

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



OFFICE OF CHEMICAL SAFETY AND  
POLLUTION PREVENTION

**MEMORANDUM**

Date: October 4, 2011

SUBJECT: **Pyrethroid Cumulative Risk Assessment**

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MRID No.: NA

40 CFR: NA

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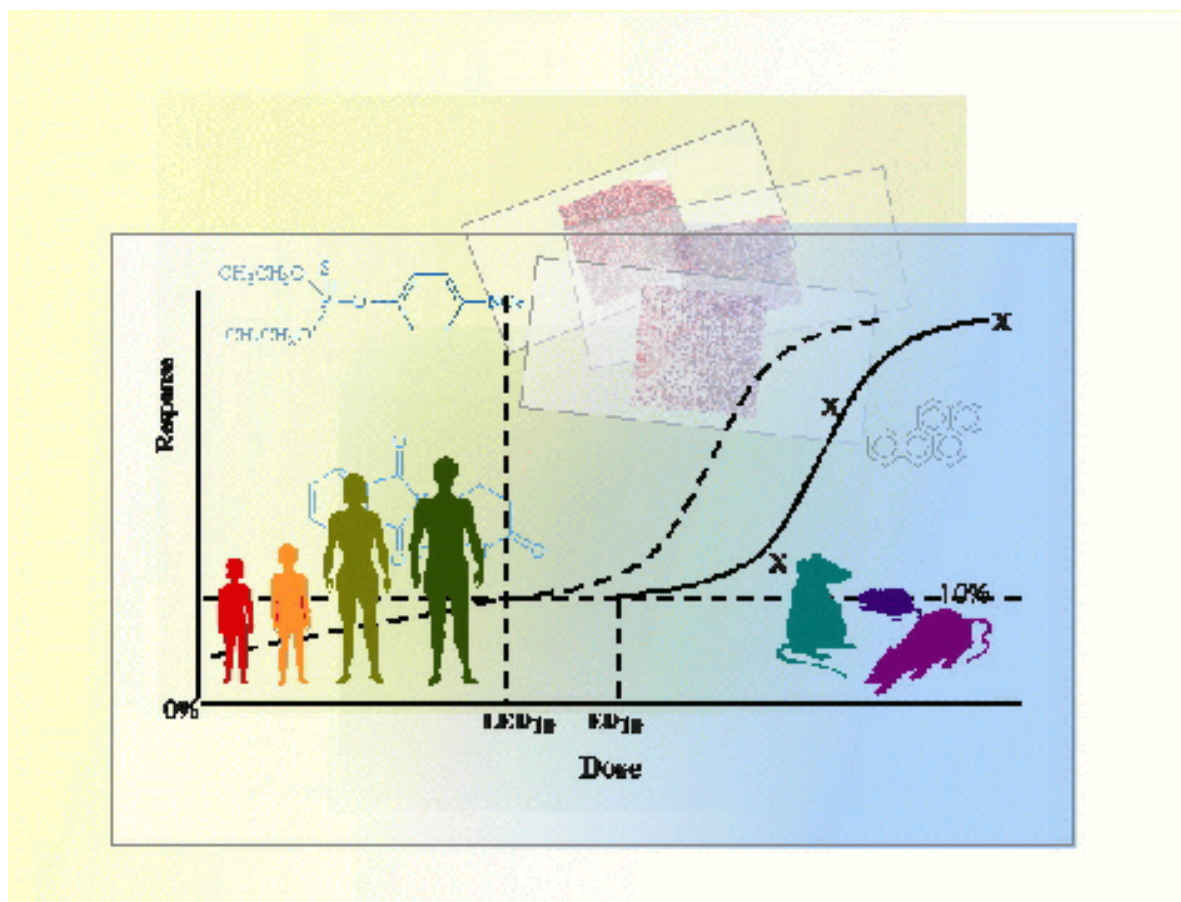
*[Signature]* 10/4/11

TO: **Richard P. Keigwin, Jr.**  
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Attached please find the human health cumulative risk assessment for the class of pesticides known collectively as the pyrethroids. The assessment incorporates multiple high-end inputs and combines the highest exposures/risk estimates across all pathways in a deterministic fashion resulting in a screening level assessment which is highly conservative and health protective. This cumulative assessment considered all registered uses of pyrethrins/pyrethroids and included exposure from food, drinking water and residential settings from the oral, dermal and inhalation routes of exposure. This screening level assessment supports the conclusion that cumulative estimated risks from existing pyrethrins/pyrethroid uses are not of concern. Further, there is sufficient room in the pyrethroid cumulative risk cup to support consideration of new pyrethroids (i.e., currently unregistered pyrethroid pesticides) and new uses of existing pyrethroids having similar toxicity profiles and use patterns to those in this assessment.

<b>Chemical</b>	<b>PC Code</b>	<b>CAS No.</b>
Allethrin	004001	584-79-2
Bioallethrin	004003	28057-48-9
S-Bioallethrin	004004	28434-00-6
D-Allethrin	004005	84030-86-4
Esbiothrin	004007	84030-86-4
Bifenthrin	128825	82657-04-3
Cyclethrin	004052	97-11-0
Cyfluthrin	128831	68359-37-5
Cyfluthrin, beta-	118831	68359-37-5
Cyhalothrin	128867	68085-85-8
Cyhalothrin, lambda-	128897	91465-08-6
Cyhalothrin, gamma-	128807	76703-62-3
Cypermethrin	109702	52315-07-8
Cypermethrin, alpha-	209600	67375-30-8
Cypermethrin, beta-	109902	65731-84-2
Cypermethrin, zeta-	129064	52315-07-8
Cyphenothrin	129013	39515-40-7
Deltamethrin	097805	52918-63-5
Esfenvalerate	109303	66230-04-4
Fenvalerate	109301	51630-58-1
Fenfluthrin	109705	75867-00-4
Fenpropathrin	127901	39515-41-8
Imiprothrin	004006	72963-72-5
Metofluthrin	109709	240494-70-6
Permethrin	109701	52645-53-1
Prallethrin	128722	23031-36-9
Pyrethrins (not synthetic)	069001	8003-34-7
Resmethrin	097801	10453-86-8
Sumethrin (phenothrin)	069005	26002-80-2
Tau-fluvalinate	109302	102851-06-9
Tefluthrin	128912	79538-32-2
Tetramethrin	069003	7696-12-0
Tralomethrin	121501	66841-25-6

# Pyrethrins/Pyrethroid Cumulative Risk Assessment



U.S. Environmental Protection Agency  
Office of Pesticide Programs  
October 4, 2011

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## 1.0 Introduction

With the passage of the Food Quality Protection Act of 1996 (FQPA), EPA is required to consider available information concerning the cumulative effects on human health resulting from exposure to multiple chemicals that have a common mechanism of toxicity when making decisions related to pesticide tolerances. Pyrethroids are a class of synthetic insecticides which are structurally based on the pyrethrins, botanical insecticides extracted from *Chrysanthemum cinerariaefolium* (Soderlund et. al. 2002). Pyrethrins are potent insecticides with relatively low mammalian toxicity but are sensitive to air and light. Hence, the use of pyrethrins for crop protection and to control disease-carrying insects is limited. With an altered structure, the pyrethroids are more photostable, while retaining the insecticidal activity of the pyrethrins. Thus, pyrethroids are widely used today in agriculture and in medical and veterinary products. The Agency has determined that a growing class of pesticides, the naturally occurring pyrethrins and synthetic pyrethroids, has a common mechanism of toxicity and are thus subject to cumulative risk assessment under the FQPA.

The cumulative risk assessment discussed in this document incorporates multiple high-end inputs and combines the highest exposures/risk estimates across all pathways in a deterministic fashion resulting in a screening level assessment which is highly conservative and health protective. This cumulative assessment considered all registered uses of pyrethrins/pyrethroids and included exposure from food, drinking water and residential settings from the oral, dermal and inhalation routes of exposure. Having completed this screening level assessment, the Agency concludes that cumulative estimated risks from existing pyrethrins/pyrethroid uses are not of concern.

The Agency also concludes that there is sufficient room in the pyrethroid cumulative risk cup to support consideration of new pyrethroids (i.e., currently unregistered pyrethroid pesticides) and new uses of existing pyrethroids having similar toxicity profiles and use patterns to those in this assessment given the multiple conservative inputs into the assessment. Per Agency policy, all new uses/new pyrethroid registration actions submitted to the Agency will undergo a single chemical assessment and also an evaluation of their potential contributions to cumulative risk. But the Agency believes that most of these are unlikely to have a significant impact on this screening-level cumulative assessment, provided they meet the parameters outlined above.

Details of the cumulative risk assessment process can be found in the OPP guidance document entitled *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA 2002). Briefly summarized here, the cumulative risk assessment (CRA) is developed by a multi-step process. The first step is the identification of a group of pesticides, called a Common Mechanism Group (CMG), which induce a common toxic effect by a common mechanism of toxicity. Pesticides are determined to have a “common mechanism of toxicity” if they act the same way in the body – that is, the same toxic effect occurs in the same organ or tissue by essentially the same sequence of major biochemical events. Once a CMG is established, the next step is to evaluate registered and proposed uses for each CMG member in order to identify potential exposure pathways (food, drinking water, residential) and routes

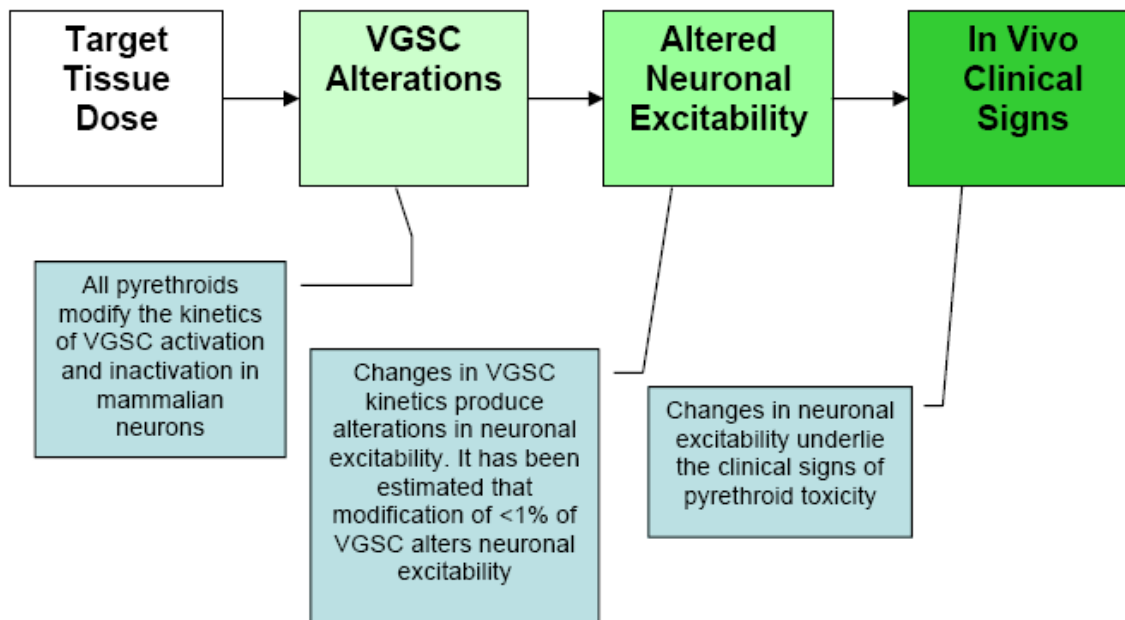
(i.e., oral, inhalation, dermal). During the hazard characterization phase, the various endpoints associated with the common mechanism of toxicity are identified, as well as the test species/sex that might serve as a uniform basis for determining relative potencies among the chemicals of interest. The common effect is also evaluated to determine if it is expressed across all exposure routes and durations of interest for each CMG member. The temporal aspects (e.g., time to onset and peak effects, duration of effects, and time to recovery) of the common mechanism of toxicity are characterized to determine the exposure durations relevant for the common toxic effect. As part of the process, it is important to determine which chemicals from the CMG should be included in the quantification of cumulative risk. Therefore a subset of the CMG called the cumulative assessment group (CAG) is identified which excludes those CMG members which have a minimal toxic contribution to the cumulative hazard or are limited to minor exposure pathways, routes, or uses. A dose response analysis is performed for each CAG member to determine its toxic potency for the common toxic effect. When physiologically-based pharmacokinetic (PBPK) models are not available, EPA uses the relative potency factor (RPF) method to determine the combined estimated risk associated with exposure to the members of the CAG. Briefly, the RPF approach uses an index chemical as a point of reference for comparing the toxicity of the other members of the CAG. A point of departure is determined for the index chemical and relative potency factors are calculated (i.e., the ratio of the toxic potency of a given chemical relative to that of the index chemical). RPFs are used to convert exposures of all chemicals in the CAG to exposure equivalents of the index chemical. A quantitative cumulative risk assessment is conducted by comparing the exposure equivalents to the point of departure for the index chemical across all pertinent exposure routes and durations. The last step in the CRA process is to characterize risk (i.e., an appraisal of the science supporting the risk assessment including choices made about methods, strengths and limitations of the available data, and assumptions).

The Agency's common mechanism grouping decision and screening level cumulative risk assessment for the pyrethrins and pyrethroid pesticides are presented in this document. Throughout the remainder of the document, references to the "pyrethroid CRA" include consideration of both the naturally occurring pyrethrins and the synthetic pyrethroid chemicals.

## 2.0 Determining the Common Mechanism & Establishing the CMG

As previously noted, the first step in conducting a cumulative risk assessment is the identification of a Common Mechanism Group (CMG), chemicals that induce a common toxic effect by a common mechanism of toxicity. Pesticides are determined to have a "common mechanism of toxicity" if they act the same way in the body – that is, the same toxic effect occurs in the same organ or tissue by essentially the same sequence of major biochemical events. In 2009, the Agency developed the *"Draft Science Policy Paper: Proposed Common Mechanism Grouping for the Pyrethrins and Synthetic Pyrethroids"* which proposed the common mode of action for pyrethroids. This common mechanism grouping is based on 1) shared structural characteristics; and 2) shared ability to interact with voltage-gated sodium channels (VGSC), resulting in disruption of membrane excitability in the nervous system, and 3)

ultimately neurotoxicity characterized by two different toxicity syndromes (Figure 2.0). The steps involved in this common toxicity pathway are summarized below. (USEPA 2011a). This proposal was reviewed and supported by the FIFRA Scientific Advisory Panel (SAP)<sup>1</sup>.

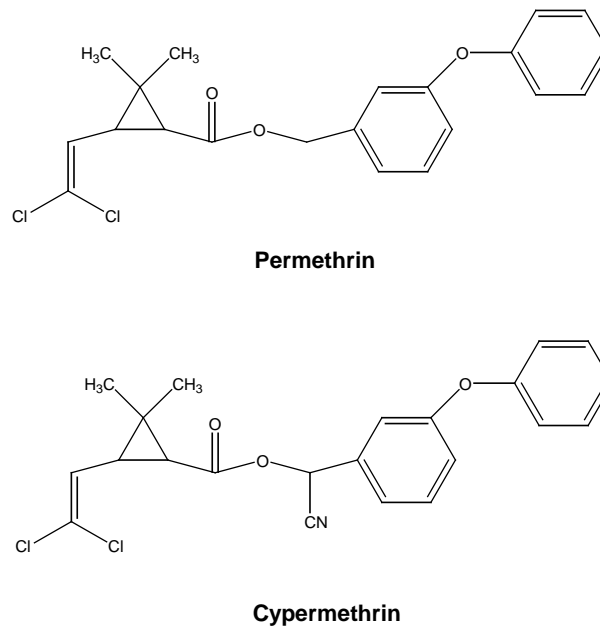


**Figure 2.0. Common Toxicity Pathway of the Pyrethrins & Pyrethroids**

## 2.1 Pyrethroid Structure

Pyrethroids are composed of two basic structural moieties; an acid and an alcohol. For first generation pyrethroids, such as allethrin, tetramethrin, and resmethrin, the acid portion is based on chrysanthemic acid, a cyclopropane ring bonded to a carboxylic acid moiety and a variety of halogenated and non-halogenated substituents. More recently developed pyrethroids, such as fenvalerate, do not have a cyclopropane ring. The alcohol portion is either a primary or a secondary alcohol, which is bound to a variety of heterocyclic structures. In addition, several of the pyrethroids have a cyano substituent bound to the  $\alpha$ -methylene of the alcohol, which results in enhanced toxicity of the compound. Pyrethroids lacking the  $\alpha$ -cyano substituent are generally termed Type I compounds and the pyrethroids with the  $\alpha$ -cyano substituent are generally termed Type II compounds. Figure 2.1, below, shows the structures of a Type I pyrethroid, permethrin, and a Type II pyrethroid, cypermethrin.

<sup>1</sup> [http://www.epa.gov/scipoly/sap/meetings/2007/august/pyrethroidpbpk\\_sap\\_2007\\_finalv1.pdf](http://www.epa.gov/scipoly/sap/meetings/2007/august/pyrethroidpbpk_sap_2007_finalv1.pdf)



**Figure 2.1. The Structures of Permethrin (Type I) and Cypermethrin (Type II)**

## 2.2 Voltage Gated Sodium Channels (VGSCs)

The naturally occurring pyrethrins and synthetic pyrethroids share the same mode of action, namely the interaction VGSCs (Narahashi 1996; Soderlund et. al. 2002; Shafer et. al. 2005; Weiner et. al. 2009). The effects of pyrethroid exposure on neuronal tissue (both insects and mammals) have been extensively reviewed (Soderlund and Bloomquist 1989; Vijverberg and Bercken 1990; Narahashi 1992; Bloomquist 1993; Clark 1995; Soderlund 1995; Bloomquist 1996; Narahashi 1996). Pyrethroids delay the inactivation of affected VGSCs, allowing for an increase in sodium ion influx and resulting in delayed repolarization. The delay is more pronounced in cyano-containing (Type II) pyrethroids ( $\gg 200$  ms) resulting in depolarization-dependent block of the neuronal action potentials and toxicity. The delay is considerably shorter for non-cyano (Type I) pyrethroids (20ms) and results in repetitive firing of action potentials and toxicity. Mixed-Type pyrethroids (*e.g.* esfenvalerate and fenpropathrin) produce delays intermediate between the characteristic Type I and Type II pyrethroids.

Figure 2.2 depicts generalized pyrethroid effects on individual channels, whole-cell sodium currents, and action potentials (extracted from Shafer et. al. 2005). Depolarization opens VGSCs (top left) allowing sodium to enter the cell. To limit sodium entry and depolarization length, VGSCs inactivate and must return to a “resting” state before reopening. Pyrethroids inhibit the function of two different “gates” that control sodium flux through VGSCs (top right), delaying inactivation (indicated by double arrows between states) of the channel and allowing continued sodium flux (Open\*). If sodium current through an entire cell is measured, depolarization leads to a rapidly inactivating current under normal circumstances (bottom left, Sodium Current). Pyrethroid-modified VGSCs remain open when depolarization ends (bottom right, Sodium Current), resulting in a “tail” current (the notch at the end of example currents). If

membrane voltage is examined, depolarization under normal circumstances generates a single action potential (bottom left). VGSCs modified by type I compounds (bottom right, Action Potential) depolarize the cell membrane above the threshold for action potential generation, resulting in a series of action potentials (repetitive firing). Type II compounds cause greater membrane depolarization, diminishing the sodium electrochemical gradient and subsequent action potential amplitude. Eventually, membrane potential becomes depolarized above the threshold for action potential generation (depolarization-dependent block) (Shafer et. al. 2005).

While interaction with the VGSC has been established as a key event by the Agency, pyrethroids have been reported to inhibit other types of ion channels, including chloride-permeable ion channels, voltage-gated calcium channels and ligand-gated chloride channels (Vijverberg and Bercken 1990; Narahashi 1996; Narahashi et. al. 1998; Ray and Forshaw 2000; Ray 2001; Soderlund et. al. 2002; Burr and Ray 2004; Shafer and Meyer 2004). It has been suggested that pyrethroid actions at these separate target sites combine to prolong neuronal membrane depolarization, resulting in massive neurotransmitter release (Clark and Brooks 1989). While pyrethroid actions on VGSCs and neuronal excitability are well understood, information on the other channels were conducted using different experimental models and are often contradictory (Shafer and Meyer 2004; Clark and Symington 2008; Cao et. al. 2011b). Thus, relative to sodium channels, the level of evidence supporting modes of action via other channels is not compelling.

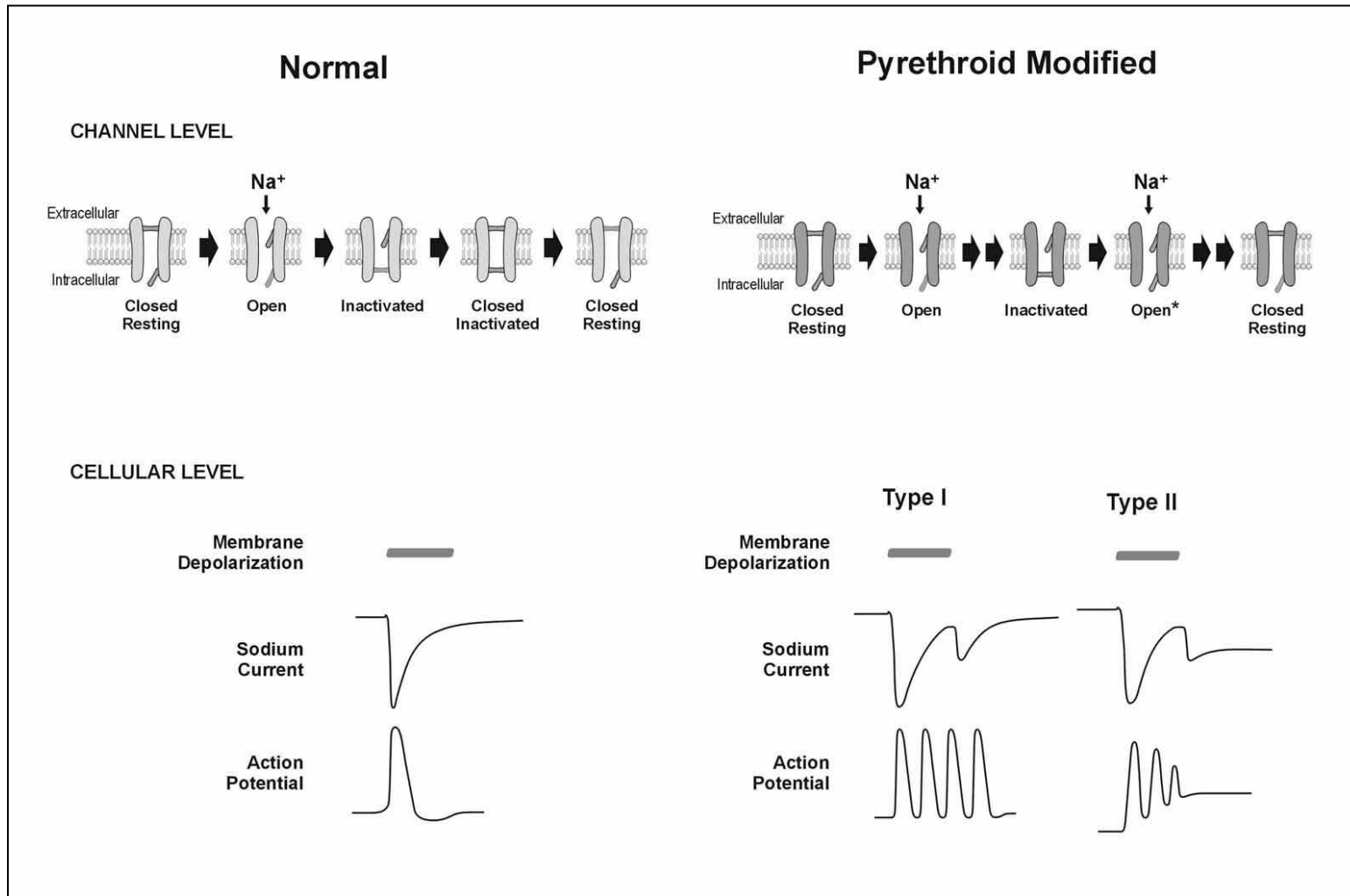


Figure 2.2. Effects of pyrethroids on Na channels, currents, and action potentials (From Shafer et al. (2005))

## 2.3 *In vivo* Toxicity

High doses of pyrethroids in laboratory animals result in one of two syndromes; the T-syndrome associated with Type I pyrethroids, and the CS-syndrome associated with Type II pyrethroids. The neurotoxic behaviors elicited by Type I pyrethroids are aggression, hyperexcitability, fine tremor, prostration with coarse whole body tremor, increased body temperature, coma and death. These neurobehavioral responses are termed the T-syndrome because of the fine tremors induced by the Type I pyrethroids. For Type II pyrethroids, the neurotoxic behaviors include pawing and burrowing, salivation, hyperexcitability, abnormal hind limb movements, coarse whole body tremor, sinuous writhing, coma and death. These neurobehavioral responses are termed the CS-syndrome for the choreoathetosis (i.e., whole body writhing) and salivation. Some pyrethroids such as fenpropathrin and esfenvalerate, are considered mixed (Type I/II) because they elicit mixed behaviors of both the T- and CS-syndromes. The T- and CS-syndromes are considered to be acute responses to pyrethroid exposure and are dose-dependent. In mammals, the onset of neurobehavioral effects occur within a few minutes to over an hour, depending on the route of exposure and chemical, but can take 2-8 hours to peak. Recovery from pyrethroid toxicity is rapid, typically within 24-48 hours. Mammals, unlike insects, have extensive enzyme systems capable of metabolizing and detoxifying the pyrethroids. This difference in physiology makes pyrethroids an order of magnitude less toxic in mammals compared to insects.

