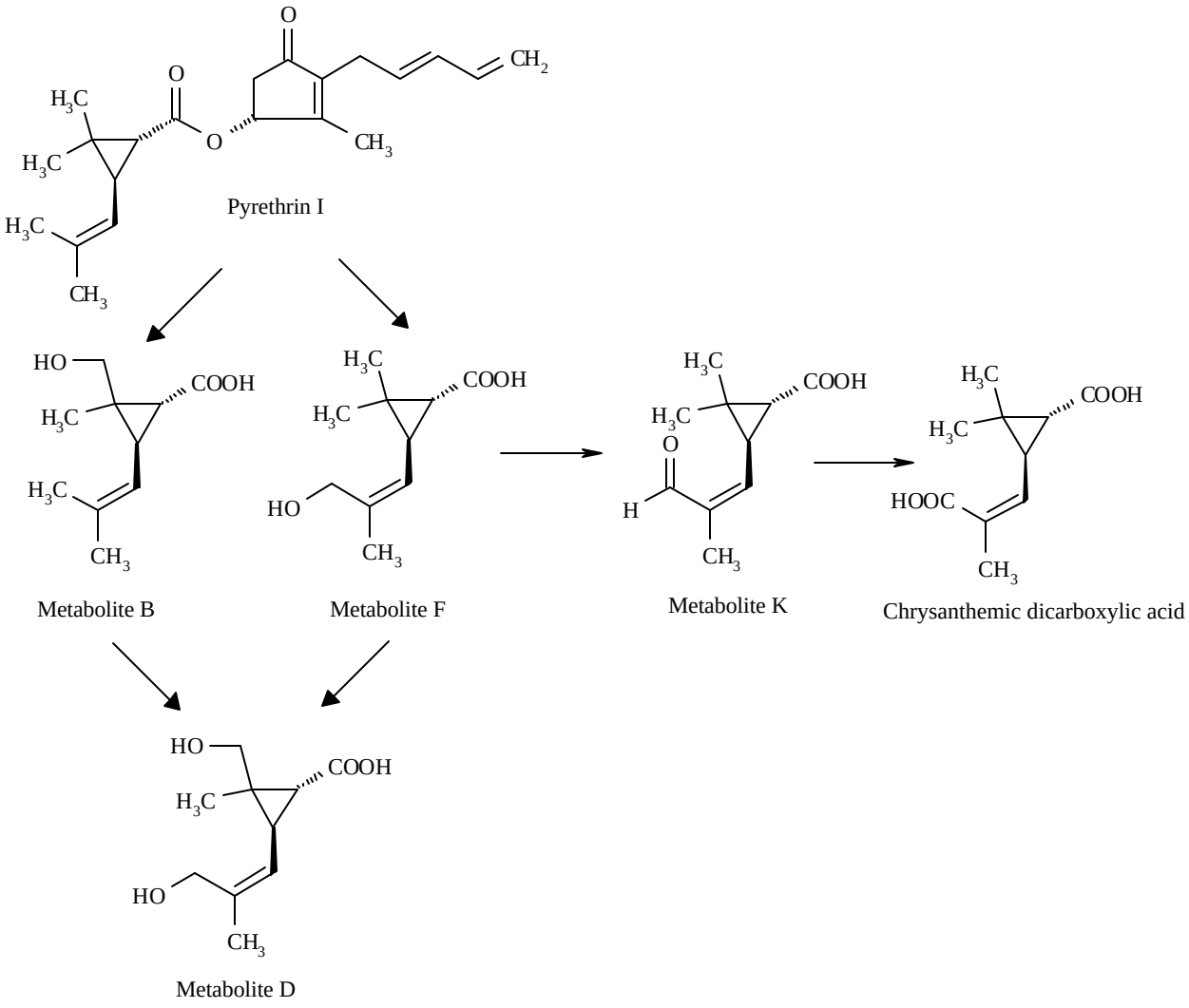
Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Surface - General	0.056 lb/ 1,000 sq. ft	NA	NA	Remove or cover exposed food and water before application. Remove or cover dishes, utensils, food processing equipment, and food preparation surfaces, or wash them thoroughly before use. Do not apply more than 1 time per day. Do not reapply within 1 day. Except in Federally inspected meat and poultry plants, food processing operations may continue when the product is applied as a general surface spray with care and in accordance with the directions and precautions on the label, at a maximum rate of 0.011 lb pyrethrins per 1,000 sq. ft.
Surface - Crack and crevice or spot	0.22 lb/ 1,000 sq. ft	NA	NA	Remove or cover exposed food and water before application. Remove or cover dishes, utensils, food processing equipment, and food preparation surfaces, or wash them thoroughly before use. Do not apply more than 1 time per day. Do not reapply within 1 day. Except in Federally inspected meat and poultry plants, food processing operations may continue when the product is applied as a crack and crevice treatment with care and in accordance with the directions and precautions on the label, at a maximum rate of 0.22 lb pyrethrins per 1,000 sq. ft.
Surface - Crack and crevice or spot [in the presence of food or feed in multi-wall or cloth bags]	0.22 lb/ 1,000 sq. ft	NA	NA	
Space - General	0.00033 lb/ 1,000 cu. ft	NA	NA	Do not make space spray applications when facility is in operation. During space spray operations, cover or remove food. During space spray operations, cover food processing surfaces or clean after treatment with a suitable detergent and rinse with potable water before use. Do not apply more than 1 time per day. Do not reapply within 1 day.

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.

Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Space - Metered release	0.005 lb/ 1,000 cu. ft/ day	NA	NA	Do not place metering device directly over or within 8 feet of exposed foods, dishes, utensils, food processing equipment, and food handling or preparation areas.
Outdoor Eating Establishments				
Outdoor Eating Establishments and Equipment and Utensils: Drive-in restaurants				
Surface - General	0.0075 lb/ 1,000 sq. ft	NA	NA	Do not apply more than 1 time per day. Do not reapply within 1 day. Remove or cover exposed food and drinking water before application.
Surface - Crack and crevice or spot	0.22 lb/ 1,000 sq. ft	NA	NA	
Impregnated mat	1.0% pyrethrins	NA	NA	
Combustible coil	1.0% pyrethrins	NA	NA	
Food Stored in Bags				
Feed/Food Commodities (Bagged/Temporary Storage): Surfaces of bags of stored food products; Stored food in multi-wall paper or cloth bags				
Surface - General	0.010 lb/ 1,000 sq. ft	NA	NA	Do not apply more than 1 time per day. Do not reapply within 1 day.
Surface - Crack and crevice	0.22 lb/ 1,000 sq. ft	NA	NA	
Bag/container treatment	in accordance with 40 CFR 180.128	NA	NA	
Space	0.00033 lb/ 1,000 cu. ft	NA	NA	
Mosquito Abatement - Adulticide				
Agricultural Crops/Soils: Groups of Agricultural Crops Which Cross Established Crop Groupings (Croplands)				
Thermal fog	0.0025 lb/A	NA	NA	
Non-thermal fog ULV	0.008 lb/A	NA	NA	For control of *Aedes Taeirorhynchus* and other difficult species
Agricultural Uncultivated Areas: Fallow lands, Pastures, and Rangelands				
Thermal fog	0.0025 lb/A	NA	NA	
Non-thermal fog ULV	0.008 lb/A	NA	NA	For control of *Aedes Taeirorhynchus* and other difficult species
Intermittently Flooded Areas/Water				

Table A1-1. Food/Feed Uses of Pyrethrins Which Are Being Supported by the Pyrethrin Joint Venture for Reregistration.				
Site Application Type	Max. Single Application Rate, ai	Max. No. of Applications Per Season	PHI (Days)	Use Directions and Limitations
Thermal fog Non-thermal fog ULV	0.0025 lb/A	NA	NA	
	0.008 lb/A	NA	NA	For control of *Aedes Taeirorhynchus* and other difficult species
Irrigation Systems				
Thermal fog Non-thermal fog ULV	0.0025 lb/A	NA	NA	
	0.008 lb/A	NA	NA	For control of *Aedes Taeirorhynchus* and other difficult species

Appendix 2. Proposed Metabolic Pathway of pyrethrin 1 after application to plant surfaces.


Pyrethrin I
Metabolite B
Metabolite F
Metabolite K
Chrysanthemic dicarboxylic acid
Metabolite D

Appendix 3 Tabular Summary of Plant and Livestock Metabolites

Table A3.1. Tabular Summary of Metabolites and Degradates

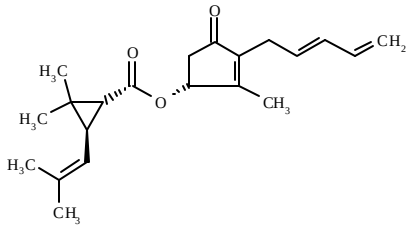
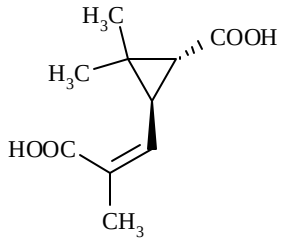
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM)[1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
Parent	Lettuce	39 (Day 0)	2 (Day 10)	
	Potato	N/A	<1 (Tubers); 2 (Leaves)	
	Tomato	13 (Fruit)	1 (Leaves)	
	Ruminant Oral	43 (Milk), 52 (Fat), 10 (Liver), 52 (Muscle)	2 (Kidney)	
	Ruminant Dermal	69 (Milk), 17 (Fat), 11 (Liver)	ND (Kidney)	
	Poultry Oral	39 (Egg Yolk); 15 (Egg White); 92 (Fat); 21 (Thigh Muscle)	1 (Liver); ND (Breast Muscle)	
	Poultry Dermal	81 (Fat); 77 (Egg Yolk); 58 (Untreated Skin); 39 (Thigh Muscle)	5 (Liver)	
E-CDCA (E)-trans-chrysanthemic dicarboxylic acid	Lettuce	N/A	7 (Day 0) 5 (Day 10)	
	Potato	ND	ND	
	Tomato	ND	ND	
	Ruminant Oral	N/A	2 (Kidney); 3 (Liver); ND (Muscle, Milk, Fat)	
	Ruminant Dermal	N/A	7 (Kidney); 3 (Liver); ND (Milk, Fat)	
	Poultry Oral	12 (Breast Muscle); 10 (Liver)	8 (Thigh Muscle); 2 (Egg White); ND (Egg Yolk, Fat)	

