

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



**OFFICE OF PREVENTION, PESTICIDE
AND TOXIC SUBSTANCES**

MEMORANDUM

Date: January 20, 2010

SUBJECT: **Pyrethroids: Evaluation of Data from Developmental Neurotoxicity Studies and Consideration of Comparative Sensitivity**

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FROM: Edward Scollon, Ph.D., Toxicologist
Risk Assessment Branch II
Health Effects Division (7509P)

Edward Scollon 1/21/10

THROUGH: Tina E. Levine, Ph.D., Director
Health Effects Division (7509P)

Tina E. Levine

And

Christina Swartz, Branch Chief
Risk Assessment Branch II
Health Effects Division (7509P)

Christina Swartz

TO: Cathryn OConnell, Team Leader
Risk Management and Implementation Branch II
Pesticide Re-Evaluation Division (7508P)

The Office of Pesticide Programs recently evaluated the contributions of developmental neurotoxicity studies (DNTs) to human health risk assessments for pyrethroids. Based on the review of available DNTs for six pyrethroids (bifenthrin, cyfluthrin, cyhalothrin, cypermethrin, fenpropathrin and deltamethrin), the Agency has determined that there is little value added in conducting DNTs for additional pyrethroids, even though these studies have been required as conditions of registration, or through reregistration and

registration review. It has been determined that, for pyrethroid pesticides, DNTs do not provide sensitive endpoints for risk assessment or provide sufficient information related to the susceptibility of infants and children; furthermore, the effects they do show can be found in other guideline studies. Certain results were similar across the six submitted pyrethroid DNT studies. As a result the Agency has concluded that the six available DNTs on pyrethroids, when considered together, provide sufficient information to determine that the conclusions drawn from DNTs are applicable to all pyrethroids (Memo, R. Keigwin, Director, PRD/OPP, 9/4/2009). The attached document provides the major scientific evidence supporting the Agency's conclusion.

Chemical	PC Code	CAS No.
Allethrin Stereoisomers	004001	584-79-2
Bifenthrin	128825	82657-04-3
Bioallethrin	004003	28057-48-9
Cyclethrin	004052	97-11-0
Cyfluthrin	128831	68359-37-5
Cyfluthrin, beta-	118831	68359-37-5
Cyhalothrin, lambda-	128897	91465-08-6
Cyhalothrin	128867	68085-85-8
Cyhalothrin, gamma-	128807	76703-62-3
Cypermethrin	109702	52315-07-8
Cypermethrin, beta-	109702	65731-84-2
Cypermethrin, zeta-	129064	52315-07-8
Cyphenothrin	129013	39515-40-7
D-Allethrin	004005	84030-86-4
Deltamethrin	097805	52918-63-5
Esbiothrin	004007	84030-86-4
Esfenvalerate	109303	66230-04-4
Etofenprox	128965	80844-07-1
Fenfluthrin	109705	69409-94-5
Fenpropathrin	127901	39515-41-8
Fenvalerate	109301	51630-58-1
Imiprothrin	004006	72963-72-5
Metofluthrin	109709	240494-70-6
Permethrin	109701	52645-53-1
Phenothrin	069005	26002-80-2
Prallethrin	128722	23031-36-9
Pyrethrins (not synthetic)	069001	8003-34-7
Resmethrin	097801	10453-86-8
S-Bioallethrin	004004	28434-00-6
Sumithrin (D-phenothrin)	069005	26046-85-5
Tau-fluvalinate	109302	102851-06-9
Tefluthrin	128912	79538-32-2
Tetramethrin	069003	7696-12-0
Tralomethrin	121501	66841-25-6

Pyrethroids: Evaluation of Data from DNTs & Consideration of Comparative Sensitivity

EPA has evaluated the data and information provided by the available guideline developmental neurotoxicity studies (DNTs) for pyrethroids, as well as data pertaining to the effects of pyrethroids on juveniles from the scientific literature. This evaluation was initiated, in part, by EPA's preparation for registration review and also for the anticipated cumulative risk assessment of pyrethroids. In addition, EPA has received requests from some stakeholders to re-consider the utility of the DNT studies for pyrethroids and/or to consider bridging proposals where the DNT study for one pyrethroid satisfies the requirement for another. EPA has evaluated multiple lines of scientific information about pyrethroids including their mode of action (MOA); the *in vivo* toxicity syndromes typical for Type I and II pyrethroids; their pharmacokinetic (PK) properties, the critical effect(s) used in OPP's single chemical risk assessments; the results reported for the available pyrethroid DNT studies; and information from the open scientific literature.