## 2.4 CMG for CRA

At the present time, EPA has designated the naturally occurring pyrethrins and synthetic pyrethroids as a common mechanism grouping for purposes of conducting a cumulative risk assessment under the FQPA. Consistent with the screening-level nature of this cumulative assessment, the pyrethroid CRA includes an interim decision to evaluate the Type I and Type II pyrethroids in a single group (i.e., one risk cup) (USEPA 2011a).

In the 2009 CMG proposal, EPA considered the science that supported separating the pyrethroid CMG into two subgroups representing Type I and II pyrethroids. This subgrouping is consistent with historical categorization of pyrethroids and is supported by *in vitro* and *in vivo* studies from both older studies and new research. As described previously in Section 2.1, the designation of Type I and Type II pyrethroids is based upon differences in structure; the  $\alpha$ -cyano moiety is absent in Type I pyrethroids (e.g., permethrin) and present in Type II (e.g., deltamethrin). The absence/presence of the  $\alpha$ -cyano group is correlated with length of time the sodium channel is inactivated (-CN=shorter; +CN=longer) which in turn corresponds with the two distinct toxicity syndromes (-CN=T syndrome; +CN=CS syndrome). Two pyrethroids, esfenvalerate and fenpropathrin, though structurally similar to Type II pyrethroids, are considered mixed Type I/II because they demonstrate properties of both groups during *in vitro* and *in vivo* evaluations. As noted above, this screening level assessment demonstrates that the cumulative estimated risk to pyrethrins and pyrethroids is not a concern. In the future, if the

Agency determines that a more refined cumulative assessment is appropriate, the Agency may consider evaluating the cumulative risk to the Type I and Type II pyrethroids separately.

### 3.0 Cumulative Assessment Group (CAG)

As part of the cumulative risk assessment process, it is important to determine which chemicals from the CMG should be included in the quantification of cumulative risk. Therefore, a subset of the CMG called the CAG is identified which excludes those CMG members with minimal toxic contribution to the cumulative hazard or those with limited uses or minor exposure pathways or routes.

For the pyrethroid CAG, those chemicals which pose very low risk were considered unlikely contributors to cumulative risk and were precluded from the assessment. Criteria for not including CMG chemicals in the CAG include:

- Pyrethroids with low hazard potential for the common mechanism endpoint(s) were excluded. Specifically, tetramethrin and sumithrin were excluded due to no observed adverse effects at 5000 mg/kg in a specially designed functional observational battery for evaluating pyrethroid toxicity syndromes in the rat.
- For the dietary exposure assessment, pyrethroids without any residues in any crop in the Pesticide Data Program monitoring data were not included in the dietary assessment;
- For the residential exposure assessment, the Agency focused on only those residential uses that have potential for significant exposure (turf, pets, gardens, and indoor uses). Only pyrethroids with these residential uses were included in the CAG and assessed in the residential part of the CAG. In addition, those pyrethroids with residential uses that do not have a potential for significant exposure or have an insignificant amount of use (*e.g.*, such as metofluthrin which is only registered for use in personal insect repellent systems) were considered minor contributors to the residential part of the CRA and therefore not included in the CAG.

A total of 15 synthetic pyrethroids and the naturally occurring pyrethrins (including pyrethrins I and pyrethrins II) are included in the CAG and are presented. Table 3.0 contains a list of pyrethroids registered with the Agency, highlighting those that were included in the CAG and offering brief explanations for those that were not.

Pyrethroid Cumulative Risk Assessment

Chemical Name <sup>1</sup>	Type	Registrations		PDP Data		Included in Screening Level Pyrethroid CRA/Comments <sup>3</sup>
		Food Use Registration	Non-food Use Registration (e.g. Residential Uses)?	PDP Data	PDP Detects	
<b>Allethrin</b>	<b>I</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Bifenthrin</b>	<b>I</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Cyfluthrin</b>	<b>II</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Cyhalothrin</b>	<b>II</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Cypermethrin</b>	<b>II</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Cyphenothrin</b>	<b>I</b>		<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Deltamethrin</b>	<b>II</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included – index chemical</b>
<b>Fenpropathrin</b>	<b>I/II</b>	<b>X</b>	-	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Fenvalerate<sup>2</sup> /Esfenvalerate</b>	<b>I/II</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
Flucythrinate	II	X		X		No PDP detects; not included in CAG
<b>Fluvalinate</b>	<b>II</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Imiprothrin</b>	<b>I</b>	-	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
Metofluthrin	I	-	X			No food use registrations and does not have major residential use registrations; not included in CAG
<b>Permethrin</b>	<b>I</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Prallethrin</b>	<b>I</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Pyrethrins</b>	<b>I</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
<b>Resmethrin</b>	<b>I</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>X</b>	<b>Included</b>
Sumithrin	I	X	X	X	X	Did not elicit a toxic response consistent with the common mechanism at limit dose of 2000 mg/kg; not included in CAG
Tefluthrin	II	X	-	X	-	No PDP detects and no residential uses; not included in CAG
Tetramethrin	II	X	X	X	X	Did not elicit a toxic response consistent with the common mechanism at limit dose of 2000 mg/kg; not included in CAG
<b>Tralomethrin<sup>4</sup></b>	<b>II</b>	<b>X</b>	<b>X</b>	<b>X</b>	-	<b>Included</b>

<sup>1</sup> Refers to all isomeric variations.

<sup>2</sup> The registration for Fenvalerate has recently been cancelled and therefore future uses are not expected.

<sup>3</sup> Pyrethroids that do not have registered uses were not included in the CAG (i.e., acrinathrin, barthrin, bioethanomethrin, cismethrin, cyclethrin, cycloprothrin, dimefluthrin, dimethrin, empenthrin, fenfluthrin, furethrin, profluthrin, pyresmethrin, terallethrin, and transfluthrin).

<sup>4</sup> Due to recent cancellation of uses (<http://www.federalregister.gov/articles/2010/11/17/2010-28823/tralomethrin-notice-of-receipt-of-request-to-voluntarily-cancel-pesticide-registrations>), tralomethrin is included in the CAG, but will not be assessed as part of the cumulative risk assessment.

## 4.0 Hazard Assessment/Characterization

As described above, the Agency has designated a CMG for the pyrethroids (USEPA 2011a) based on the shared structural similarities and their shared ability to alter VGSCs. Further, the Agency has determined which members of the CMG should be quantitatively included in the cumulative risk assessment by designating the CAG with an interim decision to include both Type I and Type IIs together in a single CAG. Because at this time PBPK models are only available for a small number of pyrethroids (Permethrin - Tornero-Velez et. al. 2007; Deltamethrin - Godin et. al. 2010), this screening level cumulative assessment relies on the RPF approach using administered dose as the metric for quantifying chemical potency. In the RPF approach, the toxic potency of each chemical in the CAG is determined. One member of the CAG is selected as the index chemical which is used as the point of reference for standardizing neurobehavioral potency of the other members of the CAG. In the case of the screening level pyrethroid CRA, deltamethrin is being used as the index chemical.

The following discussion describes the Agency's approach for:

- Determination of the appropriate toxicity data for consideration in the CRA
- Determination of relative potency factors for each chemical in the CAG;
- Selection of the index chemical used as the point of reference to standardize the potency of each pyrethroid/pyrethrins;
- Establishment of a point of departure used to estimate potential risk for the oral, dermal, and inhalation routes of exposure; and
- Identification of the intra-species, inter-species, and FQPA safety factors

### 4.1 Endpoints and Toxicology Studies

As stated previously, relative potency for cumulative risk assessments should be based, whenever possible, on data from the same species and sex to provide a uniform measure of relative potency among the cumulative assessment group (USEPA 2002). The following section describes the studies evaluated and scientific factors considered in establishing a uniform measure of potency.

#### 4.1.1 Establishing a Uniform Measure of Toxicity

##### 4.1.1.1 Common Mechanism Endpoint

In cumulative risk assessment, the focus of the hazard characterization is on the common mechanism effect(s) and relevant duration of exposure. Use of *in vivo* data from a precursor event is preferred over apical endpoints. However, in the case of pyrethroids, practical methods for evaluating pyrethroid effects on VGSC *in vivo* are not currently available (Shafer et. al. 2005). Additionally, *in vivo* biomarkers of toxicity are not available for use in cumulative risk assessment. Data from *in vitro* microelectro array studies (Losa et. al. 2009; Cao et. al. 2011a) using intact neuronal systems could potentially be used to consider relative potency. However,

using such *in vitro* studies in the absence of pharmacokinetic data and/or PBPK models to evaluate internal dosimetry of *in vitro* measures is problematic and would introduce significant uncertainty into the CRA. As such, the Agency has used these *in vitro* studies as qualitative characterization (See Hazard Characterization, Section 8.1) but not for quantitative relative potency calculations.

As recently reviewed (Wolansky and Harrill 2008) and discussed in OPP's CMG science policy paper (USEPA 2011a), many studies have shown that behavioral responses, particularly measured in the rat, can be used as sensitive indicators of pyrethroid toxicity. Table 4.1.1.1 provides a summary of several early behavioral studies with pyrethroids.

<b>Pyrethroid</b>	<b>Verschoyle and Aldridge (1980)</b>	<b>Lawrence and Casida (1982)</b>	<b>Gammon et. al. (1981)</b>
<b>Allethrin; S-Bioallethrin</b>	T	I	I
<b>Permethrin</b>	T	I	I
<b>Resmethrin</b>	T	I	I
<b>Fenpropathrin</b>	CS/T	I/II	I/II
<b>Esfenvalerate</b>	CS	II	II
<b>Cypermethrin</b>	CS	II	II
<b>Deltamethrin</b>	CS	II	II

More contemporary studies were designed to detect behavioral changes at a broad range of doses including both lower doses as well as high-doses. Some of these studies include evaluation of motor activity, coordination, neuromuscular response, tremors, acoustic startle response, learning and memory, somatosensory response, social/sexual interactions and behavior to handling, and the functional observational battery (FOB) (McDaniel and Moser 1993; Sheets et. al. 1994; Soderlund et. al. 2002(review); Wolansky et. al. 2006; Raffaele et. al. 2008; Wolansky and Harrill 2008(review); Breckenridge et. al. 2009). Given the lack of an *in vivo* biomarker for VGSC interaction, measures of behavior in laboratory animal studies are therefore considered appropriate endpoints for extrapolating risk to humans in the pyrethroid screening cumulative risk assessment.

The primary target organ of pyrethroids is the brain and therefore brain tissue concentration could potentially be a useful indicator of internal exposure. However, few studies have examined the brain concentration of pyrethroids and of these, only a small number of pyrethroids are represented (Deltamethrin (Anadón et. al. 1991; Sheets et. al. 1994; Kim et. al. 2008); resmethrin (White et. al. 1976; Brodie 1983); and permethrin (Khanna et. al. 2002)). Similar limitations prevent the use of blood plasma concentrations as an indicator of toxicity. The Agency is aware of efforts by the Council for the Advancement of Pyrethroid Human Risk Assessment (CAPHRA), a group of pyrethroid registrants and product formulators which is currently developing PBPK models for additional pyrethroids. As those research efforts progress, the Agency may, if appropriate, consider using such data in future revisions to the

CRA. However, in this absence of measures of internal dose for a sufficient number of pyrethroids, the Agency will use administered dose as the metric for estimating relative potency.

#### 4.1.1.2 Experimental Laboratory Studies with Behavioral Measures

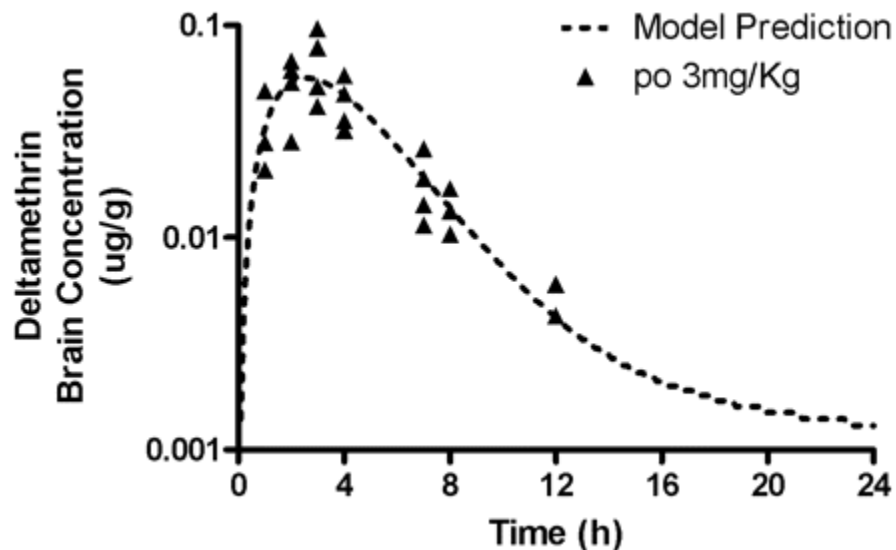
The Agency has evaluated multiple sources of data for potential endpoints, including guideline and non-guideline studies submitted for pesticide registration (Table 4.1.1.2), data developed by EPA’s Office of Research and Development (ORD), and other literature data. Under FIFRA, toxicology studies in various species (e.g., dog, mouse, rat and rabbit) are submitted to EPA. For the pyrethroids, toxicology studies in the rat provided the most extensive behavioral data for all routes and both sexes. Studies in the dog often provide sensitive endpoints (particularly through the observation of tremors) for use in single chemical, aggregate risk assessment. However, studies in the rat are the focus for cumulative risk assessment as rats are most often evaluated in neurotoxicity studies where a broad array of neurobehaviors are evaluated. Specifically, rat neurotoxicity studies may include measures of behavior or response to stimuli such as motor activity, auditory startle response, grip strength, righting ability, in-cage and handling observations and physiological parameters such as body temperature or catalepsy, and, are therefore more likely to detect adverse responses to pyrethroids compared to other guideline studies. Appendix 1 (*Toxicity Data for Screening Level Cumulative Risk Assessment*) provides a summary of guideline studies considered as sources of data for estimating relative potency the CRA. Noteworthy literature sources of behavioral studies with pyrethroids include an acute motor activity study (Wolansky et. al. (2006) and two special FOB studies (Herberth (2010) and Weiner et. al. (2009)), which are discussed in detail below.

<b>Guideline #</b>	<b>Type of Study</b>
870.3100	90-day Toxicity Study in Rodents
870.3150	90-day Toxicity Study in Non-Rodents
870.3200	21/28 Dermal Toxicity
870.3465	90-day Inhalation Toxicity
870.3700	Prenatal Developmental Toxicity Study
870.3800	Reproduction and Fertility Effects
870.4100	Chronic Toxicity
870.4200	Carcinogenicity
870.4300	Combined Toxicity/Carcinogenicity
870.6200	Neurotoxicity Screening Batter
870.6300	Developmental Neurotoxicity Study

#### 4.1.1.3 Scientific Considerations in Evaluating Experimental Animal Studies

As noted above, one of the most important components in cumulative hazard assessment is establishing a uniform measure of potency such that the relative rank of each pesticide can be confidently evaluated. There are properties of pyrethroids that must be taken into account when evaluating existing experimental laboratory studies.

- *Duration of Exposure:* The toxicokinetic and toxicodynamic properties of pyrethroids create a narrow window for capturing peak neurotoxic effects; peak effects may last from only a few minutes to over an hour. Pyrethroids are acutely toxic and do not increase in potency with repeated dosing, as demonstrated in guideline studies. The rapid metabolism of pyrethroids is related to the acute nature of the neurotoxic effects. Oxidative and hydrolytic enzymes metabolize pyrethroids quickly rendering these pesticides inactive following *in vivo* exposure (Anand et. al. 2006). For example, plasma half-lives following neurotoxic doses are generally 9-15 hours; that is it takes approximately 9-15 hours for the plasma concentration of the pyrethroid to be reduced by 50%. Brain tissue half-lives may be slightly longer, depending on the pyrethroid (Anadón et. al. 1991; Anadón et. al. 1996; Anand et. al. 2006; Kim et. al. 2008). Plasma half-lives generally decrease in a dose-dependent manner such that lower doses generally have significantly shorter half-lives (< 6 hours) (Kim et. al. 2008). Therefore, human exposures which are expected to be orders of magnitude less than the experimental animal studies would be expected to be considerably shorter still. Because of the rapid clearance rates, pyrethroid concentrations do not accumulate in tissues following subsequent exposures. Thus, given the short temporal nature of pyrethroids, the CRA focuses on acute (24 hour), single dosing studies and involves exposure periods of only 24 hours.
- *Timing of behavioral measures:* The determination of the time-to-peak for behavioral effects and/or target tissue concentration is a critical component of study design for pyrethroids. As shown in Figure 4.1.1.3, levels of deltamethrin, a Type II pyrethroid, in brain tissue peaking 2-3 hours after a single oral bolus dose of 3 mg/kg (i.e., minimally neurotoxic effects), followed by a rapid decrease in concentration (Godin et. al. 2010). In general, brain concentration time course typifies the progression of neurotoxic signs in mammalian species, which appear within 1 hour of oral exposure, peak within 4-8 hours, and recover in 12–48 hours (Wolansky and Harrill 2008). If the animals are not examined near these peak tissue concentrations, the potency of the pyrethroid may be underestimated. As such, for purposes of determining relative potency, the Agency has focused on studies which measured effects at or near the peak time of effect.



**Figure 4.1.1.3. Model simulation and time course of brain concentration of deltamethrin after an oral dose. Dashed line represents the best-fit curve to the data points. Adapted from Godin, DeVito et al. (2010).**

- Gavage dosing vs. Feeding:* Longer term repetitive dosing studies are typically conducted using dietary administration whereas acute, single dose studies tend to use gavage dosing. The extended exposure period (i.e., over 12 hours during feeding) of dietary administration compared to the bolus dose in capsule and acute studies, results in much lower peak plasma/brain concentrations. As a result, neurotoxicity consistent with the pyrethroid mode of action (MOA) is more commonly observed in acute, gavage studies in rats; thus, such *gavage studies are being used in the CRA.*
- Vehicle & Volume in Gavage Dosing:* Variations in laboratory protocols such as dosing vehicle and volume, lead to altered toxicokinetics and inconsistent results. For example, the Effective Dose (ED<sub>50</sub>) for deltamethrin in an acute oral motor activity study was 5.1 mg/kg when administered with corn oil, but > 1000 mg/kg when carboxymethylcellulose was used as the vehicle (Crofton et. al. 1995). In another acute oral study, bifenthrin was administered at 1 ml/kg or 5 ml/kg in corn oil to rats. The higher dose volume decreased potency by 50% as determined by motor activity and other observational assays (Wolansky et. al. 2007). Many of the guideline studies and those available in the literature contain such variations making cross-study comparisons of pyrethroid potency difficult. This is shown in Table 4.1.1.3 where the vehicle and volume vary considerably across studies making quantitative comparisons challenging. In contrast to the guideline studies, two studies - Wolansky et al. (2006) and the special WIL FOB (Herberth 2010; Weiner et. al. 2009) - used a consistent (within study) vehicle and volume for each chemical evaluated. Specifically, Wolansky used 1 ml/kg corn oil for assessing motor activity in 11 pyrethroids and the WIL FOB study used 5 ml/kg corn oil in the evaluation of 17 pyrethroids; thus making the results across multiple pyrethroids comparable within each of these studies.

Table 4.1.1.3. Guideline Acute Oral Gavage Studies in the Rat.		
Pyrethroid <sup>1</sup>	MRID	Vehicle; Volume
Allethrin; S-Bioallethrin	44517801	(1% CMC; 10 ml/kg)
Bifenthrin	44862102	No vehicle
Cyfluthrin, beta-cyfluthrin	00157802	2% aqueous cremophor EL
lambda-cyhalothrin	44861510	Corn oil; 10ml/kg
Cypermethrin; zeta-cypermethrin	43152001	Corn Oil, 5% solution, total volume varied by dose group
	44962201	No Vehicle
Deltamethrin	44557901	Corn Oil; 5 ml/kg
Esfenvalerate	45228301	(Corn Oil; 10 ml/kg)
Fenpropathrin	473745605	Corn oil, 5 mL/kg
Fluvalinate, tau	43433901	Corn oil, 10 ml/kg
Permethrin	43046301	Corn Oil, 1-30 ml/kg
Pyrethrins	42925801	Corn oil vehicle 5-10% pyrethrins, total volume varied by dose group

<sup>1</sup>This table captures all of the Guideline acute neurotoxicity studies available for the pyrethroids included in the CAG. Cyphenothrin, imiprothrin, and prallethrin, although included in the CAG, do not have acute neurotoxicity studies.

- *Consistent evaluation of behavioral endpoints:* There is considerable variability among laboratories in scoring procedures used in behavioral measures thus making across laboratory comparisons of behavioral findings challenging. Moreover, assessing rat behavior can be challenging and is often subjective. Therefore, it is important for individuals doing such measurements in the laboratory to be well-trained. Thus, given the inter-laboratory variability inherent in behavioral studies, it is desirable for relative potency to be based, to the extent possible, on data collected from a single laboratory.

#### 4.1.1.4 Selection of Critical Study for Estimating Relative Potency

Section 4.1.1.3 described desirable characteristics of experimental laboratory studies for use in establishing a uniform measure of potency for the pyrethroids. Based on a review of the available rat studies, the Agency has concluded that guideline studies submitted for pesticide registration do not provide sufficient data for establishing relative potency. As shown in table 4.1.1.3, the vehicle and volume used in gavage dosing vary considerably among pyrethroids thus making quantitative comparisons difficult. Moreover, some of these studies do not measure behavioral endpoints at or near the time of peak effect and the behavioral scoring procedures used in these studies vary considerably among laboratories. Similarly, the differences in study design among many literature studies limits their usefulness for quantifying relative potency across a large number of pyrethroids.

There are, however, two recently conducted large literature studies available which provide acute oral neurobehavioral data appropriate for establishing a uniform measure of potency.