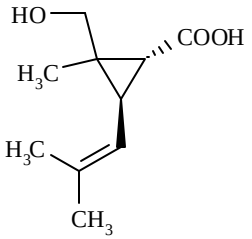
Table A3.1. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM)[1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
	Poultry Dermal	N/A	3 (Liver); ND (Thigh Muscle, Egg White, Egg Yolk, Fat)	
Lettuce Metabolite A Potato Metabolite B Tomato Metabolite A 5-hydroxy-1(1R trans) chrysanthemic acid or 2-hydroxymethyl-2-methyl-3-(2-methyl-1-propenyl)-cyclopropanecarboxylic acid	Lettuce	21 (Day 10)	4 (Day 0)	
	Potato	N/A	4 (Tubers) ND (Leaves)	
	Tomato	22 (Fruit)	6 (Leaves)	
	Ruminant	ND	ND	
	Poultry	ND	ND	

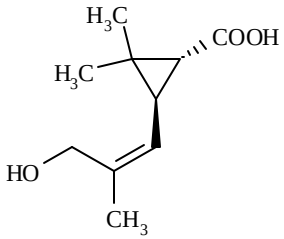
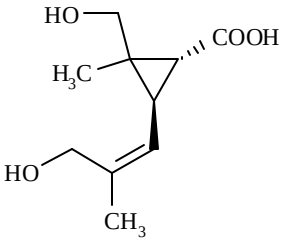
Table A3.1. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM)[1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
Potato Metabolite F Tomato Metabolite H 10-hydroxy (1R trans) chrysanthemic acid or 2,2-dimethyl-3-(2-hydroxymethyl-1-propenyl)-cyclopropanecarboxylic acid	Lettuce	ND	ND	
	Potato	N/A	3 (Tubers) <1 (Leaves)	
	Tomato	N/A	ND (Fruit) 2 (Leaves)	
	Ruminant	ND	ND	
	Poultry	ND	ND	
Lettuce Metabolite B Potato Metabolite D Tomato Metabolite B 5,10-dihydroxy-(1R trans) chrysanthemic acid or 2-hydroxymethyl-2-methyl-3-(2-hydroxymethyl-1-propenyl)-cyclopropanecarboxylic acid	Lettuce	N/A	3 (Day 0) 6 (Day 10)	
	Potato	34 (Tubers)	<1 (Leaves)	
	Tomato	14 (Fruit)	2 (Leaves)	
	Ruminant	ND	ND	
	Poultry	ND	ND	

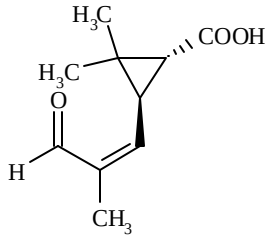
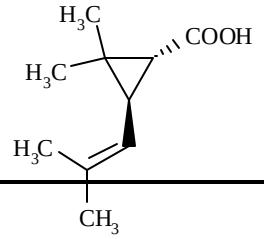
Table A3.1. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM)[1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
Potato Metabolite K 10-oxo-(1R trans) chrysanthemic acid or 2,2-dimethyl-3-(2-oxo-1-propenyl)-cyclopropanecarboxylic acid	Lettuce	ND	ND	
	Potato	ND	ND (Tubers) 2 (Leaves)	
	Tomato	ND	ND	
	Ruminant	ND	ND	
	Poultry	ND	ND	
Animal Metabolite B[c] glucoronic acid ester of (1R trans) chrysanthemic acid: Chrysanthemic acid glucoronyl ester	All Primary Crops	ND	ND	
	Ruminant Oral	46 (Kidney)	7 (Liver); ND (Muscle, Fat, Milk)	
	Ruminant Dermal	15 (Kidney)	ND (Liver, Fat, Milk)	
	Poultry Oral	ND (Kidney, Fat, Milk)	7 (Liver); 3 (Egg White); 3 (Breast Muscle); ND (Egg Yolk, Fat, Thigh Muscle)	
	Poultry Dermal	N/A	1 (Liver); ND(Egg Yolk, Fat, Thigh Muscle, Untreated Skin)	
Chr Ac trans-chrysanthemic acid	All Primary Crops	ND	ND	
	Ruminant Oral	ND (Kidney, Fat, Milk)	7 (Liver); 5 (Kidney); 4 (Muscle); ND (Fat, Milk)	
	Ruminant Dermal	12 (Liver)	ND (Kidney, Fat, Milk)	

Table A3.1. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM)[1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
	Poultry Oral	30 (Egg White); 21 (Liver); 17 (Thigh Muscle); 13 (Breast Muscle)	2 (Egg Yolk); 1 (Fat)	
	Poultry Dermal	38 (Liver); 11 (Thigh Muscle)	;ND(Egg Yolk, Fat, Untreated Skin)	
Animal Metabolite C Cyclopropanecarboxylic acid, 2,2-dimethyl-3-(2-carboxy-1-propenyl)-, 2-methyl-4-oxo-3-(4,5-dihydroxy-2-pentenenyl)-2-cyclopenten-1-yl-ester	All Primary Crops	ND	ND	
	Ruminant Oral	11 (Kidney)	6 (Liver); ND (Muscle, Fat, Milk)	
	Ruminant Dermal	16 (Kidney)	ND (Liver, Fat, Milk)	
	Poultry Oral	N/A	6 (Liver); 5 (Breast Muscle); 3 (Egg White, Thigh Muscle); ND (Egg Yolk; Fat)	
	Poultry Dermal	N/A	5 (Liver); ND(Egg Yolk, Fat, Thigh Muscle, Untreated Skin)	
Animal Metabolite E cyclopropanecarboxylic acid, 2,2-dimethyl-3-(2-carboxyl-1-propenyl)-, 2-methyl-4-oxo-3-(2,4-pentadienyl)-2-cyclopenten-1-yl-ester	All Primary Crops	ND	ND	
	Ruminant Oral	N/A	2 (Fat); 1 (Kidney); 6 (Liver); ND (Milk)	
	Ruminant Dermal	N/A	1 (Fat); ND (Kidney, Liver, Milk)	
	Poultry Oral	13 (Egg White, Liver)	3 (Thigh & Breast Muscle); 2 (Egg Yolk, Fat)	
	Poultry Dermal	14 (Liver)	3 (Thigh Muscle); ND (Egg Yolk, Fat, Untreated Skin)	

Table A3.1. Tabular Summary of Metabolites and Degradates				
Chemical Name (other names in parenthesis)	Commodity	Percent TRR (PPM)[1]		Structure
		Matrices - Major Residue (>10%TRR)	Matrices - Minor Residue (<10%TRR)	
Animal Metabolite F cyclopropanecarboxylic acid, 2,2-dimethyl-3-(2-methyl-1-propenyl)-, 2-methyl-4-hydroxy-3-(2,4-pentadienyl)-2-cyclopenten-1-yl-ester	All Primary Crops	ND	ND	
	Ruminant Oral	10 (Liver)	7 (Fat); 5 (Muscle); ND (Kidney, Milk)	
	Ruminant Dermal	12 (Liver)	5 (Fat); ND (Kidney, Milk)	
	Poultry Oral	N/A	4 (Fat); 2 (Egg White, Breast Muscle); ND (Egg Yolk, Liver, Thigh Muscle)	
	Poultry Dermal	NR	NR	
Tomato: 43554302, 43628402, and 45900802; 5 x 0.5 lb ai/A; 5x max rate; 5 day PHI Potato: 43554301, 43628401, and 45900802; 5 x 0.5 lb ai/A; 5x max rate; 5 day PHI. Lettuce: 43554303, 43668001, and 45900802; 5 x 0.5 lb ai/A; 5x max rate; 0 & 10 day PHIs. Goats (43628301, 43837601, and 45900802) Oral; 12345678; 179 ppm; 44X MTDB (also 7.9 ppm, 2x); 5 days; 4-6 hour PSI. Goat Dermal:5 day; 2% solution; oil and water formulations Poultry Oral: 475 ppm; 47,500x (also 7.66 ppm, 766x) Poultry Dermal: 5 day; 1% solution; oil and water formulations. Rotational Crops: none submitted				

Appendix 4. Tables Describing Residential and Occupational Exposure and Risk for Pyrethrins

Table 1: Pyrethrin Inhalation Margins of Exposure (MOEs) for Agricultural Handlers							
Exposure Scenario	Inhalation Unit Exposure (μg/lb ai)	Crop	Application Rate (lb ai per acre)	Area Treated (acres/day)	Inhalation Dose (mg/kg/day)	Short Term MOE	Intermediate/ Long Term MOE
Mixer/Loader							
Mix/load liquids for aerial application or chemigation	1.2	Field Crops	0.05	350	0.003	26000	8500
Mix/load liquids for aerial application	1.2	High Acre Crops	0.05	1200	0.001	7500	2500
Mix/load liquids for ground-boom application	1.2	Field Crops	0.05	80	0.000069	110000	37000
Mix/load liquids for airblast application	1.2	Field Crops	0.05	40	0.000035	220000	75000
Mix/load WP for aerial application or chemigation	43	Field Crops	0.05	350	0.011	710	240
Mix/load WP for aerial application	43	High Acre Crops	0.05	1200	0.037	210	69
Mix/load WP for ground-boom application	43	Field Crops	0.05	80	0.0025	3100	1000