In a September 4, 2009 letter from Richard Keigwin, Director of the Pesticide Review Division, the Agency noted that the six available DNT studies on pyrethroids, when considered together, provide sufficient information to determine that the conclusions drawn from the DNTs are applicable to all pyrethroids. This document provides the major scientific evidence supporting the Agency's conclusion¹.

Mode of Action & Toxicity Syndromes:

Pyrethroids, the synthetic derivatives of the pyrethrins, have evolved structurally over the past several decades. However, the basic components of pyrethrins, a chrysanthamic acid linked to an aromatic alcohol through an ester linkage have been conserved (Fig. 1). Structural modifications such as the addition of halogens to the chrysthanthamic acid and aromatic alcohol moieties and the addition of the α -cyano group have increased photostability, insecticidal potency, and in some incidences, stereoisomerism of the pyrethroids. As a point of reference, pyrethroids lacking the α -cyano group are referred to as Type I and those with the α -cyano group are referred to as Type II pyrethroids.

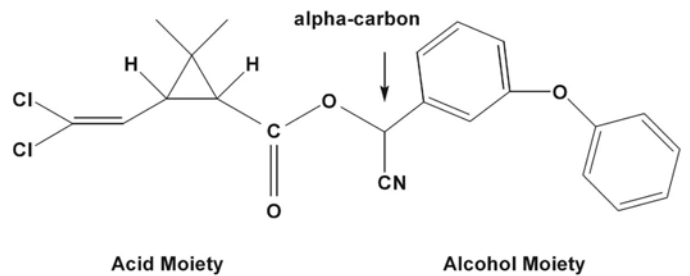
The naturally occurring pyrethrins and synthetic pyrethroids share the same mode of action (USEPA, 2009): interaction with voltage-gated sodium channels (VGSCs). The interaction results in disruption of membrane excitability in the nervous system, leading to neurotoxicity that is generally characterized by two different toxicity syndromes, T- (fine tremors) and CS-syndromes (choreoathetosis and salivation) observed in rats. The T-syndrome has been historically characterized by aggressive sparring, increased sensitivity to external stimuli and fine whole body tremors and is associated with Type I pyrethroids. The CS-syndrome has been historically characterized by initial pawing and burrowing, salivation, and choreoathetosis and is typically associated with Type II pyrethroids. In a modified functional observational battery (FOB) study supported by the Pyrethroid Working Group², the T-syndrome was associated with elevated temperature, tremors, and myoclonus. The CS- behaviors were associated with lower temperature, excessive salivation, and impaired mobility. A few pyrethroids, including esfenvalerate and fenpropathrin, elicit symptoms that are a combination of the T- and CS-syndromes³.

¹ This document is not an exhaustive review of pyrethroid toxicity. For readers interested in more detailed information, see Soderlund and Bloomquist (1989), Vijverberg and van den Berken (1990), Narahashi (1992), Clark (1995), Soderlund (1995), Bloomquist (1996), Narahashi (1996), Shafer et al. (2005), Wolansky and Harrill (2008), and Nemecek (2006).

² The Pyrethroid Working Group (PWG) is a consortium of registrants including Bayer CropScience, DuPont Crop Protection, FMC Corporation, Pytech Chemicals (including Cheminova and Dow AgroSciences), Syngenta Crop Protection, and Valent USA Corporation.

³ Note: The Agency is currently reviewing the SAP report and may consider additional pyrethroids as showing mixed syndromes

Figure 1. Typical structure of a pyrethroid pesticide including acid and alcohol moieties and location of the alpha-cyano group when present. Cypermethrin is illustrated below.