- Wolansky et. al. (2006) evaluated 11 pyrethroids after a single oral dose using a common vehicle (corn oil) and volume (1 mL/kg). The Wolansky study measured motor activity at the time of peak effect after exposure. All 12 chemicals were evaluated on the same instrument by the same scientist. Dose-response relationships were determined using 6-11 doses per pyrethroid and 3-18 rats per dose group, minimizing variability and increasing the confidence in the benchmark dose (BMD) estimates determined from this study. Increasing exposure to a pyrethroid generally decreased the rat's ability to navigate through the maze and therefore reduced motor activity. Motor activity is considered an apical endpoint because it measures alterations in the activity level of an intact rat. However, altered movement patterns can result from any number of adverse outcome pathways resulting in general malaise or altered energy levels, and does not necessarily measure the targeted mechanism of action (i.e., interaction with the VGSC). Although the Wolansky study provides a potential data source for a uniform measure of potency, because of the lack of specific relevance to the common mechanism of action, this study is less desirable for the CRA.
- Two special FOB studies conducted by the WIL laboratory and supported by pesticide registrants evaluated 17 pyrethroids in a comprehensive FOB. Twelve were evaluated in an initial study (Weiner et. al. 2009) and 5 more in a second study<sup>2</sup> (Herberth 2010). The special FOB WIL study considered behavioral changes at the time of peak effect, using a common vehicle (corn oil) and volume (5 mL/kg). Each pyrethroid was evaluated by the same technicians who were specially trained to recognize pyrethroid toxicity. Therefore potency values generated in the Weiner et. al. (2009) and Herberth (2010) studies are directly comparable between studies since a conservative and uniform measure of toxicity was employed in the two special FOB WIL studies. These special studies examined many behaviors, including key ones for evaluating neurotoxicity specific to pyrethroids. Unlike motor activity which measures general behavior patterns, such as was measured in the Wolansky study, the FOB measures behaviors that are associated with the central and peripheral nervous system. For this reason, the specially designed FOB is more reflective of toxicity directly related to the pyrethroid mode of action and therefore, more appropriate for defining relative potencies related to pyrethroid cumulative risk. It is notable that the key parameters identified in the WIL FOB study are directly relevant to the Type I and Type II syndromes. Specifically, hyperthermia tremors, and clonus are important in Type I pyrethroids and hypothermia, salivation, and mobility are key for Type II pyrethroids (see Section 4.2 and 4.3 below).

***Given the strengths of the study design of the special FOB WIL study and the relevance of behavioral measures to pyrethroid toxicology, the Agency has determined that for the CRA, the special FOB WIL study provides the most robust source of data for the cumulative risk assessment.*** The Agency has used this study to derive RPFs and PoDs for the index chemical; the dose-response analysis is discussed in detail below.

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<sup>2</sup> Throughout the remainder of this document, the Weiner et al (2009) and Herberth (2010) studies conducted at the WIL laboratories will be collectively referred to as the "WIL study."

## 4.2 WIL FOB Study & Determining a Uniform Measure of Potency

### 4.2.1 Introduction

As described in the guidance document for cumulative risk assessment (USEPA 2002), dose-response modeling is preferred over the use of NOAEL/LOAELs (i.e., no- or lowest-observed-adverse-effect-levels) for determining relative toxicity potency. NOAELs and LOAELs can be greatly influenced by study dose selection and dose spacing and thus do not necessarily reflect the relationship between dose and response for a given chemical, nor do they reflect a uniform response across different chemicals. In the present analysis, benchmark dose (BMD) modeling has been used to determine the toxic potency of the pyrethroids, providing a constant threshold of toxicity for each pyrethroid and more uniform comparisons. EPA's draft BMD guidance (USEPA 2000) suggests that the central estimate on the BMD provides an appropriate measure for comparing chemical potency (i.e., RPF) and that the lower limit on the central estimate (i.e., BMDL) provides an appropriate measure for extrapolating risk (i.e., PoD for the index chemical in a cumulative risk assessment). The point of comparison for four of the least potent pyrethroids (cyphenothrin, d-allethrin, imiprothrin, and prallethrin) was based on selecting a dose used in the WIL FOB study (see Section 4.2.5.1 below).

The following sections provide a discussion of the WIL study and how the data from this study have been used by OPP to estimate relative potency for the oral route of exposure.

The WIL study is the most appropriate study available for determination of the pyrethroid potency because it reflects acute toxicity at the level of the common mechanism (i.e. neurotoxicity), standardizes testing conditions for a large number of pyrethroids (i.e. strain, vehicle, dosing volume), and reflects the most relevant route (oral) and duration (acute) of exposure. Furthermore, the WIL dosing levels are appropriate for determination of PoDs for this cumulative risk assessment. As indicated in the previous section, pyrethroids are rapidly metabolized *in vivo* by oxidative and hydrolytic enzymes. Doses that are sufficiently high enough to cause neurotoxicity overwhelm these clearance mechanisms and interfere with the proper functioning of the sodium channels. Human exposures are expected to be much lower, significantly less likely to saturate the metabolic processes, and therefore less likely to result in neurotoxicity.

As previously noted, the WIL study is a FOB study including numerous assays designed to quantify neurotoxicity caused by pyrethroids. The FOB is a series of evaluations to determine gross neurological function in the animal. In general, observations and short-duration tests are administered to determine effects on the autonomic, motor, and sensory systems. These simple tests take approximately 5-10 minutes after which rats are returned to their home cage. The FOB is a noninvasive procedure designed to detect gross functional deficits resulting from exposure to chemicals and to quantify neurotoxic effects. In the WIL study, observations included home cage handling, open field, sensory, neuromuscular, and physiological parameters, conducted at the time of peak effect (2 to 8 hours post-dose). In many cases, the

FOB measures behaviors that are closely associated with toxicity related to the central and peripheral nervous system. Studies have demonstrated the ability of a FOB to describe and differentiate the known pyrethroid syndromes (McDaniel and Moser 1993; Weiner et. al. 2009). For this reason, the FOB is more reflective of a toxicity directly related to the pyrethroid mode of action and therefore, more appropriate for defining relative potencies related to pyrethroid cumulative risk.

#### 4.2.2 WIL Study Design

Pyrethroids were administered as a single bolus dose via oral gavage using corn oil as the vehicle at 5 ml/kg. Ten adult male Crl:CD(SD)IGS BR rats were used per dose group. Numerous oral Guideline and literature studies conducted in both males and female rats indicate similar neurotoxic responses between the sexes, therefore the WIL study was restricted to a single sex. FOB measurements were taken at the pyrethroids respective time to peak effect for adverse neurological behaviors (as determined in previous pilot studies). Table 4.2.2 provides a summary of pyrethroids examined in the WIL study.

<b>Pyrethroid</b>	<b>Doses (mg/kg)</b>	<b>Time- to-peak-effect (hours)</b>
D-Allethrin <sup>b</sup>	200, 320, 500	2
S-Bioallethrin <sup>a</sup>	150, 200, 300	2
Bifenthrin <sup>a</sup>	40, 55	8
Beta-cyfluthrin <sup>a</sup>	12.5, 25, 45	2
Lambda-cyhalothrin <sup>a</sup>	10, 20	4
Cyphenothrin <sup>b</sup>	60, 100, 160	2
Cypermethrin <sup>a</sup>	65, 100, 150	4
Deltamethrin <sup>a</sup>	12.5, 25, 35	4
Esfenvalerate <sup>a</sup>	15, 25, 50	8
Fenpropathrin <sup>a</sup>	15, 30	2
Imiprothrin <sup>b</sup>	900, 1200, 1500	2
Permethrin <sup>a</sup>	200, 250	4
Prallethrin <sup>b</sup>	150, 250, 400	2
Pyrethrins	400, 800	4
Resmethrin <sup>a</sup>	350, 500, 750	4
Tefluthrin <sup>a</sup>	10, 15	8

<sup>a</sup>(Weiner et. al. 2009)

<sup>b</sup>(Herberth 2010)

#### 4.2.3 Results from the WIL & Severity Scoring

The Agency has reviewed both Weiner et. al. (2009) and Herberth (2010); data evaluation records (DERs) for these studies can be found as Appendices 2 and 3, respectively. In brief, a total of 46 neurobehavioral parameters were evaluated including home cage, handling, open field, sensory, neuromuscular and physiological observations. In the original (Weiner et al, 2009) study, the FOB data for 11 pyrethroids in addition to pyrethrins were analyzed using principle component analysis to determine dissimilarity/similarity across endpoints and

treatments (Breckenridge et. al. 2009). These pyrethroids were segregated into two composite factors, T including the Type I pyrethroids, and CS including the Type II pyrethroids. This analysis revealed that three endpoints sufficiently described each factor: T was comprised of hyperthermia, tremors, and clonic convulsions, and CS included hypothermia, salivation, and mobility. These results agreed well with the substantial literature describing the differential toxicity of Types I and II pyrethroids (Verschoyle and Aldridge 1980; Lawrence and Casida 1982; Gray 1985; Vijverberg and Bercken 1990). Thus from the 46 endpoints measured, there were a total of five endpoints accounting for the majority of the dose-response relationships and were capable of differentiating Type I and Type II pyrethroids. This was especially true for the pesticides showing clear differential effects whereas mixed type pyrethroids (e.g., esfenvalerate) showed characteristics of both syndromes.

For purposes of dose-response analysis for the CRA, the raw data from the WIL study for the five endpoints and 12 pesticides identified in the principle component analysis were converted using a severity scoring approach. Moser and colleagues have developed a procedure for normalizing individual data for all measures to a single 1-to-4 scale, where '1' reflects what was observed in control rats, and '4' reflects a rare occurrence in control rats. This approach has been used successfully for delineating profiles of effects of different classes of chemicals including pyrethroids (Moser 1991; McDaniel and Moser 1993; Moser et. al. 1995; Moser et. al. 1997).

Of the endpoints examined, only body temperature was a continuous variable; a continuous variable is one where any value may be recorded, including fractions, with no clear cut or sharp breaks between possible values. Tremors and convulsions are ordinal variables; an ordinal variable is a variable whose values are not numerical but have an ordering (e.g. low, medium, and high). Body temperature was determined at the time-to-peak-effect. Muscle tremors and clonic convulsions were observed in both the home cage and open field; the observation with the most severe effect was used for this analysis. For example, if muscle tremors were observed in both home cage and open field scenarios, but were more severe in the home cage, the severity score for the home cage tremors was used for the calculation of the severity score. Clonic convulsions were scored in a similar fashion. Essentially, continuous data (body temperature) were converted on the basis of the control group mean  $\pm$  multiples of standard deviation, and categorical data were converted based on severity of the original scoring criteria (Table 4.2.3). These scores were then summed for each animal to derive the T and CS composite severity scores.

Each animal was assigned a score from 3 to 12 for both T and CS. For example, if an animal did not demonstrate a dose-response in any of the 5 critical assays, it would have received a score of 3 for the T domain (1+1+1 = 3 for each T endpoint) and a 3 for the CS domain (1+1+1=3 for each CS endpoint). However, if it demonstrated a dose-response for hyperthermia, tremors, and/or clonus, it would have received a score of up to 12 (depending on the severity of the 3 endpoint responses) for T, and a score of 3 for CS (due to the lack of response in the hypothermia, salivation, and mobility assays). This example would be characteristic of a Type I pyrethroid. Conversely, an animal given a Type II pyrethroid would most likely have received a

score of 3 for T and up to 12 for CS. A mixed-type pyrethroid (e.g. fenpropathrin) would have demonstrated a dose response in tests for both the T and CS domains, resulting in T and CS scores between 4 and 12.

<b>Table 4.2.3. Conversion of Individual Data to Severity Scores to be Summed into the T or CS Domains.</b>			
<b>Endpoint</b>	<b>Severity conversion</b>	<b>Score</b>	<b>Domain</b>
Body temperature; hyperthermia	Within X to X+SD	1	T
	Between (X+SD) and (X+1.5SD)	2	
	Between (X+1.5SD) and (X+2SD)	3	
	>(X+2SD)	4	
Tremors	None	1	T
	Slight	2	
	Moderately coarse	3	
	Markedly to extremely coarse	4	
Clonic Convulsions	Absent	1	T
	Myoclonus	4	
Body temperature; hypothermia	Within X to X-SD	1	CS
	Between (X-SD) and (X-1.5SD)	2	
	Between (X-1.5SD) and (X-2SD)	3	
	>(X-2SD)	4	
Salivation	None	1	CS
	Slight	2	
	Severe	3	
	Profuse	4	
Mobility	Normal	1	CS
	Slightly impaired	2	
	Moderately impaired	3	
	Totally impaired	4	

#### 4.2.4 Variable Coding

As described in section 4.2.3, the principal variables were utilized to calculate composite severity scores. These variables, T and CS, were defined as composites of five outputs measured in the WIL FOB study as follows:

- body temperature: T (hyperthermia) and CS (hypothermia)
- tremors: T
- clonic convulsions: T
- excessive salivation: CS
- impaired mobility: CS

Continuous data (body temperature) were converted on the basis of the control group mean  $\pm$  multiples of standard deviation, and categorical data were converted based on severity of the original scoring criteria. Before the composite indices were constructed, body temperature was re-coded to 2 categorical variables, T and CS. Hyperthermia flags an increase, while hypothermia flags a decrease in body temperature. Each variable is based on the difference

between an observation and the concurrent control means. The data were analyzed in terms of pooled variance of all of the control groups, i.e. the overall control standard deviation.

The resulting T and CS variables were dichotomized as 1 or 0; 1 if  $T > 4$  or  $CS > 4$ , and 0 for individuals with scores of 3 or 4 (i.e., had little or no response to any of the 3 endpoints). The incidents of scores that were assigned a value of 1 were then plotted against administered dose to achieve a dose-response curve from which the BMDs were calculated. For example, if 4 out of 10 animals tested achieved scores  $> 4$ , the fraction affected for the given dose-group would be 0.4. FOB scores used in the determination of BMD estimates can be found in Appendix 4.

### 4.2.5 Dose-Response Modeling and Derivation of Benchmark Dose (BMD) Estimates for Dichotomous Data

Before dose-response modeling of the 12 pesticides in Weiner et. al. (2009), each data set was tested for significant trend (e.g., Chi-Squared Test for Trend in Proportions; Tukey's Trend Test). Only if a trend was statistically significant was a BMD computed. Statistical trends were limited to T for Type I pyrethroids and CS for Type II pyrethroids, that is, trends for T were not statistically significant for Type II pyrethroids and trends for CS were not significant for Type I pyrethroids. While all pyrethroids could have resulted in significant trends for both the T and CS variables, this only occurred with the mixed type pyrethroid esfenvalerate. The Agency used the trend (T or CS) that resulted in the lowest BMD estimate (i.e. CS) for determining RPFs.

The BMDs were modeled using a model averaging approach described in Wheeler and Bailer (2007). Model averaging is a statistical technique that allows for the incorporation of model uncertainty in quantitative risk estimation. The technique averages BMD dose estimates from several models using data derived from dichotomous dose-response experiments. This calculation is accomplished through a weighted average of multiple dose-response functions considered in the analysis, where the weights reflect the relation of the fitted function to the observed experimental data. The dose-response models utilized include the following: logistic, log-logistic, gamma, multi-stage, probit, log-probit, quantal-linear, quantal-quadratic and Weibull. Due to the limited doses and small samples sizes, this technique was considered more appropriate to account for model uncertainty compared to the Agency's Benchmark Dose Software (BMDS) that is more commonly used to determine BMDs for risk assessment. This model averaging approach has been used in other studies (Benford et. al. 2010).

The BMD lower bound (BMDL) for the index chemical (deltamethrin) was computed through a parametric bootstrap technique. The BMDL and standard deviation of the natural log-transformed BMD were based on 4999 bootstrap samples. The confidence limits for the relative potency ratios were based on 500 random samples from the appropriate distributions. A 20% change from controls was selected as the BMD threshold (i.e.,  $BMD_{20}$ ). Based on data variance and sample size, the  $BMD_{20}$  was the most conservative estimate able to predict a significant change from control values. Behavioral data, such as the WIL FOB data, tends to have a higher level of variability compared to other biomarkers of toxicity. The  $BMD_{20}$  used in

this analysis is consistent with threshold levels used in other pyrethroid behavior studies (Wolansky et. al. 2006; Raffaele et. al. 2008).

The model algorithms along with detailed results of model outputs and graphs for each pyrethroid are presented in Appendix 5: *BMDs for T and CS from WIL FOB Study, April 1, 2009*. Although severity scores were determined for the pyrethrins and the results analyzed by BMDS software, the lack of a dose-response precluded the model from fitting a curve for either T or CS variables (Table 4.2.5). Because of the flat response across the dose groups and effects which are comparable to the toxicity observed in the other pyrethroids at their BMD<sub>20s</sub>, the Agency is using 800 mg/kg (the highest dose tested) as the point of comparison for pyrethrins.

#### 4.2.5.1 Points of Comparisons for Pyrethroids Studied in Herberth (2010)

As mentioned in section 4.2.1, two FOB studies were conducted at the WIL laboratories; the first described in Weiner et. al., (2009) included 11 pyrethroids in addition to the pyrethrins, and the second described in Herberth (2010) included an additional 7 pyrethroids; cyphenothrin, imiprothrin, metofluthrin, prallethrin, sumithrin, tetramethrin, and d-allethrin. An essential part of any CRA is defining an endpoint for the purpose of a uniform measure of toxicity. Although 46 behaviors were observed in the FOB study, the Agency is using the five parameters identified in the principle component analysis (Breckenridge et. al. 2009): body temperature, tremors, clonic convulsions, salivation, and mobility, to determine relative potency factors for purposes of the CRA. Furthermore, Type I and Type II pyrethroids can be separated based on the observation of hyperthermia, tremors, or clonus (Type I) or hypothermia, salivation, and mobility (Type II). Since the 7 pyrethroids in the Herbert (2010) study are all structurally Type I pyrethroids, alterations in body temperature, tremors and clonus can be expected at doses capable of inducing toxicity. Two pyrethroids from this study, tetramethrin and sumithrin, did not demonstrate toxicity at doses of 5,000 mg/kg and so were not included in the CAG. Due to minimal use and exposure, metofluthrin was also excluded from the CRA. The remaining four pyrethroids, cyphenothrin, imiprothrin, prallethrin, and d-allethrin, were included in the CAG and required RPFs. These four pyrethroids are among the least potent members of this class. Because of that, and consistent with the screening nature of this assessment, the Agency has selected to use the defined doses instead of completing a refined BMD analysis. In the future, if appropriate, the Agency may determine BMD<sub>20s</sub> for these. The basis for OPP's points of comparison is described below.

***Imiprothrin:*** Rats were administered 900, 1200 or 1500 mg/kg. Moderate to severe tremors were observed in all three dose groups. Severe salivation was noted in one male in the high-dose group that had tremors. No other clinical findings were noted at any dose. In the open field, 1 rat in the 1200 mg/kg group exhibited slightly impaired mobility, ataxia, moderately coarse tremors and considerable gait impairment. Clonic convulsions were noted for 1 rat in the 900 mg/kg group. In a pilot study, there were no adverse effects noted at any of the administered doses of 300, 500, or 800 mg/kg. Based on the observation of moderate tremors in a single rat, the Agency conservatively, selected a lower dose level, 750 mg/kg, for the point of comparison for imiprothrin in the CRA.

## Pyrethroid Cumulative Risk Assessment

Observations		900 mg/kg	1200 mg/kg	1500 mg/kg
Clinical <sup>a</sup>	Tremors (#rats/#incidences)	1/1	3/3	3/3
	Salivation	0	0	1/1
	Convulsions	1	0	0
Open Field	Mobility & Tremor	0	1	0

<sup>a</sup>Clinical observations were made prior to FOB testing. Observations in all other scenarios were made at the time to peak effect

**Prallethrin:** Rats were administered 150, 250, or 400 mg/kg. Moderate tremors and body twitches were noted prior to the 2-hour FOB assessment for 1 male each in the 250 and 400 mg/kg groups. Tremors were also observed in the low -and mid-dose groups and convulsions in the high dose group during home cage observations. Similar results were observed in the pilot study where five rats/group were given 120, 240, or 480 mg/kg. Mild tremors were observed in one animal in the 120 mg/kg group, and one animal in the 240 mg/kg group had an abnormal gait. Based on the mild tremors in 1 rat out of 10, the Agency selected 150 mg/kg as the point of comparison for prallethrin.

Observations		150 mg/kg	250 mg/kg	400 mg/kg
Clinical <sup>a</sup>	Tremors (#rats/#incidences)	0	1/1	1/1
Home Cage	Tremors	1	3	0
	Convulsions	0	0	1
Physiological	Body Temperature	38.4±0.63	37.8±0.48	37.2±0.61*

<sup>a</sup>Clinical observations were made prior to FOB testing. Observations in all other scenarios were made at the time to peak effect

\*Indicates a significant change from control group at P>0.05.

**Cyphenothrin:** Rats were administered 60, 100, or 160 mg/kg. Two males in the 160 mg/kg group were found dead on study day 1. These deaths were considered to be test substance-related as these males had multiple signs of overt toxicity during the 2-hour FOB evaluation. All other males in the 160 mg/kg group survived to the scheduled euthanasia. All males in the 60 and 100 mg/kg cyphenothrin groups survived to the scheduled euthanasia. Similar to prallethrin, tremors were also observed in 1 rat in the low-dose group . The Agency selected 60 mg/kg from the definitive study for a point of comparison based on mild tremors in 1 rat out of 10.

Observations		60 mg/kg	100 mg/kg	160 mg/kg
Clinical <sup>a</sup>	Tremors (#rats/#incidences)	0	1/1	2/2
	Deaths	0	0	2
Home Cage	Tremors	1	1	5*
	Convulsions	0	0	2
Open	Mobility	0	1	5*
	Convulsions	0	1	1
	Tremor	0	1	8*

<sup>a</sup>Clinical observations were made prior to FOB testing. Observations in all other scenarios were made at the time to peak effect

\*Indicates a significant change from control group at P>0.05.

**D-Allethrin:** Rats were administered 200, 320, or 500 mg/kg. Four males were found dead between 2 hours and 3 hours following dose administration, or on study day 1 (1 in the mid- and 3 in the high-dose groups). Moderate tremors were noted for 1 male in the 500 mg/kg group at 1 hour 20 minutes following dose administration. Slight or moderately course tremors were noted in 2, 4, and 8 males in the low-, mid-, and high-dose groups, respectively, in the home cage. The most prevalent finding in the open field included slightly impaired mobility, convulsions, slight to moderate tremors and slight gait impairment.

D-allethrin and s-bioallethrin are both enrichments of the pyrethroid allethrin. As noted in section 4.5, a BMD<sub>20</sub> of 135 mg/kg was calculated for s-bioallethrin. Although available as separate commercial products, d-allethrin and s-bioallethrin contain similar amounts of the d-trans isomer of the chrysanthemic acid, 80 and >90%, respectively. The greater concentration of the d-trans isomer in the s-bioallethrin resulted in slightly greater toxicity compared to d-allethrin at a shared dose of 200 mg/kg. For example, in the open field, convulsions and tremors were observed in 5 and 6 rats out of 10 for s-bioallethrin but were limited to 2 and 2 out of 10 for d-allethrin. Given the similarity of their compositions and in lieu of selecting a dose from Herbert (2010) for d-allethrin, the Agency is using 135 mg/kg (the BMD<sub>20</sub> for s-bioallethrin) for determination of the relative potency factor of d-allethrin.

**Table 4.2.5.1d. FOB Effects Observed in D-Allethrin-Treated Rats in WIL Study (Herberth 2010)**

Observations		200 mg/kg	320 mg/kg	500 mg/kg
Clinical <sup>a</sup>	Tremors (#rats/#incidences)	0	1/1	1/1
	Found Dead	0	1	3
Home Cage	Tremors	2	4	8*
	Convulsions	0	0	2
Open Field	Mobility	0	1	4
	Convulsions	2	4	7
	Tremor	2	4	8

<sup>a</sup>Clinical observations were made prior to FOB testing. Observations in all other scenarios were made at the time to peak effect  
 \*Indicates a significant change from control group at P>0.05.