Table 1: Pyrethrin Inhalation Margins of Exposure (MOEs) for Agricultural Handlers							
Exposure Scenario	Inhalation Unit Exposure (µg/lb ai)	Crop	Application Rate (lb ai per acre)	Area Treated (acres/day)	Inhalation Dose (mg/kg/day)	Short Term MOE	Intermediate/ Long Term MOE
Mix/load WP for airblast application	43	Field Crops	0.05	40	0.0012	6200	2100
Applicator							
Aerial application	0.068	Field Crops	0.05	1200	0.000058	130000	44000
Ground-boom application	0.74	Field Crops	0.05	80	0.00004	180000	61000
Airblast application	4.5	Field Crops	0.05	40	0.0012	60000	20000
Mixer/Loader/Applicator							
Mix/load/apply liquids for HP handwand	120	Greenhouse	0.15	10	0.0026	3000	1000
Mix/load/apply liquids for LP handwand or backpack sprayer	30	Greenhouse	0.15	2	0.0001	60000	20000
Mix/load/apply WP for LP handwand or backpack sprayer	1100	Greenhouse	0.15	2	0.0047	1600	240
Mix/load/apply liquids for LP handwand or backpack sprayer	30	Outdoor Premise & Equipment	0.1	2	0.0001	89000	30000
Flagger							
Aerial application	0.35	Field Crops	0.05	350	0.0001	88000	29000

Table 2 – Pyrethrin Inhalation MOE's for Pest Control Operators								
Exposure Scenario	Inhalation Unit Exposure (µg/lb ai)	Use	Application Rate (lb ai/1000 sf)	lb ai / day	Area Treated (sf)	Inhalation Dose (mg/kg/day)	Short Term MOE	Intermediate/ Long Term MOE
Mixer/Loader								
Mix/load/apply liquids for LP handwand	30	Surface Spray	0.056	0.63	11200	0.0003	29000	9500
Mix/load/apply liquids for LP handwand	30	Crack and Crevice	0.22	2.46	11200	0.0011	7300	2400
Mix/load/apply liquids for LP handwand	30	Crack and Crevice	0.22	0.35	1600	0.0002	51000	17000
Mix/load/apply WP for LP handwand	1100	Surface Spray	0.056	0.63	11200	0.0099	780	260
Mix/load/apply WP for LP handwand	1100	Surface Spray	0.056	0.09	1600	0.0014	5400	1800
Mix/load/apply WP for LP handwand	1100	Crack and Crevice	0.22	2.46	11200	0.0387	200	66
Mix/load/apply WP for LP handwand	1100	Crack and Crevice	0.22	0.35	1600	0.0055	1400	460
Mix/load/apply liquids with turfgun	1.8	Lawn	0.002	0.44	217800	0.000011	700000	240000
Mix/load/apply WP with turfgun	62	Lawn	0.002	0.44	217800	0.00039	20,000	6800
Mix/load/apply liquids for LP handwand and backpack sprayer	30	SG	0.05	0.25	5000	0.00011	72000	24000

Table 2 – Pyrethrin Inhalation MOE's for Pest Control Operators								
Exposure Scenario	Inhalation Unit Exposure (µg/lb ai)	Use	Application Rate (lb ai/1000 sf)	lb ai / day	Area Treated (sf)	Inhalation Dose (mg/kg/day)	Short Term MOE	Intermediate/ Long Term MOE
Mix/load/apply liquids for HP handwand	120	SG	0.05	0.25	5000	0.00043	18000	6000
Mix/load/apply liquids for LP handwand	30	SP	0.01	0.5	50000	0.00021	36000	12000
Applicator								
Aerosol application	1300	Surface Spray	0.003	0.04	N/A	0.0007	12000	3900
Aerosol application	1300	Surface Spray	0.001	0.02	N/A	0.0003	25000	8200

Table 3 - Pyrethrin Inhalation MOEs for Mosquito Abatement Applicators							
Exposure Scenario	Inhalation Unit Exposure (µg/lb ai)	Use	Application Rate (lb ai/acre)	Daily Area Treated (acres/day)	Inhalation Dose (mg/kg/day)	Short Term MOE	Intermediate/ Long Term MOE
Mixer/Loader							
Mix/load liquids for aerial application	1.2	Mosquito Control	0.008	7500	0.001000	7500	2500
Mix/load liquids for ULV truck mounted spray application	1.2	Mosquito Control	0.008	3000	0.000410	19000	6200
Mixer/Loader/Applicator							
Aerial Application	0.068	Mosquito control	0.008	7500	0.000058	130000	46000
ULV truck mounted spray (Airblast Surrogate Unit Exposure)	4.5	Mosquito control	0.008	3000	0.000200	50000	17000
Mix/load/apply liquids for backpack sprayer	30	Mosquito Control	0.008	2	0.000007	1100000	370000

Footnotes for Tables 1-3:

* Baseline inhalation unit exposures represent no respirator. Unit Exposure values are from PHED or the ORETF (See Table 12)
* Application rates are based on maximum values provided in the master label
* Inhalation dose (mg/kg/day) = [unit exposure (µg/lb ai) * 0.001 mg/ g * Application rate* Area Treated)] / Body weight (70 kg).
* MOE = NOAEL/Dose where the NOAEL is 7.67 mg/kg/day for short term exposures and 2.56 mg/kg/day for intermediate/long term exposures.
*Short Term Target MOE = 100 ; Intermediate/Long Term Target MOE=1000

Table 4 - Pyrethrin Inhalation MOEs for Pet Groomers and Veterinary Technicians							
Exposure Scenario	Inhalation Unit Exposure (µg/lb ai)	Use	Application Rate (lb ai/16 oz can)	Amount Used (total # 16 oz cans)	Inhalation Dose (mg/kg/day)	Short Term MOE	Intermediate/ Long Term MOE
Aerosol Application	1300	Pet Spray	0.003	4	0.00022	34000	11000

* Baseline inhalation unit exposures represent no respirator. The unit exposure value is from PHED.
* The application rate is based on maximum value provided in the master label
* Inhalation dose = [unit exposure value * 0.001 mg/ g * Application rate* Amount Used)] / Body weight (70 kg).
* MOE = NOAEL/Dose where the NOAEL is 7.67 mg/kg/day for short term exposures and 2.56 mg/kg/day for intermediate/long term exposures.
*Short Term Target MOE = 100; Long Term Target MOE = 1000

Table 5 – Pyrethrin Occupational Post-Application Inhalation Risks Following Metered Release

Exposure Scenario	Application Rate [A] (lb ai/1000 cf)	Initial Concentration [B] (mg/m^3)	Interior Volume [C] (ft^3)	Ventilation Rate [D] (CFM)	Average Concentration [E] (mg/m^3)	Exposure (mg/day)	Integrated Inhalation Dose [F] (mg/kg/day)	Short Term MOE [G]	Intermediate Term MOE [G]
Metered Release Space Spray in a Dairy Barn	0.000079	1.27	50,000	5,000	0.055	0.44	0.0063	1,200	400

A. Application Rate is master label rate of 0.000476 lb ai/1000 cf /day divided by 6 to account for 1 metered release every four hours.
B. Initial concentration is 0.000079 lb ai/1000 cf converted to mg/m^3 (1 cubic foot = 28.3 liters, 1 cubic meter = 1000 liters, 1 lb = 454,000 mg)
C. Interior Volume is based upon 50 square feet per cow times 10 foot ceiling height times 100 cows per barn
D. Ventilation rate is 50 CFM per cow times 100 cows.
E. Inhalation Exposure = Average Air $concentration_t$ * Breathing rate * Exposure Duration

where: Air $Concentration_t$ = Air concentration (mg/m^3) at time t minutes calculated using the rate of purging formula
Breathing rate = 1.0 m^3 per hour
Exposure Duration = 8 hours

F. Inhalation Dose = Inhalation Exposure / BW
G. MOE = NOAEL/Dose where the NOAEL is 7.67 mg/kg/day for short term exposures and 2.56 mg/kg/day for intermediate/long term exposures.