It has been suggested that the neurotoxicity syndromes are attributed to the nature of interaction between the specific pyrethroids and the VGSCs. Sodium channel activation (opening) allows sodium ions to cross the plasma membrane and enter the cell; this typically results in membrane depolarization. In neurons, this results in initiation of an action potential if sufficient numbers of sodium channels are activated. Sodium channels normally inactivate, or close, after a very brief time, limiting the time that the membrane is depolarized. Pyrethroids modify VGSCs such that they remain open for longer periods of time than under normal conditions. Type I pyrethroids modify the channels such that there is a slight prolongation of the open time (i.e. sodium tail currents of approximately 20 ms), often resulting in long trains of action potentials. Type II pyrethroids significantly prolong channel open time (sodium tail currents 200ms to minutes) typically resulting in increased resting membrane potential and often inducing depolarization-dependent block of action potentials. While this mode of action (MOA) clearly contributes to pyrethroid neurotoxicity, all the steps between these changes in excitability at the cellular level and the resulting behavioral syndrome are not completely understood.

The pattern of toxicity is somewhat unique to this class of pesticides and can be attributed to the pharmacokinetic and pharmacodynamic properties. The parent pyrethroid is the toxicologically active compound. As such, no metabolic activation is required; instead, metabolism results in detoxification. As evidenced by the rapid onset of toxicity, these pesticides are rapidly absorbed, distributed, and cleared from the body. As shown in Figure 2, levels of deltamethrin, a Type II pyrethroid, in brain tissue clearly peak 2-3 hours post-dosing followed by a rapid decrease in concentration (Godin et al., *In Press*). In general, time course typifies the progression of signs in mammalian species, which appear within 1 hour of sub-lethal oral exposure, peak within 4-8 hours, and recover in 12-48 hours (Wolansky and Harrill, 2008).

Pyrethroid neurotoxicity is correlated to peak concentrations of pyrethroid. Research on a limited number of them (i.e., deltamethrin, cismethrin, and bioresmethrin) has shown a direct link between the concentration of pyrethroid in tissue and neurotoxicity (Gray et al. 1980, White et al., 1976). More recently, Wolansky et al. (2006) have demonstrated a dose-response relationship for 11 pyrethroids (including Type I and Type II chemicals) following acute gavage dosing. Increasing dose levels resulted in decreased motor activity as measured during the time-to-peak-effect. The pharmacokinetics that determine specific tissue concentrations are critical and can be greatly influenced by the manner of feeding (e.g., gavage vs. dietary feeding). The details of how pharmacokinetics influence the results of the DNT studies will be discussed throughout this document.

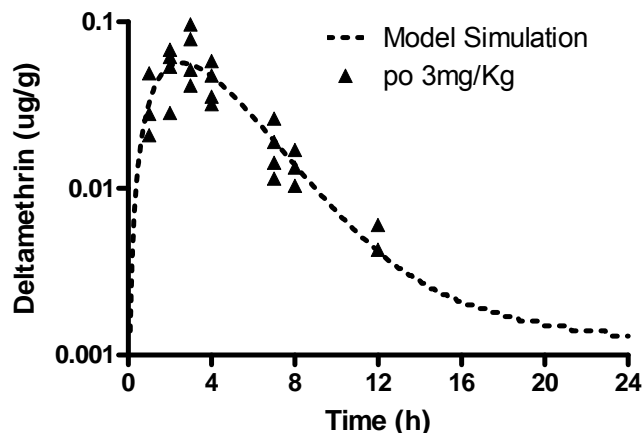


Figure 2. Model simulation and time course of brain concentration of deltamethrin after an oral dose. Dashed line represents the simulation of the optimized diffusion-limited model. ▲ represents individual data points after an oral dose (3 mg/kg) of deltamethrin (N=4). *Adapted from Godin et al, in press.*

Results of DNT Studies:

Clinical Effects and Neurotoxicity

Six DNTs are currently available for pyrethroids; one Type I (bifenthrin), four Type II's (cyfluthrin, lambda-cyhalothrin, zeta-cypermethrin, deltamethrin) and one mixed syndrome pyrethroid (fenpropathrin). These studies are summarized in Table 1.

Generally, the toxic effects to offspring observed in DNTs are decreases in pup weight, pup weight gain, and/or brain weight. The Health Effects Division typically uses pup weight decrements greater than 5% in DNT studies as a response level of concern. In five of six DNT studies, decreased pup weight and/or pup weight gain were noted at the LOAEL. These decreases in pup weight measures were seen in combination with indications of neurotoxicity in only two of the six studies (deltamethrin—vocalizations; fenpropathrin—auditory startle), indicative that weight changes are a more sensitive indicator of toxicity in the pups than are neurological effects.