### 4.3 Routes and Duration of Exposure for Potency Determination

#### 4.3.1 Routes of Exposure

Humans may be exposed to pyrethroids through their diet (food and drinking water) and in and around residences, schools, commercial buildings, etc. via the oral, dermal, and inhalation routes of exposure. Therefore, the potency of pyrethroids needs to be determined for all three routes of exposure<sup>3</sup>. Dermal and inhalation assessments are required for some pyrethroids; however, they generally do not significantly contribute to the overall risk picture. Oral exposure is the route of exposure of greatest concern with respect to pyrethroid toxicity for the screening level cumulative assessment.

<sup>3</sup> More detail related to exposure can be found in Sections 5.0 and 6.0

#### 4.3.1.1 Oral

Oral relative potency values were needed for all pyrethroid pesticides included in the CAG because of potential dietary exposures from food and drinking water and hand to mouth exposures associated with residential/non-occupational uses. The Agency has determined that the WIL study is the most appropriate study available for determination of the pyrethroid BMDs via the oral route because it reflects acute toxicity at the level of the common mechanism (i.e. neurotoxicity due to alterations of the VGSC), standardizes testing conditions for a large number of pyrethroids (i.e. strain, vehicle, dosing volume), and reflects the most relevant duration (acute).

#### 4.3.1.2 Dermal and Inhalation

Compared to the database for oral toxicity studies, the number of inhalation and dermal studies examining neurotoxic effects consistent with the pyrethroid common mechanism is much smaller. Several *in vivo* dermal studies are available to evaluate pyrethroid toxicity. However, these studies do not evaluate the full range of behavioral endpoints needed to assess pyrethroid toxicity, nor do they establish critical time-to-peak-effect windows. There are even fewer inhalation studies available for the determination of pyrethroid toxicity compared to the dermal studies, and these too lack critical endpoint evaluation and appropriate time-to-peak-effect determination. Furthermore, the Agency's limited ability to predict the impact of route-specific pharmacokinetics precludes the extrapolation of estimating RPFs from oral, dermal, and inhalation exposures. As PBPK models are further developed for this class of pesticides, limitations such as route-to-route extrapolation may be overcome. However, at the current time limitations in methodology and lack of coverage for all pyrethroids preclude the inclusion of dermal and inhalation studies in the calculation of the RPFs. As such, the Agency is assuming that the relative rank estimated for oral exposure applies to both the dermal and inhalation routes.

In lieu of determining BMDs for dermal and inhalation routes, the Agency is using the BMDs determined from oral studies and using a 5% dermal absorption factor and assuming inhalation toxicity is equivalent to oral toxicity. Pyrethroid dermal absorption estimates used in single chemical risk assessment for the pyrethroids included in the CMG range from 0.2 to 33%. Dermal absorption estimates greater than 5% are either based on structural similarity which entails a high level of uncertainty and are therefore very conservative, or measurements of total skin absorption which is also highly conservative since pyrethroids bound to the upper dermis layers are not likely to be absorbed into the body. Furthermore, approximately half of these estimates are based on systemic toxicity, such as decreased body weights, decreased food consumption, or as a weight of evidence from the database, and therefore are not consistent with the pyrethroid common mechanism being used for the CRA. Those studies based on neurotoxic effects are not examined in a consistent manner and therefore such *in vivo* dermal studies are not appropriate for the determination of BMDs for the purposes of the CRA. Estimates  $\leq 5\%$  are based on potency comparisons between oral and dermal studies within the same rat strain, direct measures of *in vitro* skin penetration (Hughes and Edwards 2010), or

penetration rates based on lower dermis levels of skin that are more likely to be absorbed by the body. Since these lower estimates are more robust and contain significantly less uncertainty, the Agency is confident that an estimate of 5% absorption is protective for human exposures.

The Agency has guideline inhalation studies for 10 pyrethroids which are included in the CAG. Of these 10, the effects observed in the studies for five of these are either based on route of entry effects or other more generalized toxic effects such as decreased body weights. For the remaining five pyrethroids, s-bioallethrin, cyfluthrin, imiprothrin, lambda-cyhalothrin, and permethrin, the effect seen in the inhalation studies are based on adverse neurotoxic effects including convulsions, tremors, and vocalizations during handling. Although these effects are consistent with the recognized pyrethroid common mechanism, these studies are lacking in consistent evaluation and scoring of neurotoxic behaviors, determination of the appropriate time-to-peak-exposure, and consistent exposure techniques, and thus are not appropriate for estimating relative potency.

### 4.4 Index Chemical

The cumulative risk assessment guidance document (USEPA 2002) states that the index chemical should be selected based on the availability of high quality dose-response data (preferably in each route of interest) for the common mechanism endpoint and that it acts toxicologically similar to other members of the common mechanism group. High quality dose-response data allow the calculation of points of departures (PoD) with greater confidence, because the PoDs for the index chemical are used to extrapolate risk to the exposure levels anticipated in the human population and any error or uncertainty in an index chemical's PoD value will be carried forward in the cumulative risk estimates.

#### 4.4.1 Candidates for Index Chemical

In previous cumulative assessments the Agency has typically evaluated those chemicals in the CAG with high quality data relevant for the CMG endpoint(s) for the oral, dermal, and inhalation routes of exposure. In the case of the pyrethroids, a complete database including dermal, oral, and inhalation studies measuring pyrethroid-specific neurotoxicity at the time-to-peak-effect is not available for any single pyrethroid. Furthermore, although dermal and inhalation assessments are being conducted for some pyrethroids, they generally do not significantly contribute to the overall risk picture; therefore the focus of this CRA is the oral route of exposure. Oral exposure is the route of greatest concern with respect to pyrethroid toxicity for this screening level cumulative assessment and the source of the most robust dose response data for purposes of deriving PODs. The WIL study provides the most robust oral FOB data from which to compare the pyrethroid chemicals (See section 4.2). Therefore, for this screening level CRA the Agency is relying on the chemicals included in the oral WIL study for determination of candidates for the index chemical.

In addition to considering the robustness of the toxicity database, the selection of the index chemical must also consider the pertinent duration of exposure. As previously discussed, the CRA assesses exposures over a 24 hour period (i.e. acute exposures); therefore it is important that the index chemical have a robust database reflecting this exposure duration.

Permethrin and deltamethrin stand out as having the most robust database of guideline and literature studies. For example, multiple studies on deltamethrin and/or permethrin have been identified examining *in vivo* neurotoxicity, *in vitro* sodium channel interaction, metabolism, pharmacokinetics following multiple routes of administration (oral, dermal, intravenous, intercerebral, etc.) and PBPK modeling. Thus, deltamethrin and permethrin are both strong candidates for selection as the index chemical.

The deltamethrin PoD derived from the FOB data is of sufficiently high quality to minimize error or uncertainty in the cumulative risk estimates. In the WIL study, permethrin was only tested with two doses which are narrowly spaced whereas deltamethrin was tested with three doses well spaced to cover the low to high dose range. As such, there is greater variability around the BMD central estimate for permethrin compared to deltamethrin based on the distance of the BMDL (lower confidence limit) from the central estimate. Specifically, the BMD and BMDL estimates for permethrin are 155.5 and 73 mg/kg, compared to the deltamethrin BMD and BMDL estimates of 14.5 and 10.5 mg/kg. Therefore, the Agency has selected deltamethrin as the index chemical in the CRA. Several key literature studies supporting the use of deltamethrin as the index chemical are listed in Appendix 6. This list of literature is not exhaustive but it does include the most salient studies covering a number of areas of deltamethrin research and it includes key seminal studies that are cited most often.

## 4.5 Relative Potency Estimates & Points of Departure for the Index Chemical

### 4.5.1 Relative Potency Factors

In this CRA, the Agency is quantifying cumulative risk to the pyrethroids using BMDs derived from the WIL study to calculate RPFs. Deltamethrin is being used as the index chemical. The RPFs for the CAG in this pyrethroid screening level cumulative are shown in Table 4.5.1. They are determined by dividing the chemical-specific BMD<sub>20</sub> by the BMD<sub>20</sub> of the index chemical, deltamethrin. Calculations for the BMDs are described in Section 4.2. Twelve of the 15 pyrethroids result in equal to or lower relative potency estimates compared to deltamethrin. Bifenthrin, cyfluthrin, and tau-fluvalinate result in similar relative potency as deltamethrin while lambda-cyhalothrin resulted in slightly greater potency than deltamethrin.

<b>Table 4.5.1. Relative Potency Estimates for Pyrethroids Included in the Screening Level Cumulative Risk Assessment</b>		
<b>Pyrethroid</b>	<b>Oral BMD<sub>20</sub></b>	<b>Oral RPF<sup>b,d</sup></b>
Allethrin <sup>c</sup>	135	0.11
Bifenthrin	14.3	1.01
Cyfluthrin	12.6	1.15
Lambda-Cyhalothrin	8.9	1.63
Cyphenothrin	100 <sup>a</sup>	0.15
Cypermethrin	76.3	0.19
<b>Deltamethrin</b>	<b>14.5</b>	<b>1.0</b>
Esfenvalerate	40.5	0.36
Fenpropathrin	29	0.50
Tau-Fluvalinate	14.5	1.0
Imiprothrin	750 <sup>a</sup>	0.02
Permethrin	156	0.09
Prallethrin	150 <sup>a</sup>	0.10
Pyrethrins	800 <sup>a</sup>	0.02
Resmethrin	291	0.05

<sup>a</sup>Values estimated from studies; these values were not calculated using BMD. See Section 4.2

<sup>b</sup>RPF = BMD<sub>20</sub> of Index Chemical (e.g., deltamethrin)/Pyrethroid BMD<sub>20</sub>; For example: Allethrin RPF=14.5/135=0.11

<sup>c</sup>Includes the isomeric enrichments S-Bioallethrin and D-Allethrin

<sup>d</sup>RPFs for Dermal and Inhalation exposures are based on oral BMD; 5% absorption values applied to dermal assessments and inhalation is considered equivalent to the oral route

## 4.5.2 Points of Departure

The deltamethrin BMD<sub>20</sub> is derived from oral data and is being applied to all three routes of exposure: oral, dermal, and inhalation. As with any risk assessment that relies on BMD analysis, the PoD is the lower confidence interval used to mark the beginning of extrapolation to determine risk associated with human exposures. The 95% lower confidence interval for the BMD<sub>20</sub>, the BMDL<sub>20</sub>, of deltamethrin is 11 mg/kg (Figure 4.5.2).

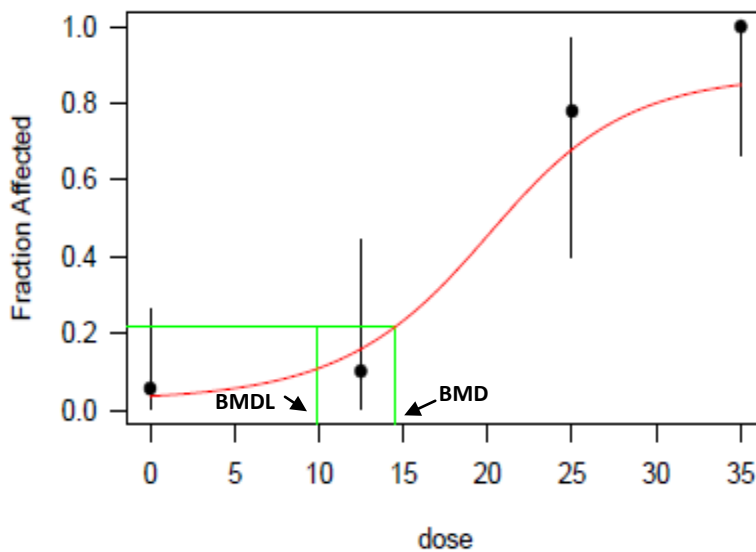


Figure 4.5.2.  $BMD_{20}$  and  $BMDL_{20}$  for FOB changes of Deltamethrin

#### 4.6 FQPA Safety Factor for Protection of Infants & Children

The FQPA (1996) instructs EPA, in making its “reasonable certainty of no harm” finding, that in “the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children, to take into account potential pre- and post-natal toxicity and completeness of data with respect to exposure and toxicity to infants and children.” Section 408 (b)(2)(C) further states that “the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.”

The Agency typically determines the appropriate FQPA safety factor on a chemical-by-chemical basis. However, there are a number of similarities between the pyrethroids (e.g., relative potency, structure, and pharmacokinetics) which support the conclusion that a single FQPA safety factor is appropriate for the entire class. Based on reliable data, EPA has concluded that a safety factor less than 10X is appropriate for the pyrethroid chemicals. The Agency is reducing the FQPA Safety Factor to 1X for adults, including pregnant females, and children greater than 6 years of age (USEPA 2011b). However, the Agency is retaining a 3X FQPA Safety Factor for children from birth to 6 years of age. This conclusion is based on a wide range of information on pyrethroids that includes the exposure profile for this class of pesticides, PBPK models, and *in vitro* and *in vivo* data. The scientific information that supports the reduction of the FQPA safety factor can be found in *Re-Evaluation of the FQPA Safety Factor for Pyrethroid Pesticides* (USEPA 2011b) and is summarized below:

- Based on the available data and supporting evidence, the 10X FQPA safety factor will be reduced to 1X for all populations greater than 6 years of age, including women of child

bearing age. This is due to the absence of pre-natal sensitivity observed in 76 guideline studies for 24 pyrethroids and supporting scientific literature.

- For exposures from birth to <6 years of age, the Agency will retain a 3X safety factor due to 1) age-dependent pharmacokinetics, supported by rat PBPK model predictions of a 3-fold increase of pyrethroid concentration in juvenile brain compared to adults; 2) *in vitro* pharmacodynamic data and *in vivo* data indicating similar responses between adult and juvenile rats at low doses; and 3) data indicating that the rat is a conservative model compared to the human based on species-specific pharmacodynamics of homologous sodium channel isoforms.
- Based on pharmacokinetic data, there is evidence that indicates an increase in sensitivity to pyrethroids of the young compared to adults. These differences are largely attributed to the ability of the adults and juveniles to metabolize pyrethroids. The available PK data is primarily based on experiments with deltamethrin, one of the more potent pyrethroids. Data has shown the rate of *in vitro* metabolism of deltamethrin by plasma carboxyesterases, hepatic carboxyesterases, and hepatic microsomes are at least 6 times higher for post-natal day (PND) 90 rats compared to PND 10 rats (Anand et. al. 2006). As a consequence, higher internal doses overwhelm the clearance mechanisms in juveniles but because adults have greater enzyme activity, they are able to tolerate higher doses prior to the onset of toxicity. PBPK models have predicted, compared to adult rats (i.e., 90-days old), equivalent brain concentrations of deltamethrin would be achieved with a 3.8X fold lower oral dose in 10-day old rats and 2.5X lower dose in 21-day old rats (Tornero-Velez et. al. 2010). The difference between a 3.8- and a 2.5-fold dose is within background variability of the PBPK model and therefore the Agency approximates a 3-fold difference between adult and juvenile rats. Since there are no similar age-dependent PBPK models available for humans, the Agency cannot make any direct estimates of human infant brain concentrations following an exposure to pyrethroids. Therefore, the Agency has to rely on extrapolations from rodent studies. Comparisons between lifestages in the rat and human are difficult to make because the ontogeny of the brain development and metabolizing enzymes are not an exact match. However, 11-day old rats are considered to be equivalent in terms of development to newborn humans and 17-day old rats are believed to be developmentally equivalent to human toddlers 3 to 6 years of age (Davision and Dobbing 1966; Dobbing and Smart 1974; Benjamins and McKhann 1981).
- In part, the Agency is reducing the FQPA factor because available data do not indicate any age-related differences in the pharmacodynamics through interaction with VGSCs. For example, in a direct comparison of a homologous rat and human sodium channel isoform, NaV1.3, Tan and Soderlund (2009) found the rat isoform was 4-fold more sensitive than the equivalent human sodium channel to the pyrethroid tefluthrin, suggesting the rat is a highly sensitive model and extrapolations from the rat would be protective of human health.

- The population of greatest concern to the Agency for pyrethroid exposure is children from birth to <6 years of age. Pyrethroids have a wide variety of uses, including agricultural and residential scenarios. Despite the widespread use on food crops, residue levels in processed or whole foods, as determined by the USDA Pesticide Data Program, are generally low. Furthermore, pyrethroids are practically insoluble in water, minimizing water exposure. With respect to residential and occupational exposure scenarios, pyrethroids have low vapor pressure and are poorly absorbed dermally (Hughes and Edwards 2010). As such, the exposure assumptions made in this screening level assessment are conservative and protective of human health.

The Agency is expecting additional *in vitro* and *in vivo* data that will further inform the science behind the decision to reduce the FQPA factor. In 2010, the Agency requested proposals for study protocols which could identify and quantify potential juvenile sensitivity (USEPA 2010). There was a single response from the Pyrethrin and Pyrethroids Working Group (PPTWG), a conglomerate of pyrethroid registrants. The PPTWG protocol was reviewed during a July 2010 FIFRA SAP meeting<sup>4</sup>. Based on comments from the SAP, the initial study proposal was refined. At present time, pesticide registrants and product formulators (Council for the Advancement of Pyrethroid Human Risk Assessment (CAHRA)) are i) conducting *in vitro* studies demonstrating the interaction of pyrethroids endogenously expressed rat and human VGSCs in *Xenopus* oocytes; ii) conducting *in vitro* studies demonstrating interaction of pyrethroids in rat neurolemma cells; iii) developing rat and human PBPK models, including additional pharmacokinetic data; and iv) conducting *in vivo* behavioral testing using auditory startle testing in rats. As more data for individual pyrethroids become available, the Agency will determine whether re-evaluation of the age-related sensitivity of pyrethroids is appropriate.

### 4.7 Incorporation of Uncertainty Factors/Extrapolation Factors and the Target Margin of Exposure

In general, when performing a cumulative risk assessment using a RPF approach, as is being done with the pyrethroids, uncertainty and extrapolation factors can be incorporated into the risk assessment in two different ways: 1) adjustment of the chemical-specific RPF; or 2) incorporation into the target Margin of Exposure (MOE). For the pyrethroids, the inter-species, intra-species, and FQPA safety factor were all incorporated into the target MOE.

The magnitude of the uncertainty and extrapolation factors is the same for each member of the common mechanism group for the pyrethroid CRA. As described in detail earlier, the FQPA factor has been reduced to 3X for every pyrethroid for the subgroups of children six years old and younger and to 1X for all other subgroups. However, data are not available to reduce the 10X inter-species or 10X intra-species factor. Therefore, the 10X is retained for both of these factors. As such, the target MOEs for the pyrethroid CRA are listed in Table 4.7.

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<sup>4</sup> <http://www.epa.gov/scipoly/sap/meetings/2010/072310meeting.html>

As indicated in the previous section, the Agency is expecting additional data and PBPK models. PBPK models are able to address age- and species-specific pharmacokinetics that are key to extrapolating human health risks from rodent models. For example, Godin et. al. (2010) predicted the concentrations of deltamethrin in the adult human brain based on studies in the rat and Tornero. et al. (2010) predicted deltamethrin concentrations in the brains of rats from PND 10 up to PND 90. These Agency models form the basis for newer models currently being developed by CAPHRA for several additional pyrethroids. As the models become available to the Agency, further adjustments to the FQPA and interspecies factors will be considered during future CRA revisions.

**Table 4.7 FQPA Safety Factors for Populations Relevant to Human Health Risk Assessments**

Population	FQPA	Inter-species Factor	Intra-species Factor	Target MOE
Children 0 to 6 years	3	10	10	300
Children > 6 years	1	10	10	100
Females 13+	1	10	10	100
Adults	1	10	10	100

#### 4.8 Dose Additivity

A key assumption of the RPF method is dose-additivity. For pyrethroids, dose-additivity implies multiple pyrethroids can interact with the VGSC simultaneously, and the overall toxic response will be a summation of all the individual pyrethroids. For example, if deltamethrin and permethrin were administered at equipotent doses, the measured response would be double compared to the administration of either pyrethroid by itself. Dose-addition has recently been demonstrated in *in vivo* and *in vitro* studies. Wolanksy et. al. (2009) used a mixture of 11 pyrethroids (both Type I and II) and the same testing paradigm used in single-compound assays to test the hypothesis that cumulative neurotoxic effects of pyrethroid mixtures can be predicted using the default dose-addition theory. When subthreshold doses of individual chemicals were combined in mixtures, significant dose-related decreases in motor activity were observed; there was no departure from the predicted dose-additive curve. This study presents the first *in vivo* evidence on pyrethroid cumulative effects supporting the default assumption of dose addition. Using the same mixture of 11 pyrethroids, Cao et. al. (2011a) measured Na<sup>+</sup> influx in primary cultures of intact mammalian cerebrocortical neurons. When all 11 pyrethroids were present at an equimolar mixing ratio, their actions on Na<sup>+</sup> influx were consistent with a dose-additive model. While motor activity is an indirect measure of the common mechanism (i.e. interaction with VGSC), the measurement of Na<sup>+</sup> influx at the neuronal level provides more definitive evidence of dose-addition at the level of the common mechanism.

Furthermore, Scollon et. al. (2009) compared the rate of metabolism of the cis- and trans-isomers of permethrin in hepatic microsomal incubations separately and in a mixture. The metabolism of trans-permethrin was reduced when incubated with its diastereomer, cis-permethrin in both rat and human hepatic microsomes incubations. Since both isomers are metabolized by the same oxidative P450 enzymes, (CYP2C6 and CYP2C11), substrate

competition may have contributed to the difference in metabolic rate. While this potential interaction in metabolism does not necessarily result in dose-additivity, it may contribute and should be considered when modeling pyrethroid pharmacokinetics. OPP will continue to monitor and evaluate *in vivo* and *in vitro* studies evaluating dose-addition of pyrethroids as they become available.

In summary, given the current state of the science with respect to pyrethroid mixtures, the assumption of dose additivity is both reasonable and appropriate.

### 5.0 Dietary Cumulative Exposure and Risk Assessment/Characterization

This section discusses the cumulative estimated risk associated with the food and drinking water exposure pathways. An overview of the inputs and methodology for the dietary assessment is included here. Detailed information on conducting a cumulative dietary risk assessment is available in the *Revised N-Methyl Carbamate Cumulative Risk Assessment*, US EPA, September 24, 2007, pp. 58 – 82.

It should be noted that while the methodology developed and implemented in the assessment of the cumulative risks for the organophosphate and *N*-methyl carbamates was closely followed for the pyrethroids, in light of the screening level nature of this assessment, some conservative assumptions were made. Inclusion of those conservative assumptions did not result in dietary risks of concern; therefore, additional refinements were not required at this time.

#### 5.1 Food Exposure Pathway

As with previous cumulative assessments released by the Agency, the data for this pathway are developed from two primary sources: dietary consumption data collected by USDA's Continuing Survey of Food Intakes by Individuals (CSFII) and pesticide residue monitoring data collected by the USDA Pesticide Data Program (PDP).

##### 5.1.1 Dietary Consumption Data

The reliability of the food component of this assessment is supported by the use of the food consumption data from the USDA's Continuing Survey of Food Intakes by Individuals (CSFII 1994-1996/1998). The CSFII surveyed more than 20,000 individuals over two non-consecutive days and provides a detailed representation of the food consumption patterns of the U.S public across all age groups, during all times of the year, and across 50 states. Thus, the Agency has confidence that the consumption estimates for food are well established and consequently support reasonable risk estimates for the U.S. population.

### 5.1.2 Pesticide Residue Data

As with previous CRAs, the exposure estimates for food are based on residue monitoring data from the USDA's Pesticide Data Program (PDP). PDP data collected from 2003 through the most recent data available in 2009 were incorporated in the pyrethroid screening level assessment. While additional years of data are available, prior to 2003, PDP did not analyze for all registered pyrethroids. The PDP data provide a reliable estimate of pesticide residues in the majority of foods, with care taken to sample foods with high consumption or foods which are likely to have the highest residues, including important children's foods. The PDP data were either used directly or indirectly through the use of commodity surrogates. That is, for food not monitored in PDP, similar commodities that are measured by PDP served as surrogate data sources. This approach is consistent with the approach taken on previous CRAs and is considered to be reasonable given that it is based on the concept that families of commodities with similar cultural practices and insect pests are likely to have similar pesticide use patterns and residue levels. Additionally, PDP data provide direct measures of co-occurrence of the pyrethroid pesticides in the same samples. Consistent with prior practice for the organophosphate (OP) and *N*-methyl carbamate (NMC) pesticide cumulative assessments, PDP samples with non-detectable residues were treated in this assessment as "zero" values. Sensitivity analysis conducted for the OPs and NMC pesticides has determined that this approach for acute dietary assessments does not significantly underestimate exposures at the upper percentiles.