*Short Term Target MOE = 100; Intermediate/Long Term Target MOE = 1000

* Air Concentrations were calculated by MCCEM using the following formula taken from the ACGIH Manual of Industrial Ventilation
Air Concentration at time t = Initial Air Concentration * $0.5^{(t/0.693 * Q/V)}$
where: time (t) = 1 minute intervals
Volume (V) = 50,000 ft^3
Ventilation Rate (Q) = 5,000 cfm
Initial Air Concentration = 1.27 mg/m^3

Table 6 - Pyrethrin Inhalation MOEs for Residential Handler Activities							
Exposure Scenario	Inhalation Unit Exposure (µg/lb ai)	Site	Application Rate (per 1000 sq. ft.)	Daily Area Treated (sf)	Amount a.i. Used Per Day (lb)	Inhalation Dose (mg/kg/day)	Short Term Inhalation MOE
Aerosol Can Application	1300	Indoor (one 16 oz. can containing 0.25%) Surface Spray	N/A	N/A	0.0025	0.000046	170000
Load/Apply Dusts	620	Indoor Surface Spray	0.056	1.6	0.09	0.00079	9700
Load/Apply Dusts	620	Home Gardens	0.011	1.0	0.011	0.0000097	790000
Mix/load/apply liquids for LP handwand	30	Indoor Surface Spray	0.056	1600	0.09	0.000038	200000
Mix/load/apply liquids for LP handwand	30	Indoor Crack & Crevice	0.22	1600	0.35	0.00015	51000
Mix/load/apply liquids for LP handwand	123	Home Gardens	0.0011	1000	0.011	0.0000019	4000000
Mix/load/apply liquids for LP handwand	123	Indoor Crack & Crevice	0.22	1600	0.35	0.00015	51000
Mix/load/apply liquids for garden hose-end sprayer	17	Lawn	0.002	22000	0.044	0.000011	720000

* Baseline inhalation unit exposures represent no respirator. Unit Exposure values are from PHED or ORETF (see Table 12)
* Application rates are based on maximum values provided in the master label
* Inhalation dose = [unit exposure * 0.001 mg/ g * Inhalation absorption (100%) * Application rate * Daily area treated] / Body weight (70 kg).
* MOE = NOAEL/Dose where the NOAEL is 7.67 mg/kg/day for short term exposures
*Short Term Target MOE = 100

Table 7 - Pyrethrin Post-application Inhalation MOEs Following Mosquito Adulticide Application				
Exposed Individual	Breathing Zone Concentration (mg/m^3)	Breathing Rate (mg/m^3)	Inhalation Dose (mg/kg/day)	Short Term MOE
Aerial Spray (Fixed Wing and Rotary Aircraft)				
Adult	0.003	1	0.00009	89000
Child	0.003	0.8	0.00032	24000
Truck Mounted ULV Sprayer				
Adult	0.03	1	0.00086	8900
Child	0.03	0.8	0.0032	2400

Inhalation Dose = (BZC * BR * ED) / BW

where: BZC = Breathing Zone Concentration (mg/m^3) - from Ag Drift Model for aerial spray application; 1% of application rate for truck mounted ULV sprayer application

BR = Breathing rate, 1.0 m^3/hr for adults, 0.8 m^3/hr for children

BW = 70 kg for adult; 15 kg for toddler

ED = Exposure Duration (2 hr/day)

* MOE = NOAEL/Dose where the NOAEL is 7.67 mg/kg/day for short term exposures

*Short Term Target MOE = 100

Table 8 - Pyrethrin Post-Application Incidental Ingestion Risks to Toddlers Reentering Treated Lawns										
Inputs	Hand to Mouth Exposures			Object to Mouth Exposures			Soil Ingestion Exposures			Aggregate Exposures
Application Rate (lb ai/A)	Hand Transfer ($\mu g/cm^2$)	Daily Oral Dose (mg/kg/day)	MOE	Dislodgeable Foliar Residue ($\mu g/cm^2$)	Daily Oral Dose (mg/kg/d)	MOE	Soil Residue ($\mu g/g$)	Daily Oral Dose (mg/kg/d)	MOE	Aggregate MOE
0.1	0.056	0.001	13000	2.2	0.004	2100	7.504	0.00005	150000	1800

Hand To Mouth Exposures:

Daily Oral Dose (mg/day) = (HTF * SEF * SA * Freq * ED * 0.001 mg/μg) / BW

where: HTE = Hand Transfer Efficiency = 5% of Application Rate

SEF = Saliva Extraction Factor (50%)

SA = Surface Area of Two Fingers (20 cm^2)

Freq = Frequency of Hand to Mouth Events (20 events per hour)

ED = Exposure Duration (2 hours per day)

BW = 15 kg for a toddler

Object to Mouth Dose Exposures:

Daily Oral Dose (mg/day) = (DFR * SA * 0.001 mg/μg) / BW

where: DFR = Dislodgeable Foliar Residue = 20% of Application Rate

SA = Surface Area of grass or toy mouthed by toddler (25 cm^2 day)

Soil Ingestion Exposures:

Daily Oral Dose (mg/day) = (SR * IgR * CF1) / BW

where: SR = Application Rate * 1/cm * 0.67 c m^3/g soil [1/cm is fraction of ai available in uppermost cm of soil]

IgR = Ingestion Rate of soil (100 mg/day)

CF1 = Weight unit conversion factor (1E-6 g/μg)

Short Term MOE = Short Term Oral NOAEL (20 mg/kg/day)/**n**Daily Oral Dose (mg//**n**kg/**n**day)

Aggregate MOE = 1/(1/MOE HTM + 1/MOE OTM + 1/MOE SI)

**Short Term Target MOE = 300

Table 9 - Pyrethrin Incidental Oral Ingestion Risks To Toddlers Playing on Vinyl Floor and Carpet after Fogger Treatment

Indoor Surface	Study Application Rate [A] lb ai/1000 ft^3	Measured Indoor Surface Residue [B] ($\mu g/cm^2$)	Adjusted Indoor Surface Residue [B] ($\mu g/cm^2$)	Hand Transfer Efficiency (%)	Daily Oral Dose (mg/kg/day)	Short Term Incidental Oral MOE
carpet	0.00076	2.25	0.977	8.0	0.0021	9,500
vinyl				11.0	0.0029	6,900

A. Based upon 141 gm of a fogger product containing 0.5% pyrethrin applied to a room with an interior volume of 2048 ft^3.
B. The mean of n=32 floor residues (excluding the center coupon) measured 3 hours after fogger application. The SD was 1.35 $\mu g/cm^2$.
C. The measured residue was adjusted to account for the master label rate of 0.00033 lb ai/1000 ft^3.

Daily Oral Dose (mg/day) = (ISR * HTE * SEF * SA * Freq * ED * 0.001 mg/µg) / BW
where: ISR = Indoor Surface Residue ($\mu g/cm^2$) at maximum AR of 0.033 lbs ai/1000 ft2
HTE = Hand Transfer Efficiency (8% for carpet; 11% for vinyl)
SEF = Saliva Extraction Factor (50%)
SA = Surface Area of Two Fingers (20 cm^2)
Freq = Frequency of Hand to Mouth Events (20 events per hour)
ED = Exposure Duration = 2 hours/day
BW = 15 kg for toddler

Short Term MOE = Short Term Oral NOAEL (20 mg/kg/day)/**n**Daily Oral Dose (mg/kg/day)
Short Term Target MOE = 300

Table 10 - Pyrethrin Post-application Risks to Toddlers Playing with Pets after Treatment with Spray Formulations				
Application Method	Application Rate (mg ai/cm^2)	Transferable Residue (mg/cm^2)	Daily Oral Dose (mg/kg/day)	Short Term MOE
Aerosol Can (8)	0.0038	0.00076	0.000504	40,000

Daily Oral Dose = TR * SEF * SAhands * Freq

where: AR = Application Rate or amount applied to animal in a single treatment (mg ai/animal) = ½ of 16 oz spray container with maximum of 0.01% ai per 6000 cm^2/animal

TR = Transferable Residue (AR * 20%)

SApet = Surface Area of a treated dog (6000 cm^2/animal)

SEF = Saliva Extraction Factor (50%)

SAhands = Surface Area of the hands (20 cm^2)

Freq= Hand-to-Mouth Events (1 event/day)

BW = 15 kg for toddler

MOE = Short Term Oral NOAEL (20 mg/kg/day)/Daily Oral Dose (mg/kg/day)

Short-Term Target MOE = 300

Table 11 - Pyrethrin Inhalation Risks To Adults and Children During and After Indoor Space Spray Application

Application Method	Exposed Individual	Study Application Rate [A] (lb ai/1000 ft^3)	Measured Breathing Zone Concentration [B] (mg/m^3)	Master Label Application Rate (lb ai/1000 ft^3)	Adjusted Breathing Zone Concentration [C] (mg/m^3)	Breathing Rate (m^3/hr)	Inhalation Dose (mg/kg/day)	Short Term MOE
Aerosol Can	Adult	0.000050	0.019	0.00033	0.13	1	0.0037	2100
	Child					0.7	0.012	640

A. Based upon the application of 9.31 grams of a product containing 0.5% pyrethrins by weight to room with an internal volume of 2048 cubic feet.
B. The 2 hour TWA at the 5 foot sampler height for time t = 0 to time t = 120 minutes after application.
C. 0.019 mg/m^3(0.00033/0.000050) = 0.13 mg/m^3

Inhalation Dose = (BZC * BR * ED) / BW
where:
BZC = Breathing Zone Concentration (mg/m^3) - measured air concentration from NDETF study adjusted to reflect the application rate
BR = Breathing rate for adult or child (m^3/hr) (1.0 m^3/hr adult, 0.7 m^3/hr child)
BW = 70 kg for adult; 15 kg for toddler
ED = Exposure Duration (2 hr/day)

Inhalation MOE = NOAEL/ Inhalation Dose, where the NOAEL = 7.67 for short term exposures

Target Short Term MOE = 100

Note - The data cited above are from the NDETF Study “Measurement of Air Concentration, Dermal Exposure and Deposition of Pyrethrin and Piperonyl Butoxide Following Use of an Aerosol Spray”, Project ID 01-0024-PY01, MRID 461886-18. This study is the property of the NDETF.

Table 12 – Pyrethrin Residential Post-Application Inhalation Risks Following Metered Release

Exposed Population	Treatment Type	Application Rate (lb ai/1000 cf/day)	Initial Concentration (mg/m^3)	Air Changes per Hour[F]	Steady State Air Concentration (mg/m^3)	Inhalation Exposure[J] (mg/day)	Inhalation Dose[K] (mg/kg/day)	Short Term MOE[L]	Intermediate/ Long term MOE[L]
Adults	Single Chamber	0.0000275[A]	0.0045[C]	0.18	0.108[G]	1.14	0.021	370	**130**
Children						0.94	0.063	120	**40**
Adults		0.0000275[A]	0.0045[C]	0.45	0.045[G]	0.6	0.009	890	**310**
Children						0.39	0.026	290	**100**
Adults	Use Interzonal Flow Rates	0.00015[B]	0.025 Kitchen[D] <0.0001 ROH[E]	0.18	0.010 Kitchen[H] 0.038 ROH 0.043 TWA[I]	0.57	0.0082	940	**310**
Children						0.37	0.025	310	**100**
Adults		0.00015[B]	0.025 Kitchen[D] <0.0001 ROH[E]	0.45	0.0042 Kitchen[H] 0.014 ROH 0.017 TWA[I]	0.23	0.0033	2300	**780**
Children						0.15	0.01	770	**260**

A. The application rates are based upon the Clean Air Purge II Label (9444-161). This product contains 1% Pyrethrins by weight in a 232 gram container. One container will apply 3000 sprays per month at fifteen minute intervals and is sufficient for a 6000 cf interior space.