### 5.1.3 Pyrethroid Pesticides Included in the Dietary Risk Assessment

The pyrethroids with registered agricultural uses on human feed items are summarized in Table 5.1.3, below, along with their relative potency factors (RPFs). It is important to note that not all pyrethroids with registered food-uses were quantitatively included in this screening level assessment. As was previously noted and is captured in the CRA methodology, a pyrethroid with a relative potency that significantly lower than that of the index chemical was not included in the CAG since that specific chemical is unlikely to have an impact on the estimated cumulative risk. Further, food-use pesticides for which there are no detectable residues in the PDP monitoring data are not included in the assessment as there is not a likelihood of significant exposure.

## Pyrethroid Cumulative Risk Assessment

Table 5.1.3. Food Use Pyrethroids Considered in the Quantitative Screening Level CRA						
Chemical Name <sup>1</sup>	Included Quantitatively in Screening Level Assessment/Comments	RPF	Index Chemical POD	UF	FQPA SF	CRA Target MOE
Allethrin	Included	0.11		100	3	100 adults 300 children
Bifenthrin	Included	1.01		100	3	
Cyfluthrin	Included	1.15		100	3	
Cyhalothrin	Included	1.63		100	3	
Cypermethrin	Included	0.19		100	3	
Cyphenothrin	Included	0.15		100	3	
Deltamethrin	Included	1.0	11 mg/kg/day	100	3	100 adults 300 children
Fenpropathrin	Included	0.5		100	3	
Fenvalerate/ Esfenvalerate	Included	0.36		100	3	
Flucythrinate	No detects in PDP; therefore not included quantitatively in the CRA					
Fluvalinate	Included	1		100	3	100 adults 300 children
Imiprothrin	Included	0.02		100	3	
Permethrin	Included	0.09		100	3	
Prallethrin	Included	0.1		100	3	100 adults 300 children
Pyrethrins	Included	0.02	100	3		
Resmethrin	Included	0.05	100	3		
Sumithrin	Did not produce any signs of toxicity; therefore not included quantitatively in the CRA					
Tefluthrin	No detects in PDP; therefore not included quantitatively in the CRA					
Tetramethrin	Did not produce any signs of toxicity; therefore not included quantitatively in the CRA					
Tralomethrin	No detects in PDP; therefore not included quantitatively in the CRA					

<sup>1</sup> Refers to all isomeric variations.

In contrast to prior CRAs, processing factors were not included in this screening level assessment, that is, the processing factor was set to “1” which indicates there is no concentration or reduction from processing. For processed commodities monitored directly by PDP, the residue values found in the monitored samples were directly used in the assessment. For those processed commodities which were not directly sampled, the monitored value from the raw agricultural commodity (RAC) or its commodity surrogate was used and the processing factor was set to “1”. This approach is considered reasonable and unlikely to underestimate risk since a review of tolerances (maximum allowed legal residues) for these commodities indicated that separate, higher tolerances were not required for the associated processed commodity. In other words, the tolerance for the RAC would also cover the residues found in the processed commodities supporting a lack of concentration of residues in the processed commodity. Further, no use of reduction factors was included in this assessment. Refining this assessment to include reduction factors (i.e., cooking factors, process reduction factors) for processed commodities for which RAC residue values were used, would only reduce the estimated exposure values.

### 5.1.4 Food Commodities Included in the Dietary Risk Assessment

The universe of foods included in the cumulative dietary exposure assessment is defined by the USDA CSFII 1994-96/1998. The CSFII food diary information is expressed in terms of food *as consumed* (e.g., pizza, apple pie, lasagna, etc.). These foods, as reported in CSFII diaries, are converted to food *commodities* (e.g., tomatoes, milk, wheat flour, beef, apples, etc.) using standard recipes. The recipe information used to break down the foods was developed jointly by EPA and USDA and is one module in the EPA's Food Commodity Intake (FCID) database.

For this screening level assessment pesticide residue values were translated such that all major commodities contained in the Agency dietary exposure model, Dietary Exposure Evaluation Model-Food Commodity Index Database (DEEMFCID™), were assigned residue values. While monitoring data are not available for every commodity in DEEM, major foods are sampled by PDP and the residue values for those samples were translated to similar commodities. For example orange data was translated to limes. Translations were made based on the similarity of the commodities under the Agency's crop grouping scheme codified in the 40CFR. Translations were made regardless of registered use patterns. For example, banana residue values were translated to plantains without verification that there is a pyrethroid registered on plantains. In a more refined CRA, those crops without pyrethroid registered uses would be assigned "zero" values; therefore, this approach would only be expected to result in an overestimate of risk.

Despite the conservative assumptions with regard to processing factors and pyrethroid commodity registrations, by using the PDP monitoring data, the food component of the screening level pyrethroid CRA is considered to be refined and to provide reasonable estimates of the distribution of exposures across the U.S.

## 5.2 Drinking Water Pathway

As a class of chemicals, the pyrethroids have low solubility in water and a high affinity to bind to soils. Given these physical/chemical properties, it is unlikely that oral exposure from drinking water will be a major pathway of exposure. However, in the absence of a comprehensive set of monitoring data with sufficiently low detection limits which could be used to derive exposure values for drinking water, the Agency has incorporated modeled drinking water values into this screening level assessment. Estimated drinking water concentrations (EDWCs) were developed using FIRST, SCI-GROW and PRZM/EXAMS models. The models, including descriptions, are available at <http://www.epa.gov/oppefed1/models/water/>.

The EDWC screening level assessments modeled the maximum application rate and the minimum interval between applications for each pyrethroid. Both surface water and ground water EDWCs were developed and are shown in Table 5.2, however, modeled surface water EDWCs were used as they are significantly higher and provide a conservative estimate for the screening level cumulative assessment. Where a modeled drinking water assessment would

predict a value greater than the limit of solubility for a pesticide, the output of the model will be the chemical's limit of solubility.

The drinking water component of the screening level pyrethroid CRA is considered to be unrefined and highly conservative, both due to the use of the model and because of the level of refinement used in the modeling scenarios. The assessments are characterized as either Tier 1 or Tier 2, which is an indicator of their level of refinement. For both of these tiers, significant refinements are available which are expected to significantly lower the predicted estimated drinking water concentrations. However, these refinements were not conducted as there were no risks of concern identified based on the unrefined assessments.

Drinking water residues have to be expressed in terms of index chemical equivalents before they can be used in the cumulative risk assessment. Using the individual chemical relative potency factors (RPFs), the EDWCs for each pyrethroid were converted to deltamethrin equivalent exposure values. Since data are not available on the co-occurrence or relative amounts of individual pyrethroid in a single water sample, the Agency selected the EDWC from the pyrethroid which resulted in the highest residue value expressed as deltamethrin equivalents as surrogate for all drinking water exposure. The highest EDWC in terms of deltamethrin equivalents was derived from the lambda-cyhalothrin limit of solubility output from the model of 5 ppb. This value is included for all water in the assessment as a deltamethrin equivalent concentration of 8.15 ppb.

In summary, while the physical/chemical characteristics of the pyrethroids suggest that exposure to this class of compound through drinking water is not likely to be a major pathway of exposure; the Agency has incorporated unrefined, modeled estimated drinking water concentrations into this screening level cumulative assessment. Further, the single modeled value which represented the highest deltamethrin equivalent exposure was used to represent drinking water exposure for all pyrethroids; therefore, the drinking water inputs are considered to be highly conservative. Refinements to the modeled scenarios or availability of acceptable drinking water monitoring data is likely to significantly reduce the residue values used in a more refined cumulative assessment. The modeled EDWCs, chemical RPFs and corresponding exposures in deltamethrin equivalents are shown in Table 5.2.

**Table 5.2. Modeled EDWCs for the Pyrethroids**

Chemical Name	Ground Water Acute EDWC (ppb)	Surface Water Acute EDWC (ppb)	RPF	Surface Water Acute EDWC in Deltamethrin Equivalents (ppb)
Allethrins	Based on the use pattern, residues are not expected in drinking water.			
Bifenthrin	0.003	0.014 <sup>1</sup>	1.01	0.014
Cyfluthrin	0.457	2 <sup>1</sup>	1.15	4.228
Cyhalothrin	0.00300	5 <sup>1</sup>	1.63	<b>8.150<sup>2</sup></b>
Cypermethrin	0.0036	3.77	0.19	0.716
Deltamethrin	0.00269	0.2 <sup>1</sup>	1	0.200
Esfenvalerate <sup>3</sup>	0.009	7.54	0.36	2.714
Fenpropathrin	0.00480	10.3	0.5	5.150
Fluvalinate	0.0025	1.31	1.0	1.310
Permethrin	0.012	4.79	0.09	0.431
Prallethrin	0.00104	0.591	0.10	0.059
Pyrethrins	0.003	4.078	0.02	0.082
Resmethrin	0.065	0.20	0.05	0.010

<sup>1</sup> The modeled value exceeded the solubility limit; therefore the actual model output is a concentration at the limit of solubility.

<sup>2</sup> EDWC used in the pyrethroid cumulative risk assessment.

<sup>3</sup> Includes fenvalerate

### 5.3 Dietary (Food and Water) Assessment

As with previous cumulative risk assessments, the pyrethroid screening level cumulative dietary exposure was estimated using the Dietary Exposure Evaluation Model-Food Commodity Index Database (DEEMFCID™) software (Exponent, 2007). Estimation of dietary exposure was accomplished by combining distributions of pesticide concentrations on foods from USDA PDP with distributions of food consumption from USDA CSFII.

Consistent with OPP dietary exposure assessment guidance, separate assessments were conducted on the various sub-populations as represented in the CSFII 1994-96/1998. This screening level assessment reports on the U.S. general population and the following standard age groups:

- Infants less than 1 year old
- Children 1-2 years old
- Children 3-5 years old
- Children 6-12 years old
- Youths 13-19 years old
- Adults 20-49 years old
- Adults 50+ years old
- Females 13-49 years old

The methodology and tools used for calculating cumulative food residues described in the revised NMC cumulative document are the same methodology and tools used to develop this screening level dietary assessment for the pyrethroids. This includes the generation of tables to hold the data on residue values, processing factors, relative potency factors and bridging information (translations between residue data and food forms), along with the use of forms in MS Access to perform the appropriate calculations to express all residues as deltamethrin equivalents and to combine residues on individual samples, creating a distribution of residues by commodity. The specific algorithms used to estimate exposure from dietary sources are detailed in the NMC cumulative document cited above.

The Agency conducted an acute probabilistic dietary risk assessment for food residues and food plus water. Cumulative dietary estimated risks for food alone and food plus drinking water, resulting from exposure to pyrethroids, significantly exceed the target MOE of 100 for adults and 300 for children and; therefore, estimated risks are not of concern for any population subgroup. The results of the dietary exposure and risk assessment are summarized below for food only (Table 5.3a) and food plus water (Table 5.3b).

<b>Table 5.3a. Summary of Food Only Dietary Exposure and Estimated Risk for the Pyrethroid CRA</b>						
<b>Population Subgroup</b>	<b>Acute Dietary 95<sup>th</sup> Percentile</b>		<b>Acute Dietary 99<sup>th</sup> Percentile</b>		<b>Acute Dietary 99.9<sup>th</sup> Percentile</b>	
	<b>Dietary Exposure (mg/kg/day)</b>	<b>MOE</b>	<b>Dietary Exposure (mg/kg/day)</b>	<b>MOE</b>	<b>Dietary Exposure (mg/kg/day)</b>	<b>MOE</b>
General U.S. Population	0.000111	99,000	0.000478	23,000	0.001852	5,900
All Infants (< 1 year old)	0.000104	110,000	0.000639	17,000	<b>0.004739</b>	<b>2,300</b>
Children 1-2 years old	0.000189	58,000	0.000793	14,000	0.003320	3,300
Children 3-5 years old	0.000168	65,000	0.000710	16,000	0.002817	3,900
Children 6-12 years old	0.000116	95,000	0.000483	23,000	0.001898	5,800
Youth 13-19 years old	0.000073	150,000	0.000361	30,000	0.001530	7,200
Adults 20-49 years old	0.000101	110,000	0.000438	25,000	0.001686	6,500
Adults 50+ years old	0.000120	91,000	0.000499	22,000	0.001712	6,400
Females 13-49 years old	0.000104	110,000	0.000455	24,000	0.001766	6,200

Most highly exposed subgroup highlighted.

## Pyrethroid Cumulative Risk Assessment

**Table 5.3b. Summary of Food and Water Dietary Exposure and Estimated Risk for the Pyrethroid CRA**

Population Subgroup	Acute Dietary 95 <sup>th</sup> Percentile		Acute Dietary 99 <sup>th</sup> Percentile		Acute Dietary 99.9 <sup>th</sup> percentile	
	Dietary Exposure (mg/kg/day)	MOE	Dietary Exposure (mg/kg/day)	MOE	Dietary Exposure (mg/kg/day)	MOE
General U.S. Population	0.000521	21,000	0.001011	11,000	0.002321	4,700
All Infants (< 1 year old)	0.001722	6,400	0.002563	4,300	<b>0.005544</b>	<b>2,000</b>
Children 1-2 years old	0.000819	13,000	0.001434	7,700	0.003646	3,000
Children 3-5 years old	0.000731	15,000	0.001212	9,000	0.003157	3,500
Children 6-12 years old	0.000512	21,000	0.000864	13,000	0.002124	5,200
Youth 13-19 years old	0.000401	27,000	0.000763	14,000	0.002048	5,400
Adults 20-49 years old	0.000468	23,000	0.000872	13,000	0.001980	5,600
Adults 50+ years old	0.000431	26,000	0.000788	14,000	0.001926	5,700
Females 13-49 years old	0.000470	23,000	0.000870	13,000	0.002021	5,400

Most highly exposed subgroup highlighted.

For the U.S. population, lettuce, apples, and spinach are the food commodities which contribute the most significantly to dietary exposure from food. For “all infants”, the most highly exposed subgroup, spinach is the commodity which contributes most significantly to the dietary exposure from food. Based on residues seen in PDP, it appears that residues of permethrin on lettuce and spinach and fenpropathrin on apples are the residues most impacting the dietary exposure from food. However, it should be noted that MOEs for all foods combined are significantly above the target MOEs; therefore, while these residues are the highest contributors to exposure, they do not result in an estimated risk of concern.

For the purpose of this screening level assessment, the Agency has included highly conservative modeled drinking water estimates of concentration in this assessment. However, as previously stated given the physical/chemical properties of the pyrethroids, drinking water is not likely to be a major pathway of dietary exposure; therefore actual dietary cumulative estimated risks are more likely to be closer to those reported for food only.

## 6.0 Residential Pyrethroid Cumulative Risk

### 6.1 Introduction

In the past, the Office of Pesticide Programs (OPP) has employed calendar-based models to address the temporal aspects of the residential use of pesticides when performing a cumulative risk assessment (CRA). Considering the breadth of the pyrethroid residential uses, the use of a calendar-based model would involve significant analysis of available exposure and use data. With this in mind and seeking a less resource and time intensive resolution to the pyrethroid CRA, OPP performed a health protective, screening-level assessment to address the cumulative effects and risk of the pyrethroids.

A number of health protective assumptions were made in performing this assessment when compared to previous cumulative risk assessments performed by OPP. Further discussion of the implications of these assumptions is provided in Section 7. These assumptions include the following:

- 1) OPP limited this screening-level assessment to “users only” (i.e., only users of pyrethroid pesticides were considered in this assessment). Since OPP aggregates both dietary and non-dietary exposures from multiple chemicals of the same class, cumulative risk assessments have typically been based on the entire U.S. population which includes individuals who don’t use pesticides and individuals that use non-pyrethroid pesticides.
- 2) OPP assumed no dissipation of chemicals and as such Day 0 (or day of application) residues were used in all cases.
- 3) OPP assumed all individuals are exposed (i.e., come in contact with treated surfaces) on the day of application. Typically, cumulative risk assessments have included an activity component that incorporates the potential for “no non-dietary exposure” days, where a pesticide application occurs but no one is exposed to the treated residues after the application (e.g., no one goes out on a treated lawn after an application).
- 4) OPP assumed that exposure for each scenario occurred as a result of use of the pyrethroid with the highest risk estimate registered for that scenario. Typically, cumulative risk assessments have included probabilities of pesticide use within an exposure scenario (i.e., probability of using pesticide A vs. using pesticide B for scenario X).
- 5) OPP assumed co-occurrence of certain residential scenarios as worst-case situations. Typically, cumulative risk assessments have included use data such as the Residential Exposure Joint Venture (REJV) survey to identify the likelihood of multiple scenario applications occurring on the same day.

In addition to these assumptions, information regarding residues, exposure, and standard (non-chemical-specific) exposure factors (such as breathing rates and activity duration) were incorporated in this assessment. In nearly all cases, the residential exposure scenarios in this assessment were developed using the best available residue and exposure data (some of which is proprietary in nature). Exposure factors such as breathing rates and durations of time spent

performing specific activities were taken from various sources including the U.S. EPA Exposure Factors Handbook (USEPA, 1997) and the U.S. EPA Child-Specific Exposure Factors Handbook (USEPA, 2008). Considering the screening-level nature of this assessment, point estimates were used to represent all the exposure inputs. While the dietary and drinking water assessments address only the oral exposure route, the residential assessment considers the dermal and inhalation exposure routes, as well as the oral route (i.e., hand-to-mouth behavior of young children).

## 6.2 Residential Scenarios and Exposure Routes

There are a variety of pyrethroid pesticides currently registered for residential uses that have been considered as part of this screening-level assessment. The residential scenarios addressed in this document represent critical pyrethroid uses that have the potential for significant exposure when considered in a cumulative assessment. For this effort, the Agency focused on the four main pyrethroid residential use scenarios – turf, pets, gardens, and indoors (broadcast, fogger and crack and crevice applications). All other pyrethroid residential uses (e.g., pyrethroid impregnated clothing or personal insect repellent systems) are considered minor contributors to the pyrethroid CRA based on amount of use and exposure potential; therefore, those scenarios were not included in this screening-level assessment. The specific exposure routes and scenarios assessed in this screening level assessment are briefly described below, as well as summarized in Table 6.2.

Scenario	Lifestage	Applicator		Post-application		
		Dermal	Inhalation	Oral	Dermal	Inhalation
Lawn/Turf	Adult	X	X		X	
	1 < 2 yr old			X	X	
Gardens, Ornamentals, and Trees	Adult	X	X		X	
	6 < 11 yr old				X	
Indoors	Adult	X	X		X	X
	1 < 2 yr old			X	X	X
Pets	Adult	X	X		X	
	1 < 2 yr old			X	X	

### 6.2.1 Lawn/Turf Use

Based on an evaluation of risk assessments, reregistration eligibility documents (REDs), use reports, and labels; it was determined that a number of pyrethroids in the CAG currently have products registered for use on turf where residential exposure could occur (e.g., residential lawns, parks, recreational areas, etc.). These products include, liquid formulations for bifenthrin, cyhalothrin, cyfluthrin, cypermethrin, deltamethrin, permethrin, pyrethrins, and resmethrin; wettable powder formulations for cypermethrin; and granular formulations for cyhalothrin and permethrin.

Potential dermal and inhalation exposure was assessed for individuals mixing, loading, and applying pyrethroids to residential lawns. This assessment also considers potential dermal post-application exposure for adults and young children (1 <2 year olds) contacting treated lawns. Additionally, oral non-dietary exposure (hand-to-mouth) was considered for young children (1 <2 year olds) potentially transferring treated-turf residues from their hands to their mouths.

### 6.2.2 Garden, Ornamental, and Tree Use

Based on an evaluation of risk assessments, reregistration eligibility documents (REDs), use reports, and labels; it was determined that a number of pyrethroids in the CAG currently have products registered for use on residential gardens, ornamentals, and trees. These products include, liquid formulations for bifenthrin, cyhalothrin, cyfluthrin, cypermethrin, deltamethrin, esfenvalerate, fluvalinate, permethrin, pyrethrins, and resmethrin.

Potential dermal and inhalation exposure was assessed for individuals mixing, loading, and applying pyrethroids to gardens, ornamentals, and trees. This assessment also considered potential dermal post-application exposure for adults and children (6 < 11 years old) contacting treated gardens, ornamentals, and trees.

### 6.2.3 Indoor Use

Based on an evaluation of risk assessments, reregistration eligibility documents (REDs), use reports, and labels; it was determined that a number of pyrethroids in the CAG currently have products registered for use indoors. These products include, liquid formulations for allethrin, bifenthrin, cyhalothrin, cyfluthrin, cypermethrin, deltamethrin, esfenvalerate, permethrin, prallethrin, pyrethrins, and resmethrin; ready-to-use aerosol can formulations for allethrin, cypermethrin, deltamethrin, esfenvalerate, permethrin, phenothrin, pyrethrins, and resmethrin; and ready-to-use fogger formulations for allethrin, cyfluthrin, cypermethrin, esfenvalerate, permethrin, prallethrin, pyrethrins, and resmethrin.

Potential dermal and inhalation exposure was assessed for individuals mixing, loading, and applying pyrethroids indoors. This assessment also considers potential dermal post-application exposure for adults and young children (1 <2 year olds) contacting treated indoor surfaces. Additionally, oral non-dietary exposure (hand-to-mouth) was considered for young children (1 <2 year olds) potentially transferring treated-indoor surface residues from their hands to their mouths.

## 6.2.4 Pet Use

Based on an evaluation of risk assessments, reregistration eligibility documents (REDs), use reports, and labels; it was determined that a number of pyrethroids in the CAG currently have products registered for use on pets. These products include, ready-to-use spot-on formulations for cyphenothrin and permethrin; ready-to-use aerosol can formulations for pyrethrins and prallethrin; ready-to-use shampoo formulations for permethrin; and ready-to-use trigger pump spray formulations for allethrin and resmethrin.

Potential dermal and inhalation exposure was assessed for individuals mixing, loading, and applying pyrethroids to pets. This assessment also considers potential dermal post-application exposure for adults and young children (1 <2 year olds) contacting treated pets. Additionally, oral non-dietary exposure (hand-to-mouth) was considered for young children (1 <2 year olds) potentially transferring treated-pet residues from their hands to their mouths.

## 6.3 Residential Handler Exposure and Risk

Handler exposure refers to an exposure scenario in which an adult individual is exposed during mixing, loading, and applying a pesticide. Residential handler exposure assessments estimate dermal and inhalation exposures for individuals using pesticides in and around their homes. Dermal and inhalation handler exposure may occur from the residential use of pyrethroids. The algorithms used for estimating residential handler exposure and risk were the same for all of the residential handler scenarios. However, different assumptions and data sources were used depending on the scenario. The algorithms and assumptions are discussed in further detail below.

### 6.3.1 Handler Algorithms

Handler dermal and/or inhalation exposures are estimated by multiplying the application method-specific unit exposure by an estimate of the amount of active ingredient handled in a day, using the following algorithm:

$$E = UE * AR * A$$

where:

E = exposure (mg/day);

UE = unit exposure (mg/lb ai);

AR = application rate (e.g., lb ai/ft<sup>2</sup>, lb ai/gal); and

A = area treated or amount handled (e.g., ft<sup>2</sup>/day, gal/day).

Dermal and/or inhalation doses are estimated using the following algorithm:

$$D = \frac{E * AF}{BW}$$

where:

D = dose rate (mg/kg-day);  
AF = absorption factor (dermal and/or inhalation); and  
BW = body weight (kg).

Finally, dermal and/or inhalation margins of exposure are estimated using the following algorithm:

$$MOE = \frac{IC\ POD}{D * RPF}$$

where:

MOE = margin of exposure;  
D = dose rate (mg/kg-day);  
RPF = relative potency factor of any pyrethroid compared to the index chemical, deltamethrin; and  
IC POD = point of departure for the index chemical, deltamethrin.

### 6.3.2 Handler Data and Assumptions

The following sections describe the data and assumptions used to estimate dermal and inhalation residential handler risks for pyrethroid use on turf, on gardens, indoors, and on pets.

#### 6.3.2.1 Unit Exposure (UE)

##### Lawn/Turf Use

Dermal and inhalation exposure routes were considered in this assessment for all of the turf residential handler scenarios and application equipment. The unit exposures for each piece of application equipment and the studies from which these unit exposures were developed are presented below:

- Push-type spreader (granular) - The recommended dermal and inhalation unit exposures are 0.81 and 0.0026 mg/lb ai, respectively. The dermal unit exposure was developed based on an Outdoor Residential Exposure Task Force (ORETF) study that monitored 30 applications of a granule formulation for approximately 20 minutes to approximately 10,000 square feet of turf in North Carolina using a rotary spreader (Klonne, 1999). The inhalation unit exposure was developed based on two separate studies; the same ORETF study used in the dermal unit exposure (Klonne, 1999) and a proprietary study

(Rosenheck, 1993). The Rosenheck study monitored 15 applications of a granule formulation for approximately 30-40 minutes to turf in North Carolina using a push cyclone spreader.

- Hose-end Sprayer (liquids) - The recommended dermal and inhalation unit exposures are 15 and 0.024 mg/lb ai, respectively. Both the dermal and inhalation unit exposures were developed based on an ORETF study that monitored 30 applications of a liquid pesticide formulation for approximately 75 minutes to approximately 5000 ft<sup>2</sup> of residential lawns using a dial-type hose-end sprayer (Klonne, 1999).
- Hose-end Sprayer (wettable powders) - No exposure data are available for this application scenario and, thus, data for applying liquids via hose-end sprayer were used as a surrogate.
- Low-Pressure Handwand Sprayer (liquids) - The recommended dermal and inhalation unit exposures are 65 and 0.0054 mg/lb ai, respectively. Both the dermal and inhalation unit exposures were developed based on two ORETF studies (Merricks, 1997 and Merricks, 1998). The 1997 Merricks study monitored 40 applications of a liquid pesticide formulation for approximately 20 minutes to tomato and cucumber gardens using a low-pressure handwand. The 1998 Merricks study monitored 20 applications of a liquid pesticide formulation for approximately 20 minutes to citrus trees and shrubs using a low-pressure handwand.
- Low-Pressure Handwand Sprayer (wettable powders) - The recommended dermal and inhalation unit exposures are 69 and 1.1 mg/lb ai, respectively. The dermal unit exposure was developed based on two studies (Merricks, 1987 and Dean, 1988). The Merricks study monitored 18 applications of a wettable powder formulation in homes and commercial buildings with two 1-gallon "B&G stainless steel PCO sprayers". The Dean study monitored 16 applications of a wettable powder formulation in homes for approximately 1.0-2.5 hours using a 1-gallon hand compression sprayer. The inhalation unit exposure was developed based only on the 1988 Dean study.
- Backpack Sprayer (liquids) - The recommended dermal and inhalation unit exposures are 130 and 0.12 mg/lb ai, respectively. The dermal unit exposure was developed based on three studies (Merricks, 1988; Contardi *et. al*, 1993; and Beard, 1997). The Merricks study monitored 9 applications of three 2-gallon liquid pesticide solutions for approximately 47 minutes to poultry litter using a backpack sprayer. The Contardi study monitored 2 applications of a liquid pesticide formulation to greenhouse plants hanging overhead, on the floor, or on benches for approximately 1.5 hours using a backpack sprayer. The Beard study monitored 15 applications of a liquid pesticide formulation to approximately 6000 ft<sup>2</sup> of Christmas tree farms in Michigan, Pennsylvania, and Connecticut for approximately 4 hours using a backpack sprayer. The inhalation unit exposure was developed based on one study (King and Prince, 1995) that monitored 16 applications of a liquid pesticide formulation for approximately 63-94 minutes to greenhouse ornamentals in Florida, Maryland, and California.
- Backpack Sprayer (wettable powders) - No exposure data are available for this application scenario and, thus, data for applying wettable powders via low-pressure handwand were used as a surrogate.

- Sprinkler Can (liquids) - No exposure data are available for this application scenario and, thus, data for applying liquids via hose-end sprayer were used as a surrogate.
- Sprinkler Can (wettable powders) - No exposure data are available for this application scenario and, thus, data for applying liquids via hose-end sprayer were used as a surrogate.

### Garden, Ornamental, and Tree Use

Dermal and inhalation exposure routes were considered in this assessment for all the garden, ornamental, and tree residential handler scenarios and application equipment. The unit exposures for each piece of application equipment and the studies from which these unit exposures were developed are presented below:

- Hose-end Sprayer (liquids) - The recommended dermal and inhalation unit exposures are 15 and 0.024 mg/lb ai, respectively. Both the dermal and inhalation unit exposures were developed based on an ORETF study that monitored 30 applications of a liquid pesticide formulation for approximately 75 minutes to approximately 5000 ft<sup>2</sup> of residential lawns using a dial-type hose-end sprayer (Klonne, 1999).
- Low-Pressure Handwand Sprayer (liquids) - The recommended dermal and inhalation unit exposures are 65 and 0.0054 mg/lb ai, respectively. Both the dermal and inhalation unit exposures were developed based on two ORETF studies (Merricks, 1997 and Merricks, 1998). The 1997 Merricks study monitored 40 applications of a liquid pesticide formulation for approximately 20 minutes to tomato and cucumber gardens using a low-pressure handwand. The 1998 Merricks study monitored 20 applications of a liquid pesticide formulation for approximately 20 minutes to citrus trees and shrubs using a low-pressure handwand.
- Backpack Sprayer (liquids) - The recommended dermal and inhalation unit exposures are 130 and 0.12 mg/lb ai, respectively. The dermal unit exposure was developed based on three studies (Merricks, 1988; Contardi 1993; and Beard, 1997). The Merricks study monitored 9 applications of three 2-gallon liquid pesticide solutions for approximately 47 minutes to poultry litter using a backpack sprayer. The Contardi study monitored 2 applications of a liquid pesticide formulation to greenhouse plants hanging overhead, on the floor, or on benches for approximately 1.5 hours using a backpack sprayer. The Beard study monitored 15 applications of a liquid pesticide formulation to approximately 6000 ft<sup>2</sup> of Christmas tree farms in Michigan, Pennsylvania, and Connecticut for approximately 4 hours using a backpack sprayer. The inhalation unit exposure was developed based on one study (King and Prince; 1995) that monitored 16 applications of a liquid pesticide formulation for approximately 63-94 minutes to greenhouse ornamentals in Florida, Maryland, and California.
- Sprinkler Can (liquids) - No exposure data are available for this application scenario and thus data for applying liquids via hose-end sprayer were used as a surrogate.

### Indoor Use

Dermal and inhalation exposure routes were considered in this assessment for all of the indoor residential handler scenarios and application equipment. The unit exposures for each piece of

application equipment and the studies from which these unit exposures were developed are presented below:

- Low-Pressure Handwand Sprayer (liquids) - No exposure data are available for this application scenario and thus data for applying wettable powders via low-pressure handwand sprayer were used as a surrogate.
- Low-Pressure Handwand Sprayer (wetable powders) - The recommended dermal and inhalation unit exposures are 69 and 1.1 mg/lb ai, respectively. The dermal unit exposure was developed based on two studies (Merricks, 1987 and Dean, 1988). The Merricks study monitored 18 applications of a wettable powder formulation in homes and commercial buildings with two 1-gallon "B&G stainless steel PCO sprayers". The Dean study monitored 16 applications of a wettable powder formulation in homes for approximately 1.0-2.5 hours using a 1-gallon hand compression sprayer. The inhalation unit exposure was developed based only on the 1988 Dean study.
- RTU Aerosol can – The recommended dermal and inhalation unit exposures are 370 and 3 mg/lb ai, respectively. The dermal and inhalation unit exposures were based on a study from Knarr (1991). The Knarr study monitored 15 applications to cracks, crevices, baseboards, under sinks, and behind appliances in 15 separate houses using an entire 16 oz. aerosol can.
- Ready-to-Use (RTU) Total Release Fogger - Total release foggers are assumed to provide negligible exposure to the applicator since the label typically requires applicators to exit the treatment area immediately.

### Pet Use

Dermal and inhalation exposure routes were considered in this assessment for all of the pet residential handler scenarios and application equipment. The unit exposures for each piece of application equipment and the studies from which these unit exposures were developed are presented below:

- RTU Spot-on - The recommended dermal unit exposure is 220 mg/lb ai. Inhalation exposure data during application of spot-on treatments is unavailable; however, exposure through this route is considered negligible. The dermal unit exposure was based on a study from Meo (1997). The Meo study monitored 16 applications by commercial pet groomers to 8 dogs for approximately 14-32 minutes using a read-to-use (RTU), disposable, snap-top, plastic-backed pipette.
- RTU Shampoo - The recommended dermal and inhalation unit exposures are 2100 and 0.28 mg/lb ai, respectively. The dermal unit exposure for shampoo applications of liquid pesticide formulations to pets, animals, or children is based on two studies (Mester, 1998 and Selim, 2005). The Mester study monitored 16 applications by commercial pet groomers of shampoo to 8 dogs for approximately 149-295 minutes. The Selim study monitored 16 shampoo applications to one dog each for approximately 30 minutes. The inhalation unit exposure is based only on the Mester study.
- RTU Trigger-pump Sprayer - The recommended dermal and inhalation unit exposures are 820 and 3.3 mg/lb ai, respectively. The dermal and inhalation unit exposures for applications of liquid pesticide formulations using a trigger-pump sprayer to pets or

animals are based on a study from Meo (1997). This study monitored 16 applications by commercial pet groomers treating 8 dogs for approximately 38-72 minutes using a read-to-use (RTU) trigger-spray bottle.

- RTU Aerosol Can - No exposure data are available for this application scenario and, thus, data for using a RTU Trigger-pump sprayer were used as a surrogate.

### 6.3.2.2 Application Rate (AR)

In all cases, OPP used the maximum labeled application rate to assess dermal and inhalation handler risk estimates for all of the residential pyrethroid uses.

### 6.3.2.3 Area Treated/Amount Handled (A)

#### Lawn/Turf Use

OPP assumed two types of treatments could be performed by individuals treating turf: broadcast and spot treatments. For broadcast turf treatments using hose-end sprayers (liquids) and push-type spreaders (granular), OPP assumed  $\frac{1}{2}$  acre would be treated by a home-owner. For spot turf treatments using low-pressure handwand sprayers (liquids and wettable powders), backpack sprayers (liquids and wettable powders), and sprinkler cans (liquids and wettable powders), OPP assumed 1,000 ft<sup>2</sup> would be treated by a home-owner. Determination of these values was based mainly on the Outdoor Residential Pesticide Use and Usage Survey and National Gardening Association Survey (Johnson, 1999), which showed that 73% of the people surveyed had lawns smaller than  $\frac{1}{2}$  acre.

#### Garden, Ornamental, and Tree Use

OPP assumed 1,200 ft<sup>2</sup> would be treated by an individual when treating gardens, ornamentals, and trees. Determination of these values was based mainly on the Outdoor Residential Pesticide Use and Usage Survey and National Gardening Association Survey (Johnson, 1999), which showed that the average garden size was 1,200 ft<sup>2</sup>.

#### Indoor Use

OPP assumed broadcast and crack and crevice treatments could be performed by individuals treating indoor surfaces. Both of these types of treatments are surface-directed and could be applied with a low-pressure handwand or an aerosol can. The low-pressure handwand was assumed to be used for both broadcast and crack and crevice treatments. OPP assumed 0.5 gallons would be used by a homeowner for both types of treatments. These values are supported by data from the Pesticide Handler Exposure Database (PHED), which indicate about 0.5 gallons for a commercial applicator crack/crevice and limited surface treatment in residences. Based on the use pattern for the pyrethroids, aerosol cans are only registered for crack and crevice treatments. OPP assumed  $\frac{1}{2}$  of a 16-oz can would be used. This value is supported by data from the Pesticide Handler Exposure Database (PHED), in which studies were conducted with commercial applicators applying one 15-oz aerosol can to areas of residential homes, including cracks, crevices, baseboards, under sinks, behind appliances, etc.

### Pet Use

OPP assumed that residential handlers of pet treatment products will treat 2 animals per application. This estimate is based upon data from the American Pet Products Manufacturers Association (APPMA) 2007-2008 National Pet Owners Survey, which reports that pet owners have an average of 1.7 dogs and 2.3 cats.

### **6.3.3 Handler Risk Summary**

For all scenarios, there are no residential handler risk estimates of concern associated with the registered uses of pyrethroids. All MOEs are greater than the target MOE of 100 for adult handlers (see Appendix 7 and Table 6.4.7a).

## **6.4 Post-application Exposure and Risk**

Post-application exposure refers to an exposure scenario in which an individual is exposed through dermal, inhalation, and/or incidental oral (non-dietary ingestion) pathways as a result of being in an environment that has been previously treated with a pesticide. Post-application dermal exposure is dependent on surface residues after treatment and surface-to-skin transfer. Post-application inhalation exposure depends on concentrations in the air after treatment and inhalation rates. Post-application non-dietary oral exposures are based on the ingestion of residues that can result from transfer of residues from hand-to-mouth. Dermal, inhalation, and non-dietary oral (hand-to-mouth) post-application exposure may occur following the residential use of pyrethroids depending on the use site. The algorithms and assumptions used for estimating residential post-application dermal, inhalation, and non-dietary oral are discussed in further detail below.

### **6.4.1 Post-application Dermal Exposure**

Post-application dermal exposure may occur following the residential uses of pyrethroids.

#### **6.4.1.1 Dermal Post-application Algorithm**

The following general equation is used to calculate dermal exposures resulting from contact with treated residential surfaces.

$$E = TR * TC * ET$$

where:

- E = exposure (mg/day);
- TR = transferable residue (mg/cm<sup>2</sup>);
- TC = transfer coefficient (cm<sup>2</sup>/hr);
- ET = exposure time (hr/day).

Dermal doses are estimated using the following algorithm:

$$D = \frac{E * AF}{BW}$$

where:

- D = dose rate (mg/kg-day);
- AF = absorption factor (dermal); and
- BW = body weight (kg).

Finally, dermal margins of exposure are estimated using the following algorithm:

$$MOE = \frac{IC\ POD}{D * RPF}$$

where:

- MOE = margin of exposure;
- D = dose rate (mg/kg-day);
- RPF = relative potency factor of any pyrethroid compared to the index chemical, deltamethrin; and
- IC POD = point of departure for the index chemical, deltamethrin.

### 6.4.1.2 Dermal Post-application Data and Assumptions

#### 6.4.1.2.1 Transferable Residue (TR)

Following an application, pesticide residues, which are deposited and remain on surfaces, could be contacted and removed by an individual. The pesticide residue is then available for absorption through the skin or potential ingestion. The residue available for transfer is referred to as transferable residue (TR). If pyrethroid-specific transferable residue data were available for a specific chemical, they were used in the cumulative screen. If pyrethroid-specific data were not available, the TR was calculated based on a fraction of the pesticide applied.

Lawn/Turf Use

For the lawn/turf use scenario, chemical-specific turf transferable residue (TTR) data collected with the Modified California Roller Method are available, and directly used, for four pyrethroids: cyfluthrin (liquid formulations), cypermethrin (liquid and wettable powder formulations), deltamethrin (liquid formulations), and permethrin (liquid formulations). Cyfluthrin resulted in the highest normalized turf transferable residues out of the available liquid formulation TTR data. For the liquid formulation pyrethroids that did not have TTR data available, cyfluthrin TTR data were used as a surrogate. In all cases, the cyfluthrin TTR data were adjusted to reflect the maximum individual pyrethroid application rates. Table 6.4.1.2.1a summarizes the available pyrethroid TTR data.

Chemical	Study	Sites	Day 0 TTR (ug/cm <sup>2</sup> )	Average Day 0 TTR (ug/cm <sup>2</sup> )	Average Day 0 TTR Normalized to 0.1 lb ai/A (ug/cm <sup>2</sup> )
Cyfluthrin	Determination of Transferable Turf Residues on Turf Treated With Cyfluthrin (MRID 45149001)	GA (L)	0.023	0.021	0.011
		MS (L)	0.032		
		NY (L)	0.007		
Cypermethrin	Demon WP and Demon TC Transferable Turf Residue Study (MRID 45111501)	CA (WP)	0.081	0.071	0.012
		MO (WP)	0.041		
		PA (WP)	0.090		
		CA (L)	0.035	0.023	0.0052
		MO (L)	0.009		
		PA (L)	0.026		
Deltamethrin	Determination of Transferable Turf Residues on Turf Treated with Deltamethrin (Deltagard GC or T&O) (MRID 45251201)	NY (L)	0.008	0.014	0.010
		CA (L)	0.020		
		GA (L)	0.013		
Permethrin	Transferable Turf Residue Study: Permethrin Residues in Turf Following Application of Dagnet® SFR Insecticide/Miticide (MRID 44955501)	PA (L)	0.051	0.061	0.0070
		CA (L)	0.073		
		GA (L)	0.058		

Garden, Ornamental, and Tree Use

For the garden, ornamental, and tree use scenario, chemical-specific dislodgeable foliar residue (DFR) data are available for four pyrethroids: cyfluthrin, fluvalinate, esfenvalerate, and permethrin. Most of these DFR data were collected on orchard crops (i.e., stone fruits, apples, oranges) or in greenhouses. The esfenvalerate DFR data included analysis of foliar residues on corn and broccoli and are considered most representative of potential crops that could be found in a home garden. These data were combined and used as a surrogate for all of the pyrethroids. In all cases, the esfenvalerate DFR data were adjusted to reflect the maximum individual pyrethroid application rates. Table 6.4.1.2.1b summarizes the available pyrethroid DFR data.

## Pyrethroid Cumulative Risk Assessment

Chemical	Study	Sites	Day 0 DFR (ug/cm <sup>2</sup> )	Average Day 0 DFR (ug/cm <sup>2</sup> )
Esfenvalerate	Dissipation of Dislodgeable Foliar Residues of Esfenvalerate from Broccoli Following Application of Asana® XL Insecticide in the USA - Season 1997 (MRID 44852402)	CA1 (L)	0.157	0.132
		CA2 (L)	0.122	
	FL (L)	0.072		
	PA (L)	0.177		
	Dissipation of Dislodgeable Foliar Residues of Esfenvalerate from Sweet Corn Following Application of Asana® XL Insecticide in the USA - Season 1998 (MRID 44852403)			

### Indoor Use

For the indoor uses scenarios, no chemical-specific transferable residue (TR) data are available for the pyrethroids; therefore, the TR was calculated using the following formula:

$$TR = DepR * F_{ai}$$

where:

TR = indoor surface transferable residue (µg/cm<sup>2</sup>);

DepR = deposited residue (ug/cm<sup>2</sup>), and

F<sub>ai</sub> = fraction of ai available for transfer from carpet or hard surface (unitless).

### Deposited Residue (DepR)

**Broadcast applications:** For broadcast applications, the deposited residue was assumed to be equivalent to the application rate (a unit conversion was performed to achieve residue values in units of ug/cm<sup>2</sup>). A formal evaluation was conducted for each pyrethroid with registered indoor broadcast uses to determine the maximum application rate currently registered. These rates were used in the screening-level cumulative assessment.

**Fogger applications:** For fogger applications, data from the Non-Dietary Exposure Task Force (NDETF) were used to estimate deposited residue for the pyrethroids with registered indoor fogger uses (Rogers, 2000; Selim, 2002a; Selim, 2003a). The NDETF conducted three studies measuring the deposited residue following application of a 0.2% deltamethrin fogger, a 0.5% permethrin fogger, and a 0.5% pyrethrins fogger. In each study, the fogger was discharged in an experimental room and the resulting deposited residues were measured using deposition coupons. The average residue value (adjusted to 0.5% active ingredient, if necessary) from each study was 5.6 ug/cm<sup>2</sup> for deltamethrin, 4.8 ug/cm<sup>2</sup> for permethrin, and 5.8 ug/cm<sup>2</sup> for pyrethrins. The average residue value across the three studies was 5.4 ug/cm<sup>2</sup> for a 0.5% fogger.

A formal evaluation of all the registered uses was conducted for each pyrethroid with registered indoor fogger uses to determine the maximum percent active ingredient in registered products. In the cumulative screen, the chemical-specific residue for deltamethrin,

permethrin, and pyrethrins was used, making an adjustment for the maximum percent active ingredient registered. For the pyrethroids without chemical-specific residue data, the average residue value from the three studies was used, making the same adjustment for maximum percent active ingredient registered.

*Crack and crevice applications:* For crack and crevice applications, the Agency used a registrant-submitted study (Selim, 2008) that provided an estimate of deposited residue from a crack and crevice application for esfenvalerate. In this study, a 0.1% esfenvalerate formulation was applied using an aerosol can with an injection tube. The test container was held 12 to 18 inches above the baseboard to achieve an approximate one inch spray band at the floor/wall interface. Residues were collected 30 minutes after application using deposition coupons. The residue value for the entire room was calculated as a weighted average of the “treated area” and the “untreated area” (10% of residue in treated area plus 90% of residue in untreated area). This resulted in a weighted residue value of 0.2 ug/cm<sup>2</sup>. This value was used for all of the pyrethroids with registered crack and crevice uses. It was not adjusted for percent active ingredient because data available to the Agency do not seem to indicate a trend with respect to deposited residues and percent active ingredient (i.e., a higher percent active ingredient does not necessarily result in a higher deposited residue value for a room).

Fraction of Residue Available For Transfer ( $F_{ai}$ )

Chemical-specific data provided by the Non-Dietary Exposure Task Force (NDETF) were used for the fraction of residue available for transfer (Selim, 2004a; Selim, 2003b; Selim, 2003c; Selim, 2000; Selim, 2002b; Selim, 2002c). The NDETF studies examined the transferability of residues from bare hand-presses on carpets and hard surfaces for deltamethrin, permethrin, and pyrethrins. For carpets, the fraction transferred was 0.03, 0.02 and 0.01 for pyrethrins, permethrin and deltamethrin, respectively. For hard surfaces, the fraction transferred was 0.04, 0.03, and 0.05 for pyrethrins, permethrin, and deltamethrin, respectively. Since the values were so similar across the three chemicals, the average fraction transferred was used for all the pyrethroids in the cumulative assessment: 0.02 for carpets and 0.04 for hard surfaces.

Pet Use

For the pet uses scenarios, no chemical-specific TR data are available; therefore, the TR was calculated using the following formula:

$$TR = (AR * F_{AR}) / SA$$

where:

TR = transferable residue (mg/cm<sup>2</sup>);

AR = application rate or amount applied to animal (mg);

F<sub>AR</sub> = fraction of the application rate available as transferable residue; and

SA = surface area of the pet (cm<sup>2</sup>).

Application Rate (AR)

A formal evaluation was conducted for each pyrethroid with registered pet uses to determine the maximum application rate currently registered. These rates were used in the screening-level cumulative assessment.

Fraction Application Rate ( $F_{AR}$ )

A default  $F_{AR}$  was selected based on the review of 8 “petting” studies submitted to the Agency. Measurements of residue availability were derived by taking the ratio of the amount of active ingredient on a bare or gloved hand (on the day of highest observed transfer) to the amount of active ingredient applied. Studies were performed by means of volunteers “petting” or “stroking” animals treated with a known amount of active ingredient and determining the amount of residue transferred to the hands.  $F_{AR}$  studies varied in the number, location and intensity of petting and stroking actions. Based on the available studies, the mean  $F_{AR}$  is estimated to be 0.0096 (Hughes, 1997; Hughes, 1997b; McKeown, 2001; Brickel, et. al, 1997; Bach, 2002; Wrzesinski, 2009; Wrzesinski, 2010a; Wrzesinski, 2010b). Table 6.4.1.2.1c summarizes the available  $F_{AR}$  data.