B. Based on the use of Clean Air Purge II in the MCCEM generic kitchen which has an interior volume of 30 m^3 or 1060 cubic feet.

C. Initial concentration for whole house treatment is 0.77 mg per 6000 cubic feet converted to mg/m^3 (6000 cf = 170 m^3)

D. Initial concentration for kitchen treatment is 0.77 mg per 1060 cubic feet converted to mg/m^3 (1060 cf = 30m^3)

E. ROH = Rest of House excluding the kitchen.

F. The MCCEM air change rates per hour are 0.18 for the average summer house and 0.45 for the average fall/spring house.

G. Is the average concentration at steady state and was calculated using MCCEM in single chamber mode.

H. Calculated using MCCEM in multi-zone mode with the kitchen as zone one and the rest of house (ROH) as zone two.

I. The time weighted average (TWA) concentration is based upon 2 hours per day in the kitchen and 22 hours per day in the rest of the house.

J. Inhalation Exposure (mg/day) = Steady state air concentration (mg/m^3) * breathing rate (13.3 m^3/day for adults and 8.7 m^3/day for children)

K. Inhalation Dose (mg/kg/day) = Inhalation Exposure (mg/day) / BW (70 kg for adults and 15 kg for children)

L. MOE = NOAEL/Dose; where the NOAEL is 7.67 mg/kg/day for short term exposures and 2.56 mg/kg/day for intermediate/long term exposures.

MOEs in bold font are less than the target MOEs of 100 for short term exposure or 1000 for intermediate term exposure.

Table 13 – PHED/ORETF Inhalation Unit Exposure Values Used in Pyrethrin Occupational and Residential Exposure Assessment				
Scenario	Data Source	Unit Exposure (μg/lb ai handled)	Replicates	Grade/Confidence
Occupational				
Mix/load liquids	PHED	1.2	85	AB/High Confidence
Mix/load WP	PHED	43	44	ABC/Medium Confidence
Aerial spray application – enclosed cockpit	PHED	0.068	23	ABC/Medium Confidence
Ground-boom application – open cab	PHED	0.74	22	AB/High Confidence
Airblast application - open cab (also used for truck mounted ULV application)	PHED	4.5	47	AB/High Confidence
Mix/load/apply liquids HP handwand	PHED	120	13	A/Low Confidence
Mix/load/apply liquids LP handwand	PHED	30	80	ABC/Medium Confidence
Mix/load/apply liquids backpack sprayer	PHED	30	11	A/Low Confidence
Mix/load/apply WP Low Pressure handwand	PHED	1100	16	ABC/Medium Confidence
Flagging - liquid formulations	PHED	0.35	28	AB/High Confidence
Mix/load/apply liquids with turfgun	ORETF	1.8	15	AB/High Confidence
Mix/load/apply WP with turfgun	ORETF	62	15	AB/High Confidence
Aerosol can application	PHED	1300	15	AB/High Confidence
Residential				
Load/Apply Dusts	ORETF (MRID 44459801)	620	20	AB/High Confidence
Mix/load/apply liquids - hose-end spray	ORETF	17	30	AB/High Confidence

Table 13 – PHED/ORETF Inhalation Unit Exposure Values Used in Pyrethrin Occupational and Residential Exposure Assessment				
Scenario	Data Source	Unit Exposure (μg/lb ai handled)	Replicates	Grade/Confidence
Mix/load/apply liquids LP handwand	PHED	30	80	ABC/Medium Confidence
Mix/load/apply liquids with trigger sprayer	MRID 41054701	123	15	AB/High Confidence
WP=Wettable powders. LP=low pressure. HP=high pressure. MRID 44459801 is a study that involved the loading and application of Sevin®10 dust to tomatoes and cucumbers. MRID 410547-01 is a study that involved the trigger sprayer application of a liquid propoxur formulation (Raid) to exterior house surfaces.				

Appendix 5. Tolerance Reassessment Summary
TOLERANCE REASSESSMENT SUMMARY

Tolerance exemption under CFR §180.905(a)(6)

Pyrethrum and pyrethrins are currently exempt from the requirements of tolerances when applied to growing crops in accordance with good agricultural practices [40 CFR §180.905(a)(6)]; the tolerance exemption was previously established under 40 CFR §180.1001(b). Based on the results of limited field trials reflecting preharvest uses, HED recommends for the revocation of this tolerance exemption. The results of preharvest trials show detectable and variable residues of pyrethrins I components in/on many raw agricultural commodities following applications of one formulation class (EC) at 1.0x the maximum seasonal rate the PJV wishes to support for preharvest uses. Additional residue data reflecting preharvest uses are required for tolerance reassessment. When the requested data have been evaluated, HED will recommend for the revocation of the tolerance exemption in 40 CFR §180.905(a)(6) concomitant with the establishments of crop group tolerances, if appropriate, in 40 CFR §180.128 to support all uses.

Tolerances Established Under CFR §180.128

Tolerances are established in 40 CFR §180.128 for residues of pyrethrins, insecticidally active principles of *Chrysanthemum cinerariaefolium* in/on: (i) plant commodities resulting from postharvest uses; (ii) animal commodities; and (iii) food/feed items while in storage areas. A list of tolerances established for pyrethrins I along with our recommendations of changes to correct commodity definitions is presented in Table 19.

The qualitative nature of the residue in plants is understood based on acceptable metabolism studies conducted on three dissimilar crops: leaf lettuce, potatoes, and tomatoes. The qualitative nature of the residue in ruminants and poultry is also adequately understood based on acceptable metabolism studies reflecting both dermal and oral treatments. The results of the above plant as well as animal metabolism studies will be presented to HED for a determination of terminal residues of concern (i.e., residues that need to be regulated or included in the tolerance expression). If HED determines that additional metabolites of toxicological concern should be regulated (i.e., included in the tolerance expression), then additional data concerning residue analytical methods, storage stability, and magnitude of the residue (in plants, processed commodities, animals, and food/feed items in storage areas) may be required in the future.

The pyrethrins tolerances for plant commodities, resulting from postharvest uses [40 CFR §180.128(a)(1)], range from 0.05 ppm (potato and sweet potato) to 3 ppm (most cereal grains). The available data are inadequate to support many of the established tolerances resulting from postharvest uses (except those uses for potato and sweet potato), and additional data are required for tolerance reassessment. The required postharvest data for cereal grains will be translated to birdseed mixture since the use patterns of birdseed mixture and cereal grains are identical.

Assuming there is a linear relationship between feeding levels and tissue concentrations and provided that the residues of concern in animals are the components of pyrethrins I, the established tolerances of negligible

residues for milk and 0.1 ppm for the fat, meat, and meat byproducts of cattle, goat, hogs, horses, and sheep need to be revised. A tolerance of 0.05 ppm would tentatively be appropriate for milk, meat, and meat byproducts of cattle, goats, hogs, horses, and sheep; a tolerance of 1.0 ppm would be appropriate for fat of cattle, goats, hogs, horses, and sheep.

The remainder of tolerances and tolerance exemptions established in CFR §180.128 pertain to uses of pyrethrins in food/feed storage areas.

- According to 40 CFR §180.128(a)(2)(i), pyrethrins may be safely used in combination with piperonyl butoxide (PBO) for control of insects when used according to conditions specified in the same 40 CFR section.

- According to 40 CFR §180.128(a)(2)(ii), pyrethrins may be safely used in combination with PBO and N-octylbicycloheptene dicarboximide for insect control in accordance with 40 CFR 180.367(a)(2).

- According to 40 CFR §180.128(a)(2)(iii), a tolerance of 1 ppm is established for residues of pyrethrins *per se* in/on: (A) milled fractions derived from cereal grains when present therein as a result of its use in cereal grain mills and in storage areas for milled cereal grain products; (B) dried foods when present as a result of migration from its use on the outer ply of multiwall paper bags of 50 pounds or more capacity; (C) foods treated in accordance with 40 CFR 180.367(a)(2); (D) dried foods that contain 4 % fat, or less, when present as a result of migration from its use on the cloth of cotton bags of 50 pounds or more capacity constructed with waxed paper liners; and (E) foods from treated food processing and storage areas provided the food is removed or covered prior to such use.

- According to 40 CFR §180.128(a)(2)(iv), to assure safe use of the pesticide, its label and labeling shall conform to that registered with the U.S. Environmental Protection Agency, and it shall be used in accordance with such label and labeling.

- According to 40 CFR §180.127(a)(2)(v), where tolerances are established on both raw agricultural commodities and processed foods made therefrom, the total residues of pyrethrins in/on the processed food shall not be greater than that permitted by the larger of the two tolerances.

- According to 40 CFR §180.128(a)(3), pyrethrins may be safely used in accordance with the following prescribed conditions: (i) It is used or intended for use in combination with PBO for control of insects: (A) On the outer ply of multiwall paper bags of 50 pounds or more capacity in amounts not exceeding 6 milligrams per square foot; or (B) On cotton bags of 50 pounds or more capacity in amounts not exceeding 5.5 milligrams per square foot of cloth. Such treated bags are constructed with waxed paper liners and are to be used only for dried feeds that contain 4 percent fat or less; or (ii) It is used in combination with PBO,

whereby the amount of pyrethrins is equal to 10 percent of the amount of PBO in the formulation. Such treated bags are to be used only for dried feeds.