<b>Table 6.4.1.2.1c. Fraction Application Rate (<math>F_{AR}</math>) Transferred</b>			
<b>Study</b>	<b>MRID</b>	<b>N</b>	<b>Average Fraction of Application Rate Transferred</b>
Dislodgeable Residues of Fipronil Following Application of Frontline® Spray Treatment to Dogs	44433306	30	0.0069
Dislodgeable Residues of Fipronil Following Application of Frontline® Spray Treatment to Cats	44433307	15	0.0039
Determination of the Dislodgeability of Tetrachlorvinphos (TCVP) from the Fur of Dogs Following the Application of an Insecticide Powder, Pump Spray or Aerosol	45485501	10	0.0030
Dislodgeable Residues of Fipronil Following Topical Application of Frontline® Spot-on Treatment to Dogs	44531203	18	0.0076
Stroking Test in Dogs After Topical Application of Imidacloprid 10% (w/v) + Permethrin 50% (w/v) Spot-On	46594103	18	0.0027
Dislodgeable Residue Study of SCH 783460 (Indoxacarb) from Spot-On Treated Beagle Dogs	47834502	20	0.0208
One-Month Dislodgeable Residue Study of SCH 783460 (Indoxacarb) from Spot-On Treated Cats	48010801	20	0.0100
One-Month Dislodgeable Residue Study of Indoxacarb from Spot-On Treated Beagle Dogs	48135326	20	0.0094
One-Month Dislodgeable Residue Study of Permethrin from Spot-On Treated Beagle Dogs	48135326	20	0.0176

Surface Area (SA)

Animal surface area (SA) is determined by inputting animal weight (lbs) into an algorithm ( $12.3 * ((\text{animal body weight (lbs)} * 454)^{0.65})$ ) as referenced from U.S. EPA (1993) Wildlife Exposure Factors Handbook. For the purposes of the pyrethroid screen, the surface area of a medium dog was used in the calculations of exposure (7000 cm<sup>2</sup>).

#### 6.4.1.2.2 Transfer Coefficient (TC)

The transfer coefficient (TC) provides a measure of surface-to-skin residue transfer and is derived from concurrent measurements of exposure and surface residue. Specifically, the TC is the ratio of exposure rate, measured in mass of chemical per time (i.e., ug/hr), to residue, measured in mass of chemical per surface area (i.e., ug/cm<sup>2</sup>). Table 6.4.1.2.2 summarizes the transfer coefficients for the different residential scenarios.

##### Lawn/Turf Use

The transfer coefficients used for assessing the lawn/turf dermal scenarios were derived from data gathered while adult human volunteers performed an approximate 2-hour composite routine consisting of 12 sequential activities which children and adults routinely engage on residential turf (Klonne and Johnson, MRID 47292001). These activities represent behaviors that are reported in the National Human Activity Pattern Survey (NHAPS) for children aged 1 to 12 years (Klepeis, et. al., 2001). The two hour duration of the routine was chosen because NHAPS indicated that the upper-bound estimate of time children spend playing on turf is two hours per day. The potential dermal exposure to each study participant was measured by using whole-body dosimetry (inner and outer dosimeters), foot washes, hand washes, and face/neck wipes.

##### Garden, Ornamental, and Tree Use

The transfer coefficients used for assessing the garden, ornamental, and tree dermal scenarios were derived from data gathered while adult human volunteers performed various tasks such as weeding and picking flowers and vegetables. The data used to derive the transfer coefficients are from occupational reentry exposure studies conducted by the Agricultural Reentry Task Force (ARTF) because data to adequately characterize exposure for individuals who contact previously treated residential gardens, ornamentals, and trees are unavailable. Four separate exposure studies were used to develop the transfer coefficient: a study each for cabbage weeding (Klonne, 2000; MRID 45191701), tomato tying (Klonne, 2001; MRID 45530103), squash harvesting (Klonne, 2001; MRID 45491902), and chrysanthemum pinching (Klonne, 2000; MRID 45344501). Therefore, transfer coefficients from occupational reentry exposure studies conducted by the Agricultural Reentry Task Force (ARTF), were used to establish composite transfer coefficients representing activities likely to occur in residential settings.

##### Indoor Use

The transfer coefficients used for indoor scenarios are derived from information provided in three different studies: (1) two studies which measured exposure and surface residues while subjects performed a Jazzercise™ routine (Krieger, 2000 and Selim, 2004) and (2) a study which measured biomonitoring doses while adults performed scripted activities for 4 hours on carpet (Vaccaro, 1991). In the Krieger and Selim studies, a Jazzercise™ routine was performed to achieve maximum contact of the entire body with a surface using low impact aerobic movements. The potential dermal exposure was measured by using whole-body dosimetry. The assumption is that the dosimeter represents the skin and that the dose retained by the

dosimeter is equivalent to dermal exposure. In the Vaccaro study, adult males, dressed in bathing suits only, performed different activities over a 4-hour activity period. These activities included: sitting-playing with blocks, on hands and knees crawling, walking on carpet, laying on back, and laying on abdomen. Using information from these studies on residue transfer, exposure and dose provides an estimated transfer coefficient for indoor activities. It is assumed that the shorter duration of high contact activity (i.e., Jazzercise™) can be used to estimate exposure during longer durations of low contact activity.

**Pet Use**

The transfer coefficients used for pet exposure were derived from a study representing application and grooming activities with dogs using a carbaryl shampoo product (Mester, 1998). Data were gathered while human volunteers applied pet pesticide products to various dogs of differing sizes and fur lengths.

**Table 6.4.1.2.2. Transfer Coefficient Summary**

Scenario	Adults (cm <sup>2</sup> /hr)	6-11 year olds (cm <sup>2</sup> /hr)	1-2 year olds (cm <sup>2</sup> /hr)
Turf/Lawn Use	130,000	NA	37,000
Garden/Ornamental/Tree Use	8,400	5,000	NA
Indoor Use	6,800	NA	2,000
Pet Use	5,200	NA	1,500

**6.4.1.2.3 Exposure Time (ET)**

Table 5.4.1.2.3 summarizes the selected exposure times for the different residential scenarios.

**Lawn/Turf Use**

The exposure times used for assessing the lawn/turf dermal scenarios were selected from data presented in the Agency’s Exposure Factors Handbook Table 15-80 (USEPA, 1997). These data represent the amount of time spent outdoors rather than just on lawns. This adjustment allows for additional time that children may spend outdoors (such as parks and schools) where there is potential for additional contact with treated turf.

**Garden, Ornamental, and Tree Use**

The exposure times used for assessing the garden, ornamental, and tree dermal scenarios were derived using a residential survey (Johnson, 1999) and information from the U.S. EPA Exposure Factors Handbook (USEPA, 1997). The exposure time for gardening represents vegetable gardening and flower gardening in equal proportion (i.e., 50% each).

**Indoor Use**

A study which provides information specific to time spent on different types of surfaces indoors is not available. The Exposure Factors Handbook (U.S. EPA, 1997) and the Child Specific Exposure Factors Handbook (U.S. EPA, 2008) provide information on total time spent in a residence and time spent in various rooms within a residence. In order to develop inputs for exposure time on carpets and hard surfaces, two assumptions were made: (1) kitchens and

bathrooms would represent time spent on hard surfaces and (2) time spent in a residence, less time spent sleeping and napping, would represent time spent on carpets.

### Pet Use

The exposure time for adults and children were derived from the US EPA’s National Center for Environmental Assessment (NCEA) Exposure Factors Handbook (USEPA, 1997). The recommended data are included in Table 15-77, *Statistics for 24-Hour Cumulative Number of Minutes Spent in Animal Care*. Animal care is defined by NCEA as “care of household pets including activities with pets, playing with the dog, walking the dog and caring for pets of relatives, and friends.” The data identified the time spent with an animal while performing household activities as recorded in 24 hour diaries by study volunteers. While the activities defined do not necessarily represent the time volunteers were actively engaged in constant contact with the animal, as is implicit in the post-application dermal and incidental oral algorithms, they were used to derive the best data source available.

Scenario	Adults (hrs)	6-11 year olds (hrs)	1-2 year olds (hrs)
Turf/Lawn Use	1.1	NA <sup>1</sup>	0.9
Garden/Ornamental/Tree Use	1.4	0.7	NA <sup>2</sup>
Indoor Use	Carpets	8	5
	Hard Surfaces	2	1
Pet Use	0.77	NA <sup>1</sup>	0.99

NA<sup>1</sup> - not assessed because 1-2 yr olds are expected to be protective for 6-11 yr olds

NA<sup>2</sup> - not assessed because 1-2 yr olds are not expected to be performing gardening activities

## 6.4.2 Post-application Dermal Risk Summary

For all scenarios, there are no residential post-application dermal risk estimates of concern associated with the registered uses of pyrethroids. All MOEs were greater than the Agency’s target MOE of 300 for children and 100 for adults (see Appendix 7 and Table 6.4.7a).

## 6.4.3 Post-application Inhalation Exposure

For turf and gardens, post-application inhalation exposure is generally not assessed. The combination of the generally low vapor pressure for pyrethroids and the substantial dilution of airborne concentrations outdoors is likely to result in minimal inhalation exposure.

For pet uses, post-application inhalation exposure is generally not assessed. The combination of the generally low vapor pressure for pyrethroids and the small amounts of pesticide applied to pets is likely to result in minimal inhalation exposure.

For indoor uses, post-application inhalation exposure is dependent on the type of application made:

*Fogger applications:* Post-application inhalation exposure due to the use of indoor foggers is expected to be negligible since most fogger product labels typically state a period of no-entry following application (usually up to 4 hours), as well as a ventilation period before occupants can return.

*Crack and crevice applications:* For crack and crevice applications, there is the potential for post-application inhalation exposure to pesticide vapors emitting from the treated surfaces following application. For pyrethroids, this exposure is not expected to be significant primarily because of their low vapor pressure. HED has recently received an Office of Research and Development (ORD) exposure study that was performed in the U.S. EPA's IAQ Research House. This study is currently unpublished but HED has reviewed the data (Smith, D390098, 2011). This study simulated crack and crevice applications of four pesticides; two emulsifiable concentrates products applied via a handheld sprayer (permethrin and cypermethrin), one aerosol can product (propoxur), and one gel bait product (fipronil). Permethrin and cypermethrin air concentrations were not found in any measurable quantities in any room in the research house. Although this study provides data for only two pyrethroids, the Non-dietary Exposure Task Force (NDETF) has performed an analysis of all the pyrethroid exposure data that they produced (Osimitz and Holden, 2005; MRID 46493701). This analysis shows the exposure data for one pyrethroid can generally be used to represent the entire chemical class. Based on this NDETF analysis, the air concentration data from the ORD study can be considered representative of all pyrethroids. Given the negligible air concentration values that were reported from the ORD study, HED does not have concerns for post-application inhalation exposure from pyrethroid crack and crevice applications.

*Broadcast applications:*

Similar to crack and crevice applications, there is the potential for post-application exposure to pesticide vapors emitting from treated indoor surfaces following indoor broadcast applications. For pyrethroids, this exposure is not expected to be significant primarily because of their low vapor pressure. Pyrethroid-specific air monitoring data following a broadcast application are not available; therefore, the approach discussed below was used to estimate potential post-application exposure for the pyrethroids with broadcast uses (allethrin, esfenvalerate, permethrin, pyrethrins, and tetramethrin).

### **6.4.3.1 Post-application Inhalation Algorithms**

Post-application inhalation exposure for adults/children resulting from surface-directed spray applications made indoors can be estimated using the following algorithm:

$$E = \frac{IR * M_{label}}{ACH * V_{room}} * 1 - \left[ \frac{\left( (ACH * e^{-k*ET}) - (k * e^{-ACH*ET}) \right)}{ACH - k} \right]$$

Where:

- E = exposure (mg/day);
- IR = inhalation rate (m<sup>3</sup>/hr);
- M<sub>label</sub> = mass of active ingredient applied, determined from product label (mg);
- V<sub>room</sub> = volume of room (m<sup>3</sup>);
- ACH = air exchanges per hour (hour<sup>-1</sup>);
- k = first order decay rate; and
- ET = exposure time (hr).

Once the post-application inhalation exposure is calculated, the inhalation dose normalized to body weight is calculated as:

$$D = \frac{E * AF}{BW}$$

where:

- D = dose (mg/kg-day);
- E = exposure (mg/day);
- AF = absorption factor (inhalation); and
- BW = body weight (kg).

Finally, inhalation margins of exposure are estimated using the following algorithm:

$$MOE = \frac{IC\ POD}{D * RPF}$$

where:

- MOE = margin of exposure;
- D = dose rate (mg/kg-day);
- RPF = relative potency factor of any pyrethroid compared to the index chemical, deltamethrin; and
- IC POD = point of departure for the index chemical, deltamethrin.

### 6.4.3.2 Post-application Inhalation Data and Assumptions

#### 6.4.3.2.1 Inhalation Rate (IR)

For indoor post-application exposure, it is recommended that the inhalation rate for sedentary and passive activities be used in the exposure calculation. The values used in this assessment are 0.32 m<sup>3</sup>/hr for adults and 0.28 m<sup>3</sup>/hr for 1 to <2 year olds (U.S. EPA, 2009).

#### 6.4.3.2.2 Mass of active ingredient applied ( $M_{\text{label}}$ )

The mass of active ingredient applied was calculated based on maximum application rates determined by a formal evaluation of all the registered pyrethroid indoor uses. The application rates were in units of lb ai/square feet and it was assumed for broadcast applications that the product was sprayed over an area of 144 square feet (12 ft by 12 ft room).

#### 6.4.3.2.3 Air Changes per Hour (ACH)

Air changes per hour is the rate that air within an indoor environment is replaced by outdoor air. The value used in this assessment is 0.18 ACH, which represents the 10th percentile of the estimated national distribution for residential air exchange rates and is a conservative estimation of air exchange in residential settings (U.S. EPA, 1997).

#### 6.4.3.2.4 Volume of a Room ( $V_{\text{room}}$ )

The volume of a room is based on typical dimensions of residential rooms from Exposure Factors Handbook (U.S. EPA, 1997). For a 12 foot by 12 foot room, with an 8 foot high ceiling, the typical volume is 33 m<sup>3</sup>.

#### 6.4.3.2.5 First Order Decay Rate ( $k$ )

The decay rate,  $k$ , defines the change in the emission rate from the treated surface. As proposed by Evans (1994), the decay rate constant is based on the 90% drying time. The 90% drying time, in turn, is calculated based on the evaporation time and volatility of the chemical using equations from Chinn (1981).

#### 6.4.3.2.6 Exposure Time (ET)

For vapor emissions from surface-directed sprays, it is assumed that the vapors can continue to emit over time; therefore, exposure time is related to time spent in a residence. The value used in this assessment is 16 hours for both adults and 1 to <2 year olds (U.S. EPA, 1997 and U.S. EPA, 2008).

### 6.4.4 Post-application Inhalation Risk Summary

For all scenarios, there are no residential post-application inhalation risk estimates of concern associated with the registered uses of pyrethroids. All MOEs were greater than the Agency's target MOE of 300 for children and 100 for adults (see Appendix 7 and Table 6.4.7a).

## 6.4.5 Post-application Incidental Oral Exposure and Risk

Post-application incidental oral exposure may occur following the lawn/turf, indoor, and pet uses of pyrethroids. For gardens, post-application incidental oral exposure is not assessed as younger children are not expected to spend extended periods of time in contact with gardens, ornamentals, and trees.

### 6.4.5.1 Post-application Incidental Oral Algorithm

Post-application incidental oral exposure for children resulting can be estimated using the following algorithm:

$$E = [HR * (F_M * SA_H) * (ET * N\_Replen) * (1 - (1 - SE)^{(Freq\_Replen/N\_Replen)})]$$

Where:

- E = exposure (mg/day);
- HR = hand residue loading (mg/cm<sup>2</sup>);
- F<sub>M</sub> = fraction hand surface area mouthed / event (fraction/event);
- ET = exposure time (hr/day);
- SA<sub>H</sub> = surface area of one hand (cm<sup>2</sup>);
- N\_Replen = number of replenishment intervals per hour (intervals/hour);
- SE<sub>H</sub> = saliva extraction factor (i.e., mouthing removal efficiency); and
- Freq\_Replen = number of hand-to-mouth contacts events per hour (events/hour).

Hand residues are estimated using the following algorithm.

$$HR = (Fai_{hands} * DE) / (SA_H * 2)$$

Where:

- HR = hand residue loading (mg/cm<sup>2</sup>);
- Fai<sub>hands</sub> = fraction ai on hands compared to total surface residue from dermal exposure study (unitless);
- DE = dermal exposure (mg); and
- SA<sub>H</sub> = typical surface area of one hand (cm<sup>2</sup>).

Non-dietary incidental oral doses are estimated using the following algorithm:

$$D = \frac{E}{BW}$$

where:

- D = dose rate (mg/kg-day); and
- BW = body weight (kg).

Finally, non-dietary incidental oral margins of exposure are estimated using the following algorithm:

$$MOE = \frac{IC\ POD}{D * RPF}$$

where:

MOE = margin of exposure;

D = dose rate (mg/kg-day);

RPF = relative potency factor of any pyrethroid compared to the index chemical, deltamethrin; and

IC POD = point of departure for the index chemical, deltamethrin.

### 6.4.5.2 Post-application Incidental Oral Data and Assumptions

#### 6.4.5.2.1 Hand Residue (HR)

The available residue on hands for non-dietary ingestion is linked to dermal exposure and is calculated as a fraction of the dermal exposure. The fraction of active ingredient available on the hands was based on data from the dermal transfer coefficient studies for turf, indoors, and pets. This value was estimated by taking the average fraction of active ingredient on the hands in each dermal study and comparing that value to the average fraction of active ingredient on the entire body assuming an individual is wearing a t-shirt and shorts. The fraction of active ingredient available on the hands ( $F_{ai\ hands}$ ) for each scenario is provided in Table 6.4.5.2.1 below.

Scenario	$F_{ai\ hands}$
Turf/Lawn Use	0.06
Indoor Use	0.15
Pet Use	0.039

#### 6.4.5.2.2 Fraction of Hand Mouthed per Event ( $F_M$ )

The fraction hand surface area mouthed value was taken from the Zartarian et al. (2005) analysis of data originally presented in Leckie et al. (2000). The Leckie et al. (2000) study consisted of a data set of 20 suburban children videotaped outdoors. Part of the videotape analysis performed by Leckie was to determine the amount of the hand that was mouthed by each child every time a mouthing event occurred. The analysis in Zartarian et al. (2005) consisted of assigning numerical values to each of five scenarios (outside mouth contact, partial finger, full finger, partial palm with fingers, and partial palm without fingers). It was assumed that each finger is 10% of the hand, and that the surface area of palm that can be mouthed is

25% of the hand. For 1 “partial finger” inserted into the mouth a value of 5% of the hand was selected, 2 partial fingers 10%, *et cetera*. The fraction of hand mouthed used for all non-dietary incidental oral ingestion scenarios in this assessment is 0.13.

#### 6.4.5.2.3 Hand Surface Area ( $SA_H$ )

The hand surface area for 1 to <2 year olds is 150 cm<sup>2</sup> for one hand which is based on data from the Child-Specific Exposure Factors Handbook (U.S. EPA, 2008). This value was used for all non-dietary incidental oral ingestion scenarios in this assessment.

#### 6.4.5.2.4 Fraction of Pesticide Extracted by Saliva ( $SE_H$ )

The value for fraction of pesticide extracted by saliva is based on analysis of data collected in a study by Camann et al. (1995). This study focused specifically on fraction of pesticide extracted by saliva from hands, not objects. The fraction of pesticide extracted by saliva value used for all non-dietary incidental oral ingestion scenarios in this assessment is 0.48.

#### 6.4.5.2.5 Exposure Time (ET)

The exposure times used in the assessment of the non-dietary incidental oral ingestion scenarios is the same as described for 1 < 2 year olds above in Section 3.2.1.2.3 and Table X.

### 6.4.6 Post-application Incidental Oral Risks

For all scenarios, there are no residential post-application incidental oral risk estimates of concern associated with the registered uses of pyrethroids. All MOEs were greater than the Agency’s target MOE of 300 for children (see Appendix 7 and Table 6.4.7a).

### 6.4.7 Combined Exposure

The sections above describe the separate dermal (handler and post-application), inhalation (handler and post-application), and non-dietary oral ingestion (post-application) assessments that have been performed for the pyrethroids. In reality, exposures resulting from different routes do not occur as single, isolated events, but rather as a series of sequential or concurrent events that may overlap or be linked in time and space. Based on this, risk estimates resulting from different exposure routes are combined when it is likely that they can occur simultaneously based on the use pattern and when the toxicological effects across different routes of exposure are the same.

Table 6.4.7a presents the highest estimated risk (i.e., the lowest MOE) for each of the individual routes of exposure that could occur for a use scenario. It also presents the estimated risks for combining all of the individual routes of exposure within a use scenario. For children (1 to <2 years), all MOEs were above the target MOE of 300 when all routes of exposure were combined

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within a particular exposure scenario. For adults, all MOEs were above the target MOE of 100 when all routes of exposure were combined within a particular exposure scenario.

Table 6.4.7a. Pyrethroid Screening Level Combined Residential Assessment Within Scenario Results							
Lifestage	Scenario	Handler		Post-application Exposure Route			Combined Within Scenario
		Dermal	Inhalation	Dermal	Inhalation	HtM	
1 < 2 year olds	Turf	NA	NA	3,000	NA	21,000	2,600
				(cyfluthrin)			
	Pet	NA	NA	4,200	NA	22000	3,500
				(cyphenothrin)			
	Indoor Broadcast	NA	NA	15,000	110,000,000	3800	3,000
(esfenvalerate)							
Indoor Fogger	NA	NA	3,500	NA	900	720	
Indoor C&C	NA	NA	36,000	NA	9,700	7,600	
			(cyhalothrin)				
Adults	Turf	9,200	280,000	4,500	NA	NA	3,000
		(cyfluthrin-hose-end sprayer)		(cyfluthrin)			
	Garden	15,000	780,000	1,400	NA	NA	1,300
		(fluvalinate-backpack)		(fluvalinate)			
	Pet	27,000	10,000,000	9,800	NA	NA	7,200
		(permethrin-shampoo)		(cyphenothrin)			
	Indoor Broadcast	240,000	760,000	17,000	610,000,000	NA	16,000
(allethrin-LPHW)		(esfenvalerate)					
Indoor Fogger	NA	NA	3,900	NA	NA	3,900	
Indoor C&C	NA	NA	43,000	NA	NA	19,000	
			(cyfluthrin-LPHW)		(cyhalothrin)		

Once the screening level values for residential exposure were combined within a use scenario, the next step was to combine scenarios that could potentially co-occur. For example, a child could be exposed in the same day by contacting a treated pet and a treated indoor surface. In all cases, the MOE representing the highest residential risk estimate (i.e., the lowest MOE) was chosen to represent each scenario for adults and children (1 to <2 years). For example, there are a number of pyrethroids registered for use on turf, but the combined turf cyfluthrin MOEs were used to represent all pyrethroid turf use because cyfluthrin resulted in the lowest combined turf MOEs for adults and 1 < 2 year olds. Although combining scenarios that use high-end, health protective inputs or assumptions is not typically appropriate due to compounding conservatisms, HED performed such a health protective, screening level combined residential exposure assessment for the pyrethroids.

Table 6.4.7b presents an analysis of a number of scenario combinations. For children (1 to <2 years), all MOEs were above the target MOE of 300 for all of the scenario combinations

considered. For adults, all MOEs were above the target MOE of 100 for all of the scenario combinations considered.