The tolerance regulations establish that pyrethrins may be safely used in combination with piperonyl butoxide [40 CFR §180.128(a)(2)(i)] and piperonyl butoxide and N-octylbicycloheptene dicarboximide [40 CFR §180.128(a)(2)(ii)], for control of insects in food/feed processing areas and food/feed storage areas provided that the food/feed is removed or covered prior to use of the products. HED concludes that no additional data for pyrethrins are required to maintain the above tolerance regulations. This determination does not apply to PBO and N-octylbicycloheptene dicarboximide because the labels for these pesticide chemicals were not examined in the generation of this Residue Chapter.

Adequate data depicting the magnitude of residues of pyrethrins in food-handling establishments and food storage areas are available. These data indicate that the established tolerance of 1 ppm will not be exceeded in representative food commodities and surfaces that had been covered during space, contact, and intermittent spray aerosol treatments using representative SC/L and PrL formulations. The submitted Pyrethrins Master Label provides adequate instructions which specify that food should be removed or covered during treatment, and that all food processing surfaces should be covered during treatment or thoroughly cleaned before use.

No data are available to support uses of pyrethrins on foods stored in multi-walled paper or cloth bags, and additional data are required. Alternatively, the use of pyrethrins on foods stored in multi-walled paper or cloth bags may be removed from all product labels concomitant with the revocation of the associated tolerance.

Maximum contaminant level

No maximum contaminant level (MCL) for pyrethrins in potable water has been established. Pending label revision to specify a 10-day holding interval and provided that the aquatic uses of pyrethrins and piperonyl butoxide are limited to flooded rice fields for the control of adult mosquitos only, an MCL for pyrethrins need not be established and the reregistration requirements for aquatic uses will be considered fulfilled.

Tolerances to be Established Under 40 CFR §180.128

The data requirements to support preharvest uses, which are recommended in this Chemistry Chapter, are designed to support the establishments of crop group tolerances. Therefore, several crop group tolerances, if appropriate, will need to be proposed when the requested data have been reviewed. In addition, tolerances for the following miscellaneous commodities need to be proposed upon receipt of the requested residue data: asparagus, aspirated grain fraction, atemoya, avocado, banana, carob bean, cherimoya, coffee green bean, cranberry, date, durian, jojoba, kiwifruit, lychee, okra, papaya, persimmon, pomegranate, safflower seed, strawberry, sugarcane, sunflower seed, and tea leaves.

Table 19. Tolerance Reassessment Summary for Pyrethrins.			
Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/ *[Correct Commodity Definition]*
Tolerances Listed Under 40 CFR §180.128 (a)(1)			
Almond, postharvest	1	TBD [1]	
Apple, postharvest	1	TBD	
Barley, postharvest	3	TBD	[*Barley, grain, postharvest*]
Bean, postharvest	1	TBD	[*Bean, succulent, postharvest*]
Birdseed, mixtures, postharvest	3	TBD	
Blackberry, postharvest	1	TBD	
Blueberry (huckleberry), postharvest	1	TBD	[*Blueberry, postharvest*]
Boysenberry, postharvest	1	TBD	
Buckwheat, grain, postharvest	3	TBD	
Cattle, fat	0.1 (N)	1	
Cattle, meat byproducts	0.1 (N)	0.05	
Cattle, meat	0.1 (N)	0.05	
Cherry, postharvest	1	TBD	
Cocoa bean, postharvest	1	TBD	[*Cocoa bean, dried bean, postharvest*]
Coconut, copra, postharvest	1	TBD	
Corn (including popcorn), postharvest	3	TBD	[*Corn, field and pop, grain, postharvest*]
Cottonseed, postharvest	1	TBD	[*Cotton, undelinted seed, postharvest*]
Crabapple, postharvest	1	TBD	
Currant, postharvest	1	TBD	
Dewberry, postharvest	1	TBD	
Egg	0.1	Revoke	
Fig, postharvest	1	TBD	
Flaxseed, postharvest	1	TBD	[*Flax, seed, postharvest*]
Goat, fat	0.1 (N)	1	
Goat, meat byproducts	0.1 (N)	0.05	
Goat, meat	0.1 (N)	0.05	
Gooseberry, postharvest	1	TBD	
Grape, postharvest	1	TBD	
Guava, postharvest	1	TBD	
Hog, fat	0.1 (N)	1	
Hog, meat byproducts	0.1 (N)	0.05	

Table 19. Tolerance Reassessment Summary for Pyrethrins.			
Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/ *[Correct Commodity Definition]*
Hog, meat	0.1 (N)	0.05	
Horse, fat	0.1 (N)	1	
Horse, meat byproducts	0.1 (N)	0.05	
Horse, meat	0.1 (N)	0.05	
Loganberry, postharvest	1	TBD	
Mango, postharvest	1	TBD	
Milk fat (reflecting negligible residues in milk)	0.5	0.05	
Muskmelon, postharvest	1	TBD	
Oat, postharvest	1	TBD	[*Oat, grain, postharvest*]
Oranges, postharvest	1	TBD	[*Orange, sweet, postharvest*]
Peach, postharvest	1	TBD	
Peanut (with shell removed), postharvest	1	TBD	[*Peanut, nutmeat, postharvest*]
Pear, postharvest	1	TBD	
Pea, postharvest	1	TBD	[*Pea, dry, seed, postharvest*]
Pineapple, postharvest	1	TBD	
Plum, prune, fresh, postharvest	1	TBD	
Potato, postharvest	0.05	0.05	The reassessed tolerance is based on data reflecting residues of pyrethrins. Additional data may be required if HED determines that additional metabolites of toxicological concern should be regulated.
Poultry, fat	0.2	Revoke	
Poultry, meat byproducts	0.2	Revoke	
Poultry, meat	0.2	Revoke	
Raspberry, postharvest	1	TBD	
Rice, postharvest	3	TBD	[*Rice, grain, postharvest*]
Rye, postharvest	3	TBD	[*Rye, grain, postharvest*]
Sheep, fat	0.1 (N)	1	
Sheep, meat byproducts	0.1 (N)	0.05	
Sheep, meat	0.1 (N)	0.05	
Sorghum, grain, postharvest	1	TBD	

Table 19. Tolerance Reassessment Summary for Pyrethrins.			
Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)	Comment/ *[Correct Commodity Definition]*
Sweet potato, postharvest	0.05	0.05	The postharvest use on stored raw sweet potatoes are supported by residue data translated from potatoes.
Tomato, postharvest	1	TBD	
Walnut, postharvest	1	TBD	
Wheat, postharvest	3	TBD	[*Wheat, grain, postharvest*]
Tolerances to be Established Under CFR §180.128 [2]			
Aspirated grain fractions	None	TBD	
Atemoya	None	TBD	
Avocado	None	TBD	
Banana	None	TBD	
Carob bean	None	TBD	
Cherimoya	None	TBD	
Coffee, green bean	None	TBD	
Cranberry	None	TBD	
Date	None	TBD	
Durian	None	TBD	
Jojoba	None	TBD	
Lychee	None	TBD	
Okra	None	TBD	
Papaya	None	TBD	
Persimmon	None	TBD	
Pomegranate	None	TBD	
Safflower, seed	None	TBD	
Strawberry	None	TBD	
Sugarcane	None	TBD	
Sunflower, seed	None	TBD	
Tea, leaves	None	TBD	

[1] TBD = To be determined. Additional data are required for tolerance reassessment.

[2] Several crop group tolerances, if appropriate, need to be proposed when the requested data have been reviewed.

Codex/International Harmonization

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for residues of pyrethrins. The Codex MRLs are expressed in terms of total pyrethrins, calculated as the sum of pyrethrins 1 and 2, cinerins 1 and 2, and jasmolins 1 and 2, determined after calibration with the World Standard pyrethrum extract, which is identical to the current U.S. tolerance expression. Canadian MRLs have been established for residues of pyrethrins [4-hydroxy-3-methyl-2-(2,4-pentadienyl)-2-cyclopenten-1-one 2,2-dimethyl-3-(2-methyl-propenyl) cyclopropanecarboxylate and 4-hydroxy-3-methyl-2-(2,4-pentadienyl)2-cyclopenten-1-one 1-methyl-3-carboxy-∝,2,2-triethylcyclo-propaneacrylate ester]. Mexican MRLs have been established for residues of permetrina. A numerical comparison of the Codex MRLs and the corresponding current U.S. tolerances for pyrethrins is presented in Table 20.

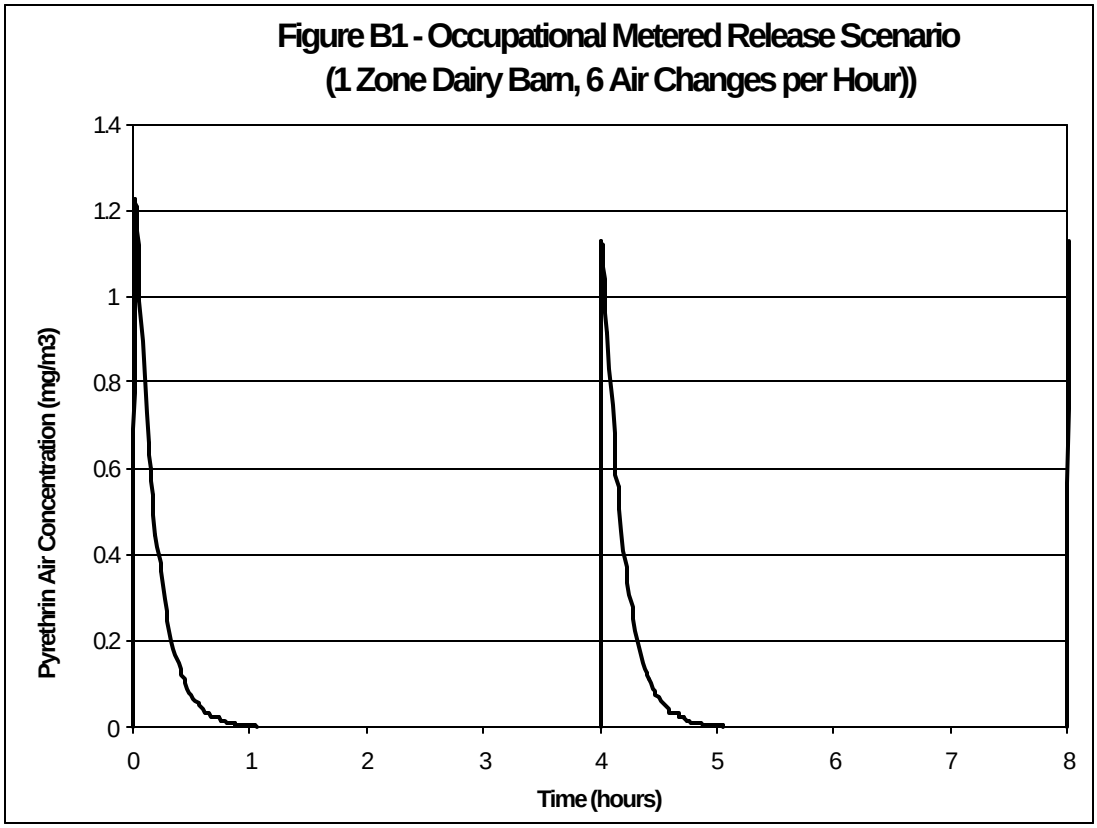
Table 20. Codex, Canadian, and Mexican MRLs and Applicable U.S. Tolerances for Pyrethrins.		
Codex		**Current U.S. Tolerance, ppm [1]**
Commodity, As Defined	**MRL (mg/kg)**	
Cereal grains	0.3 (Postharvest or Po)	1 ppm for oat and sorghum resulting from postharvest uses; 3 ppm for barley, buckwheat, corn, (including popcorn), rice, rye, and wheat resulting from postharvest uses
Citrus fruits	0.05	1 ppm for oranges resulting from postharvest uses
Dried fruits	0.2 (Po)	
Fruiting veg, cucurbits	0.05 (*)	1 ppm for muskmelon and tomato resulting from postharvest uses
Pea hay or fodder	1	1 ppm for pea resulting from postharvest uses
Pea vines (green)	10	
Peanut	0.5 (Po)	1 ppm for peanut (with shell removed) resulting from postharvest uses
Peppers	0.05 (*)	
Pulses	0.1	
Root and tuber veg	0.05 (*)	0.05 ppm for potato and sweet potato resulting from postharvest uses
Tomato	0.05 (*)	1 ppm for tomato resulting from postharvest uses
Tree nuts	1 (Po)	1 ppm for almond and walnut resulting from postharvest uses
Limits for Canada		**Current U.S. Tolerance, ppm [1]**
Commodity, As Defined	MRL (mg/kg)	
Raw cereals	3	
Almonds	1	1 ppm for almond resulting from postharvest uses
Apples	1	1 ppm for apple resulting from postharvest uses
Beans	1	1 ppm for bean resulting from postharvest uses
Blackberries	1	1 ppm for blackberry resulting from postharvest uses
Blueberries	1	1 ppm for blueberry (huckleberry) resulting from postharvest uses
Boysenberries	1	1 ppm for boysenberry resulting from postharvest uses
Cherries	1	1 ppm for cherry resulting from postharvest uses
Copra	1	1 ppm for coconut, copra resulting from postharvest uses

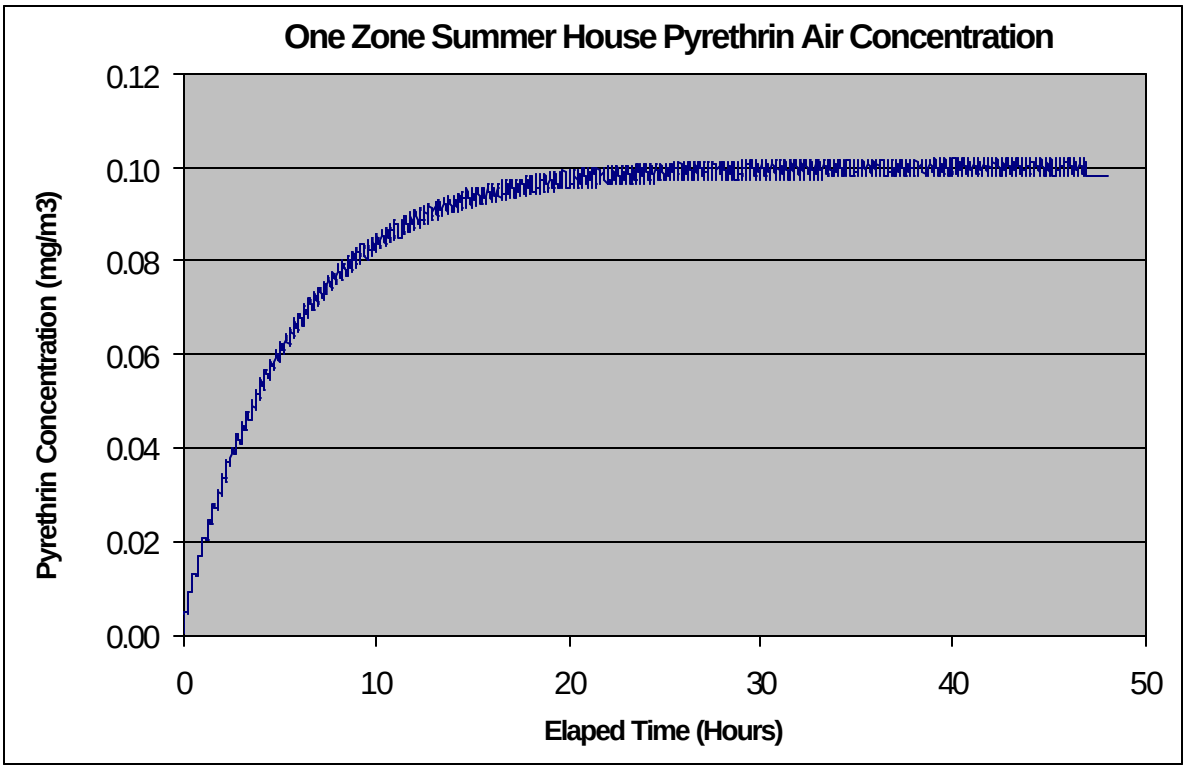
Limits for Canada		Current U.S. Tolerance, ppm [1]
Commodity, As Defined	MRL (mg/kg)	
Crabapples	1	1 ppm for crabapple resulting from postharvest uses
Cocoa beans	1	1 ppm for cocoa bean resulting from postharvest uses
Currants	1	1 ppm for currant resulting from postharvest uses
Dewberries	1	1 ppm for dewberry resulting from postharvest uses
Figs	1	1 ppm for fig resulting from postharvest uses
Gooseberries	1	1 ppm for gooseberry resulting from postharvest uses
Grapes	1	1 ppm for grape resulting from postharvest uses
Guavas	1	1 ppm for guava resulting from postharvest uses
Huckleberries	1	1 ppm for blueberry (huckleberry) resulting from postharvest uses
Loganberries	1	1 ppm for loganberry resulting from postharvest uses
Mangoes	1	1 ppm for mango resulting from postharvest uses
Muskmelons	1	1 ppm for muskmelon resulting from postharvest uses
Oranges	1	1 ppm for oranges resulting from postharvest uses
Peaches	1	1 ppm for peach resulting from postharvest uses
Nectarines	1	1 ppm for peach resulting from postharvest uses
Peanuts	1	1 ppm for peanut (with shell removed) resulting from postharvest uses
Pears	1	1 ppm for pear resulting from postharvest uses
Peas	1	1 ppm for pea resulting from postharvest uses
Pineapple	1	1 ppm for pineapple resulting from postharvest uses
Plums	1	1 ppm for plum (fresh prune) resulting from postharvest uses
Raspberries	1	1 ppm for raspberry resulting from postharvest uses
Tomatoes	1	1 ppm for tomato resulting from postharvest uses