**Table 6.4.7b. Pyrethroid Screening Level Combined Residential Assessment Across Scenario Results**

Lifestage	Scenario	Combined Within Scenario MOE	Routes of Exposure	Combined Across Scenarios		
1 < 2 year olds	Turf	2,600	PD, PHtM	1,000		
	Pet	3,500	PD, PHtM			
	Indoor Broadcast	3,000	PD, PI, PHtM			
		Turf	2,600	PD, PHtM	490	
		Pet	3,500	PD, PHtM		
		Indoor Fogger	720	PD, PHtM		
		Turf	2,600	PD, PHtM		
		Pet	3,500	PD, PHtM	1,200	
Indoor Crack & Crevice		7,600	PD, PHtM			
Adults		Garden	1,300	HD, HI, PD		910
		Turf	3,000	HD, HI, PD		
	Pet	7,200	HD, HI, PD	5,200		
	Indoor Crack & Crevice	19,000	HD, HI, PD			

PD = post-application dermal exposure, PHtM = post-application hand-to-mouth exposure, PI = post-application inhalation exposure, HD = handler dermal exposure, HI = handler inhalation exposure. PD = post-application dermal exposure, PHtM = post-application hand-to-mouth exposure, PI = post-application inhalation exposure, HD = handler dermal exposure, HI = handler inhalation exposure

## 7.0 Combined Screening Level Dietary + Residential Cumulative

Once the screening level risk estimates for exposure by the dietary and residential pathways were calculated, the next step was to combine them into a screening level pyrethroid cumulative assessment. In light of the complexity of the residential use patterns, the Agency elected to take a screening approach to the cumulative assessment, by combining the risk estimates from the dietary pathway with the highest risk estimates from the appropriate residential pathways. This approach is considered highly conservative and health protective for reasons outlined in Section 8.0. The calculations for the screening level cumulative risk assessment combine the 99.9<sup>th</sup> percentile MOE from the dietary exposure values (see Table 5.3b) for adults and children (1 to <2 years) with the combined residential scenarios (see Table 6.4.7b).

Table 7.0 provides a summary of the combined estimated MOEs for adults and children (1 to <2 years). For adults, all of the estimated MOEs are above the target MOE of 100. For children (1 to <2 years), all of the estimated MOEs are above the target MOE of 300.

Age Group	Exposure Route				Screening Combined MOE (Dietary + Residential)
	Dietary		Residential (non-dietary)		
	Scenario	MOE (at 99.9 <sup>th</sup> percentile)	Combined Scenarios (Routes of Exposure)	MOE	
1 < 2 year olds	Food+ Water	3,000	Indoor C&C (PD and PHtM) + Pet (PD and PHtM) + Turf (PD and PHtM)	1,200	860
			Indoor Fogger (PD and PHtM) + Pet (PD and PHtM) + Turf ((PD and PHtM)	490	<b>420</b>
			Indoor Broadcast (PD, PI and PHtM) + Pet PD and PHtM) + Turf PD and PHtM)	1,000	750
Adult		5,400	Turf (HD, HI, and PD) + Garden (HD, HI, and PD)	950	810
			Indoor C&C (HD, HI, and PD) + Pet (HD, HI, and PD)	5,100	2,600

## 8.0 Characterizing the Screening-Level Pyrethroid Cumulative Risk Estimates

This screening-level pyrethroid cumulative risk assessment is considered to be a conservative and health protective assessment which likely greatly overestimates exposure and risk. The extent to which the characteristics and assumptions in this cumulative assessment are considered to be conservative is detailed below. The Agency believes that refinements to address the assumptions discussed below would further support this conclusion.

### 8.1 Hazard Characterization

The Agency has determined that the pyrethroids and pyrethrins share a common mechanism of toxicity through interaction with VGSCs and leading to neurotoxicity are generally characterized by two toxicity syndromes (i.e., T syndrome or Type I and CS syndrome or Type II). As discussed throughout this CRA, the current assessment is considered a screening level analysis. In the case of the cumulative hazard assessment, as discussed in Section 2.4, the Agency has elected to combine the Type I and Type II pyrethroids together. Type I and Type II pyrethroids differ in the duration and nature of VGSC interaction, with Type II pyrethroids causing an elongated open state of the sodium channel compared to the Type I pyrethroids. Behaviorally, the Type I pyrethroids produce hyperreactivity, fine to whole body tremors, and hyperthermia (T syndrome) whereas Type II pyrethroids cause salivation, and coarse tremors leading to sinuous writhing termed choreoathetosis (CS syndrome) (Verschoyle and Aldridge 1980). As such, there is scientific support for considering these pyrethroids in separate sub-groups if appropriate in the future.

It would be preferred to use an *in vivo* endpoint related to VGSC interaction, but at this time current methods do not exist to practically measure such an *in vivo* biomarker. As such, the Agency must rely on apical endpoints related to neurobehaviors such as tremors, salivation, and changes in body temperature. An FOB study by the WIL laboratory provides the most complete and most relevant dataset from which to assess and compare pyrethroid toxicities for the purpose of developing the cumulative risk assessment. By incorporating several pyrethroids into a single study, using the same protocol and experimental design, interlaboratory differences (i.e., scoring criteria, vehicle, and vehicle volume) that complicate interpretation of behavioral responses and increase uncertainty when comparing relative potency were eliminated. This FOB study evaluated 46 measures using a standard protocol, with a few modifications to specifically describe behaviors relevant to the pyrethroid toxicity syndromes. Although the pyrethroids produced changes in numerous endpoints multidimensional analyses revealed that differential effects were arrayed across four principal components. Of these, differential syndromes could be defined by five FOB endpoints (T: hyperthermia, tremors, clonic convulsions, and CS: hypothermia, salivation, mobility); these findings agree well with earlier descriptions of the pyrethroid syndromes.

The Agency has used a refined and novel approach to deriving BMDs for the 11 of the 15 pyrethroids, including the eight most potent, for these neurobehavioral effects identified in the WIL FOB study. The approach used in the CRA to normalize the data based on relative severity of the effect (i.e., severity scores) is consistent with methods reported in the scientific literature used to differentiate profiles of effects for various neurotoxicants (Moser 1991; McDaniel and Moser 1993; Moser et. al. 1995). While the severity scoring approach combines individual effects on specific endpoints, and may thereby lose some resolution in individual differences, it provides more integrated data that may be compared across studies. In addition, the BMD analysis involved a model averaging procedure which was used to derive a 20% BMD estimate. Due to the limited doses and small samples sizes, this technique was considered more appropriate to account for model uncertainty compared to the Agency's Benchmark Dose Software (BMDS) that is more commonly used to determine BMDs for risk assessment. The severity score and modeling average approaches used in this dose-response result in maximal use of the data from multiple endpoints collected in the WIL FOB study and thus strengthens the relative potency estimates and PoD used in this CRA. The Agency used a less refined approach for four pyrethroids (cyphenothrin, d-allethrin, imiprothrin, and prallethrin), selecting doses as a point of comparison. However, performing a BMD analysis is likely to increase the dose associated with the point of comparison, thereby reducing the RPFs and increasing MOEs.

Because neurobehavior is an apical endpoint, it is important to consider the extent to which these behavioral measures compare to *in vitro* endpoints measured using neurological tissue cultures and thus are early events in the adverse outcome pathway and biologically closer to VGSC interaction. For example, Losa et. al. (2009) measured spontaneous electrophysiological activity of glutamate networks in primary cultures of cortical neurons using microelectro array techniques; and Cao et. al. (2011a) determined sodium flux in primary cultures of cerebrocortical neurons using the Na<sup>+</sup> sensitive dye SBFI. The results of these *in vitro* techniques are similar to the Agency's RPF estimates from the WIL study; Type II pyrethroids

are generally more potent than the Type I pyrethroids. There is a remarkable similarity in the relative rank of the *in vitro* measures to the RPFs based on FOB measures. These comparisons, thus, support the use of the behavioral measures for purposes of estimating cumulative risk.

<b>Table 4.5.1. Relative Potency Estimates for Pyrethroids Included in the Screening Level Cumulative Risk Assessment</b>			
<b>Pyrethroid</b>	<b>WIL FOB</b>	<b>Losa et. al. (2009)</b>	<b>Cao et. al. (2011a)</b>
Allethrin <sup>c</sup>	0.11	0.11	0.68
Bifenthrin	1.01	0.40	- <sup>a</sup>
Cyfluthrin	1.15	0.57	0.61
Lambda-Cyhalothrin	1.63	7	0.58
Cyphenothrin	0.15	Not Included	Not Included
Cypermethrin	0.19	0.97	-
<b>Deltamethrin</b>	<b>1.0</b>	<b>1.0</b>	<b>1.0</b>
Esfenvalerate	0.36	0.22	0.49
Fenpropathrin	0.50	0.12	0.31
Tau-Fluvalinate	1.0	Not Included	Not Included
Imiprothrin	0.02	Not Included	Not Included
Permethrin	0.09	0.24	-
Prallethrin	0.10	Not Included	Not Included
Pyrethrins	0.02	Not Included	Not Included
Resmethrin	0.05	0.10	-

<sup>a</sup>Included in study but effective concentration estimates could not be determined due to minimal increase in Na<sup>+</sup> influx

The Agency is using a single set of RPFs estimated for oral exposure for all relevant routes of exposure (oral, dermal, inhalation) and thus the Agency is assuming that the relative ranking of these oral RPFs applies to the other routes of exposure. The Agency has dermal and inhalation studies available for only a limited number of pyrethroids, and of those studies, neurological endpoints are not measured in a consistent manner nor are critical procedures, such as the determination of time-to-peak effect determined. Therefore, these dermal and inhalation studies are not appropriate for use in the determination of relative potency factors for the pyrethroids. However, the lack of these studies does not introduce significant uncertainty because pyrethroids are generally poorly absorbed through the skin and inhalation exposure is believed to be low. As described in Section 6.0 of this assessment, dermal and inhalation MOEs for the pyrethroids are large, ranging from 3,000 to 240,000 for dermal exposures and 130,000 to 10,000,000 for inhalation. Based on these values, the RPFs would have to be at least an order of magnitude greater than the index chemical to result in significant risk estimates.

The selection of the index chemical is a key decision point in the cumulative risk assessment as any uncertainty in the index chemical's dose-response data will be propagated through the entire risk assessment. For the CRA, deltamethrin was chosen as the index chemical because it provides robust dose-response data from which to estimate the PoD. Specifically deltamethrin was tested in the WIL FOB study with three well-spaced doses which include a dose near the BMD<sub>20</sub> such that high confidence BMD<sub>20</sub> and BMDL<sub>20</sub> estimates can be estimated, as indicated

by closely spaced BMD and BMDL estimates. Furthermore, deltamethrin was used as a laboratory method control in the second phase of the WIL study (Herberth 2010) and the findings were similar between studies. For example, at a given dose of 25 mg/kg, salivation was noted in six animals for each study, altered gait was observed in nine animals in the first and six in the second study, and finally low arousal or response was observed in four animals in the first study and in two animals in the second. In addition, deltamethrin is a commonly studied pyrethroid in research laboratories such that a large collection of literature studies is available, including a well-developed PBPK model.

Dose-additivity is the foundation assumption when using a RPF approach. At this time, there is an 11-chemical mixture *in vivo* study evaluating motor activity and one *in vitro* study measuring sodium influx in cerebrocortical neurons for the same 11-pyrethroid mixture. Each study is consistent in finding no deviation from the dose-additive model and thus supports the use of the RPF approach.

It is preferred to use a PBPK model to derive RPFs based on internal dosimetry instead of the administered dose metrics used in this CRA. The Agency has already developed PBPK models for permethrin and deltamethrin capable of extrapolating across species (Godin et. al. 2010) and age groups in rats (Tornero-Velez et. al. (2010)). There is currently a large effort by CAPHRA to develop PBPK models relevant for assessing estimated risk to children 4-6 additional pyrethroids. These models have the potential to improve the CRA by refining the metric used to estimate RPFs and by better informing route to route extrapolation, high to low extrapolation, animal to human extrapolation, and potential for PK-driven age-dependant sensitivity.

The Agency has high confidence in this cumulative hazard assessment for the pyrethroids. The cumulative assessment is considered protective given that both Type I and Type II pyrethroids were included. Furthermore, there is a high level of confidence in the selection of the WIL FOB study for BMD determinations due to the high quality of the study, because it is supported by *in vitro* studies that measure effects at the level of the common mechanism, and the robust dose-response analysis. Finally, the retention of the 3X FQPA safety factor for children < 6 years of age based on pharmacokinetic data, PBPK models, and established data (e.g., guideline and literature studies) is protective of the most susceptible population. As new data become available, particularly PBPK models, the Agency may, if appropriate, refine approaches or assumptions used in this assessment.

## 8.2 Dietary Exposure Assumptions and Characterization

### 8.2.1 Food Exposure Pathway

To provide risk estimates for the dietary portion of this cumulative risk assessment, the Agency conducted a refined, probabilistic dietary assessment and the food component of that assessment relied on PDP monitoring data. The food component of the assessment is considered a refined picture of potential acute food exposures for the U.S population and regulated subpopulations. However, two conservative assumptions were made in this assessment. The first assumption was that available residue data were translated to all food commodities in DEEM regardless of registered use pattern. The second assumption was that processing factors, which reflect potential reduction of pesticide residues, were not incorporated into the assessment. Incorporation of reduction factors and eliminating foods for which there are no registered use are expected to reduce dietary risk estimates.

### 8.2.2 Drinking Water Exposure Pathway

The pyrethroids as a class have low water solubility and tend to bind to soil. As a result of these properties, exposure from the drinking water pathway is expected to be negligible. However, in the absence of a robust set of monitoring data or refined modeling to support this contention, the Agency has taken a highly conservative approach to address drinking water exposure in this screening level cumulative assessment. The single highest modeled drinking water exposure estimate in terms of index chemical equivalents was used in the assessment for all water consumption for an individual. The Agency believes that this a health protective approach to the screening level assessment and likely to overestimate dietary risks. It is more likely that if adequate monitoring data were available, actual concentrations of pyrethroids in water would be significantly lower than the modeled values and that risk estimates from water consumption would more closely follow the food only risk estimates reported in this document.

## 8.3 Non-Dietary Exposure Assumptions and Characterization

### *Limiting the Assessment to Insecticide- and Pyrethroid-Users*

In standard cumulative assessments, dietary plus non-dietary aggregate exposures reflect those individuals who use pesticide products and those who do not. That is, those with exposures via the dietary route may or may not have exposures from the non-dietary route, depending on whether they are users of pesticides (in this case pyrethroid insecticides, specifically). The current screening-level approach represents risk estimates for individuals (adults and children) exposed via dietary consumption of pyrethroid residues as well as contacting, and potentially ingesting, surface residues (i.e., non-dietary exposure). However, based on EPA's recently released 2006-2007 market estimates for pesticide sales and usage ([http://www.epa.gov/opp00001/pestsales/07pestsales/producers\\_users2007.htm#4\\_1](http://www.epa.gov/opp00001/pestsales/07pestsales/producers_users2007.htm#4_1)), approximately 50% of U.S. households do not use insecticides. Furthermore, though likely a large portion of the residential use market, it is reasonable to assume that market share of

pyrethroids is less than 100%. Since the screening-level assessment aggregates dietary and non-dietary exposure, it does not reflect the substantial portion of the U.S. population with pyrethroid-related dietary exposure, but without pyrethroid-related non-dietary exposure. Thus, the current approach implicitly represents a population in which 100% experiences both dietary and non-dietary pyrethroid exposure. In a true population-based probabilistic assessment, approximately 50% of the modeled population would have only dietary exposure to pyrethroids, while the other 50% would experience both dietary and non-dietary pyrethroid exposure (per the estimate above). And, since those without non-dietary exposure would have correspondingly lower exposures and risk estimates, the overall distribution of exposure and risk estimates would be lower. Incorporating the likelihood of insecticide use, and, more specifically, pyrethroid use, would result in a lower estimate of risk than the current approach.

### *Limiting Non-Dietary Exposure to the “Day-of-application”*

The screening-level approach estimates non-dietary exposure using surface residues immediately following pyrethroid applications. While it is certainly the case that individuals may be exposed in this fashion, this approach does not consider the likelihood of exposures resulting from surface residues that have dissipated over time. If applications are made every day or if there is no dissipation of pyrethroid residues in and around homes, estimates based on the “day-of-application” would be representative of non-dietary exposures. However, given available pesticide use data (e.g., REJV) and known pyrethroid dissipation rates, utilizing “day-of-application” exposures is a conservative approach. A refined assessment would utilize a calendar-based approach that specifies dates of application (based on use probabilities) and incorporates residue dissipation. EPA’s Stochastic Human Exposure and Dose Simulation (SHEDS) model, for example, utilizes diaries from the Consolidated Human Activities Database (CHAD) to more accurately reflect the coincidence of applications and individuals’ locations and activities. Utilizing this methodology would reflect exposure to residues that have dissipated 5, 10 or 20 days after pyrethroid applications and result in a lower risk estimate than the current approach.

### *Consideration of Pyrethroid-Specific Use Probabilities*

The screening-level approach presents non-dietary risk estimates for only one pyrethroid for each of the major residential use scenarios. This should not be construed to imply that only one pyrethroid has uses for that scenario, or that this does not represent a cumulative methodology. Rather, the pyrethroid presented is the “highest potential risk” pyrethroid for each scenario, thus serves as a conservative benchmark to address each non-dietary scenario. For example, risk estimates for the pyrethroid cyfluthrin are presented for non-dietary exposures resulting from applications to home lawns since cyfluthrin results in the highest risk estimate of the pyrethroids registered for use on turf. Similarly, cyphenothrin is used as the benchmark pyrethroid for those with registrations for household pets. In reality, however, there are many different pyrethroids registered for each residential use scenario, with each pyrethroid having a particular share of the consumer market for each use. It may be the case that though cyfluthrin presents the highest risk estimate for a pyrethroid with lawn uses, it is

the lawn-use pyrethroid used most infrequently. Thus, utilizing cyfluthrin as the benchmark pyrethroid for the lawn-use scenario is a conservative approach. A refined assessment that accurately assigns pyrethroid-specific residential scenario market-share probabilities would result in lower risk estimates than the current approach.

### *Assuming Co-Occurrence of Non-Dietary Exposure Scenarios*

The screening-level approach presents risk estimates separately for each individual residential-use scenario, then presents an aggregate risk estimate that assumes an individual is exposed from all of the scenarios on the same day. For example, risk estimates are presented for children 1 < 2 years old exposed via contact with surfaces previously treated indoors (broadcast sprays, total release fogger, and “crack and crevice”) as well as contact with previously-treated lawns and pets. These separate risk estimates are then aggregated, which assumes a) each of those areas are treated on the same day, b) each is treated with the use-specific “highest potential risk” pyrethroid, and c) children contact those areas on the “day-of-application”. A refined approach would more accurately reflect the likelihood of experiencing pyrethroid exposure in this – likely improbable – co-occurrent fashion by incorporating its probability based on pesticide use surveys. The current approach conservatively assumes that these scenarios always co-occur (i.e., 100% co-occurrence probability). Any refinement which reduces co-occurrence would result in a lower risk estimate.

## **8.4 Aggregate Exposure (Dietary + Non-Dietary) Assumptions and Characterization**

The Agency considers this screening-level cumulative risk assessment to be highly conservative. The screening-level approach utilizes a simple point-estimate aggregate methodology that adds a high-end dietary (food and water) exposure to a high-end residential exposure, assuming co-occurrence of dietary and non-dietary exposure. In other words, the non-dietary exposure patterns discussed in Section 6.0 would coincide with consumption of food and water (discussed in Section 5.0) with pyrethroid residues. While this is a possible exposure pattern, it is highly unlikely given the temporal aspects of residential insecticide use. Not only does this assessment assume and model co-occurrence, it utilizes high-end exposures from both the dietary and non-dietary pathways, making this outcome even less likely. A refined cumulative assessment would incorporate the appropriate temporal matching of exposures through these different pathways and reflect more realistic probabilities that pyrethroid exposure results from both dietary and non-dietary routes on the same day. Additionally, the use of distributions of both dietary and non-dietary exposures would mitigate the compounding effect of aggregating high-end point estimates.

## 9.0 Conclusion

The assessment combines a high-end dietary risk estimate from a probabilistically-derived realistic food exposure estimate and a high-end modeled drinking water exposure estimate with a high-end deterministic non-dietary residential risk estimate. The refinement of each pathway varies and has been described previously in each respective section. However, given the various assumptions outlined in Section 8.0, the overall methodology provides a reasonably conservative screening-level approach for determining cumulative and aggregate estimated risk for pyrethroids. The current use of high-end exposure estimates, the general assumption of co-exposure, and compounding conservative assumptions for each exposure route would likely represent an upper percentile exposure of a fully refined cumulative assessment (i.e., likely greater than the 99.9<sup>th</sup> percentile). That is, further refinements would result in MOEs significantly above those reported here. However, since risk estimates exceed the Agency's target MOEs for adults and children, additional refinement is not required at this time.

This screening level CRA for pyrethroids uses deterministic residential and probabilistic dietary exposure models. There are alternative approaches that would be more refined, particularly the use of probabilistic estimates for all routes of exposure. OPP and ORD are working collaboratively to improve the Stochastic Human Exposure and Dose Simulator (SHEDS) model, specifically for use in such a refined risk assessment. Moreover, this collaborative effort involves linking PBPK models with the SHEDS model to estimate probabilistic population level risk. The linking of a PBPK model with a probabilistic exposure model may provide opportunities to calculate distributions of exposure to pesticides with effect levels across the U.S. population. In addition, this approach may allow estimation of data-derived uncertainty factors that consider use of toxicokinetic and toxicodynamic data to inform quantitative extrapolations for interspecies differences and human variability in dose response assessment. This research effort was reviewed by a FIFRA SAP in July, 2010<sup>5</sup>. In addition, the SAP also reviewed in February, 2011 *Chlorpyrifos Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Modeling Linked to Cumulative and Aggregate Risk Evaluation System (CARES)* in which the CARES model was similarly linked to a PBPK/PD model in an effort made by Dow AgroScience<sup>6</sup>. OPP supports such research efforts as they advance the science of risk assessment. However, consistent with the screening approach of this cumulative assessment, such a highly refined and sophisticated approach is not needed at this time for pyrethroids. In the future, OPP may consider, if appropriate, similar research for pyrethroids or other classes of pesticides.

Not only does the Agency believe that this screening level estimate indicates that there are no cumulative estimated risks of concern for the currently registered uses, the Agency also concludes that there is sufficient room in the pyrethroid cumulative risk cup to support consideration of new pyrethroids (i.e., currently unregistered pyrethroid pesticides) and new uses of existing pyrethroids having similar toxicity profiles and use patterns to those in this

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<sup>5</sup> <http://www.epa.gov/scipoly/sap/meetings/2010/072010meeting.html>

<sup>6</sup> <http://www.epa.gov/scipoly/sap/meetings/2011/021511meeting.html>

assessment. This is a screening level assessment which incorporated multiple high-end inputs and combined the highest exposures/risk estimates across all pathways in a deterministic fashion resulting in an assessment which is highly conservative and health protective. It is important to note that the pyrethroids are already registered on virtually all food crops and for all major residential use scenarios. The dietary component of the cumulative risk assessment included residues for all foods consumed – either based on monitored values or translation from monitoring data from crops in the same food group. The water exposure input was assumed to be the highest exposure value from conservative model outputs which was the limit of solubility for that specific chemical. Additionally, the residential scenarios used conservative inputs and combined in a deterministic fashion exposure from multiple residential pathways of exposure, assuming use of the most potent pyrethroid, to produce a highly conservative estimate of risk.

For any new uses or new pyrethroids, the toxicity, proposed use sites, and potential exposure factors (e.g., application rate) would be compared with the inputs and assumptions utilized in this screening level assessment. However, if the pyrethroid is not significantly more toxic than those included in this assessment and has a similar use pattern to those registered uses considered in this assessment, its registration would likely be supported from a cumulative human health risk perspective because its inclusion within this assessment would not result in a higher estimate of risk than has been currently estimated. Per Agency policy, all new uses/new pyrethroid registration actions submitted to the Agency will undergo a single chemical assessment and also an evaluation of their potential contributions to cumulative risk estimates. But the Agency believes that most of these are unlikely to have a significant impact on this screening-level cumulative assessment, provided they meet the parameters outlined above.

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