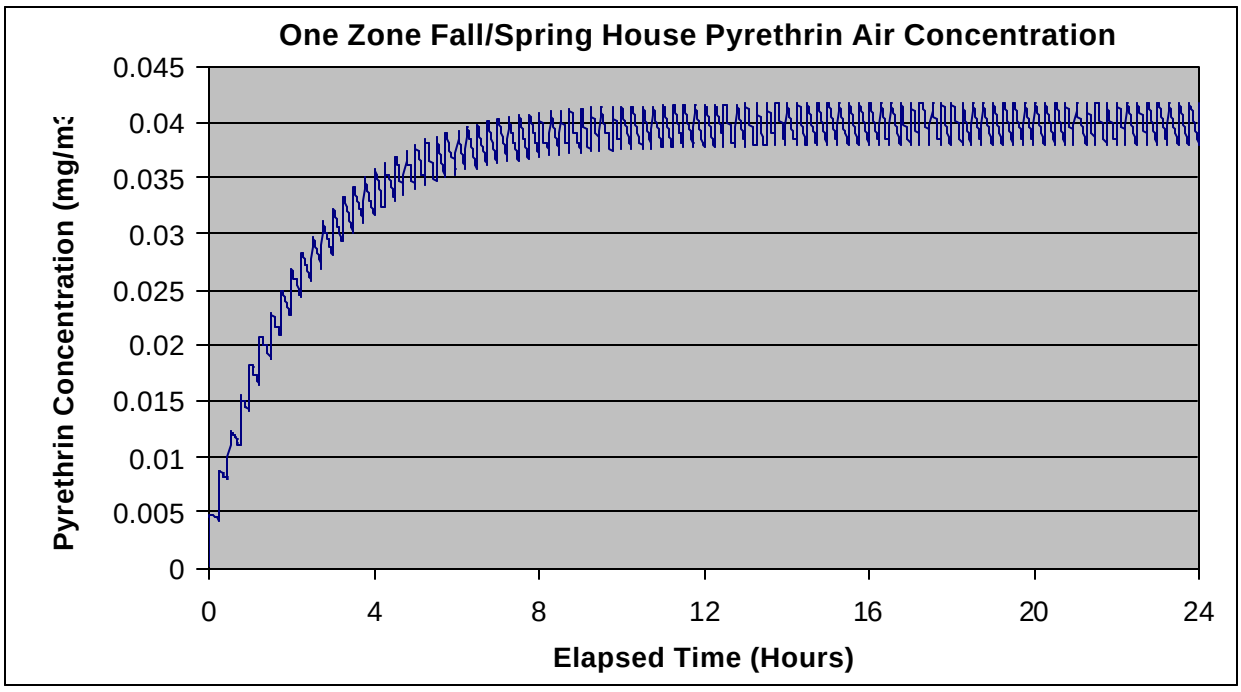
Limits for Canada		Current U.S. Tolerance, ppm [1]
Commodity, As Defined	MRL (mg/kg)	
Walnuts	1	1 ppm for walnut resulting from postharvest uses
Limits for Mexico		Current U.S. Tolerance, ppm [1]
Commodity, As Defined	MRL (mg/kg)	
Cottonseed	1	1 ppm for cottonseed resulting from postharvest uses
Celery	5	
Eggplant	1	
Broccoli	1	
Squash	3	
Bell pepper	1	
Cabbage	6	
Brussels sprouts	1	
Cauliflower	1	
Date	5	
Asparagus	1	
Spinach	20	
Tomato	2	1 ppm for tomato resulting from postharvest uses
Lettuce	20	
Corn	0.05	3 ppm for corn (including pop corn) resulting from postharvest uses
Apple	0.05	1 ppm for apple resulting from postharvest uses
Melon	3	1 ppm for muskmelon resulting from postharvest uses
Potato	0.05	0.05 ppm for potato resulting from postharvest uses
Grass	15	
Cucumber	3	
Pear	3	1 ppm for pear resulting from postharvest uses
Watermelon	3	
Sorghum	2	1 ppm for sorghum, grain resulting from postharvest uses
Soybean	0.05	

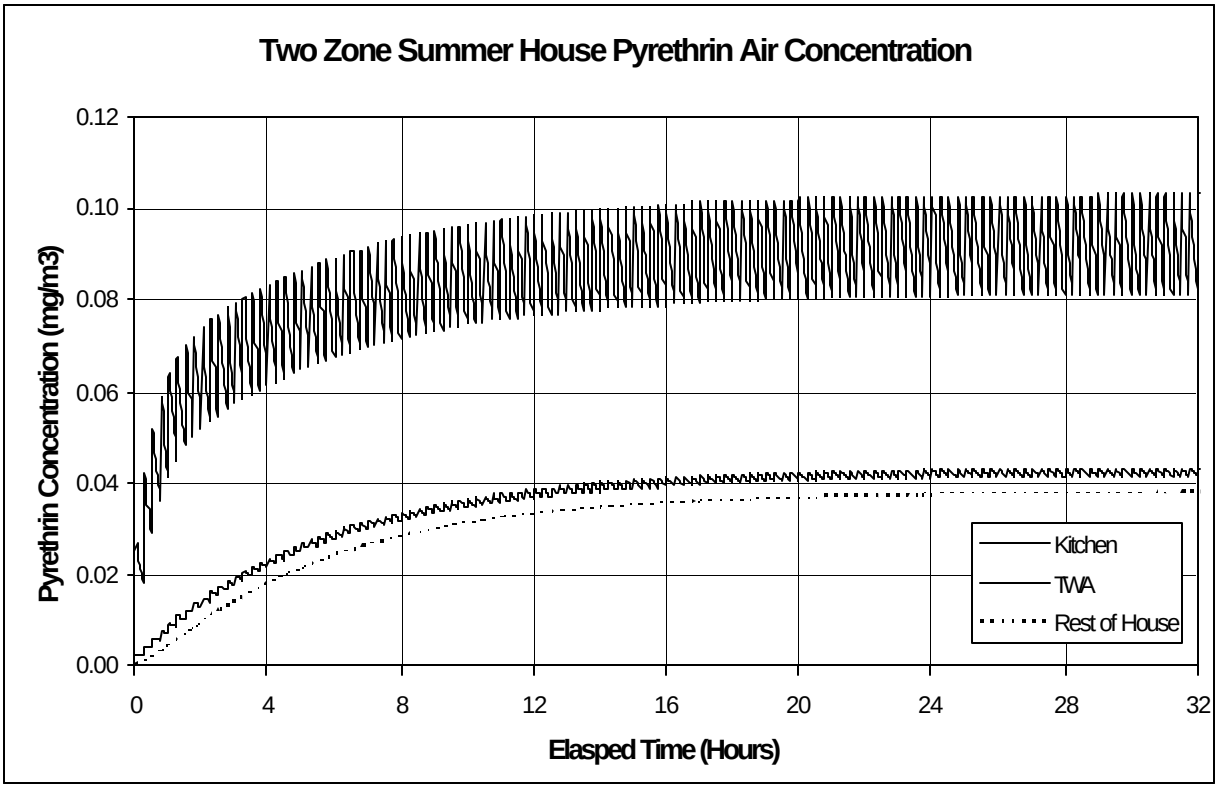
[1] Very few U.S. tolerances were reassessed in this Chapter because additional data are required for many commodities.

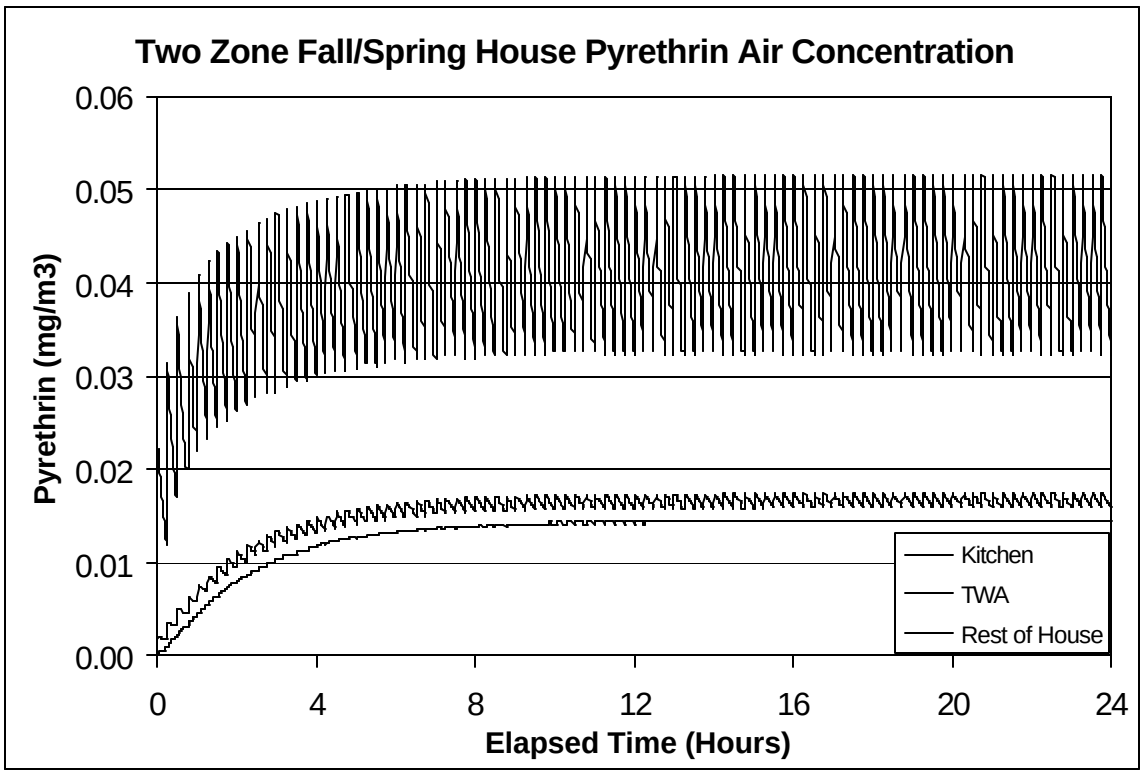
Appendix 6. Results of MCCEM Modeling for Pyrethrin Residential Metered Release Scenarios






One Zone Fall/Spring House Pyrethrin Air Concentration
Pyrethrin Concentration (mg/m3
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
0
4
8
12
16
20
24
Elapsed Time (Hours)


Two Zone Summer House Pyrethrin Air Concentration
Pyrethrin Concentration (mg/m3)
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
4
8
12
16
20
24
28
32
Elasped Time (Hours)
Kitchen
TWA
Rest of House


Two Zone Fall/Spring House Pyrethrin Air Concentration
Pyrethrin (mg/m3)
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0
4
8
12
16
20
24
Elapsed Time (Hours)
Kitchen
TWA
Rest of House