Brain weight decrements of 6-7% were noted in three of six studies at the LOAEL (beta-cyfluthrin, lambda-cyhalothrin, fenpropathrin). For all three, the pup LOAELs from the DNTs are similar to doses in other studies where frank toxicity was noted. For example, the pup LOAELs in the beta-cyfluthrin, lambda-cyhalothrin, and fenpropathrin DNT studies are 18, 10, and 19 mg/kg/day, respectively. In a special FOB study conducted by the Pyrethroid Working Group (PWG), at 12.5 mg/kg, beta-cyfluthrin produced clonic convulsions, abnormal posture, biting, and resistance to handling; at 10 mg/kg, lambda-cyhalothrin produced abnormal posture, resistance to removal, salivation, and abnormal gait; and at 15 mg/kg, fenpropathrin resulted in tremors, abnormal posture, salivation, and resistance to removal. Furthermore, for all three chemicals, the NOAELs from the DNT studies were 1.5-10X greater than the NOAELs used to determine the RfD/PAD.

With some exceptions, the available guideline DNT studies do not show effects on behaviors or parameters that are only measured in the DNT (e.g. learning, memory, auditory startle, and brain morphometrics). For example, none showed changes in learning or memory at any dose. Changes in auditory response were only observed in fenpropathrin at the study LOAEL and in combination with decreased body weight and absolute brain weight. Changes in brain morphometry were only observed for lambda-

cyhalothrin at a dose (10 mg/kg/day) where decreased pup survival and brain and body weight decreases were also noted. At the mid-dose (4.3 mg/kg/day) in the lambda-cyhalothrin study, no effects were noted in pups for any of these measures. The lambda-cyhalothrin study is lacking measures of brain morphometrics at the low- and mid-doses and is deficient in motor activity measures. However, these parameters were not affected at the low- or mid-dose in any of the other five DNT studies, decreasing our concern for the missing measurements. Furthermore, the LOAEL of 10 mg/kg/day in the lambda-cyhalothrin study is almost 10-fold higher than the dose at which neurotoxic effects were reported by Wolansky et al. (2006), and is 100-fold higher than the NOAEL used to derive the acute reference dose (RfD) and population adjusted dose (PAD).

Salivation, choreoathetosis, and tremors are typically associated with acute pyrethroid toxicity. Salivation and choreoathetosis were not observed in any DNT study; however tremors were observed in adults in the fenpropathrin (24 out of 25 animals) and bifenthrin (23 out of 25 animals) studies at the maternal LOAELs. Tremors also occurred in the pups for bifenthrin (6 out of 40). Unlike the adults, tremors were not seen in pups at the LOAEL in any DNT study.

The results of the bifenthrin DNT study show a different pattern than the other studies. For example, unlike the other pyrethroids, no decrements in body weight, body weight gain, or brain weight were noted in pups for bifenthrin. Furthermore, the bifenthrin DNT is the only study to show tremors in pups and only at a dose above the LOAEL. Tremors were observed in 6 pups out of 40 examined (4 males on post-natal day (PND) 10 and 2 females on PND 28) at the highest dose (9 mg/kg/day); the LOAEL was 7.2 mg/kg/day based on increased grooming counts. No tremors were observed at the mid- or low-doses. The tremors in pups were graded as slight and only occurred on single occasions. At 9 mg/kg/day, 23 out of 25 dams experienced tremors ranging from a few incidents to multiple days. Therefore, it is not surprising that the pups which displayed tremors were from litters whose dams also exhibited tremors. On the other hand, there was no correlation between the severity of tremors in the dams and the presence of tremors in the pups.

Bifenthrin is the only pyrethroid DNT study with reported clinical signs (increased grooming counts) in pups at the LOAEL. However, this reported increase in grooming counts showed a weak dose-response and high variability in all dose groups. Specifically, in the control and low-dose groups, mean counts were 0.4 ± 0.8 and in the mid- and high-dose groups, counts were 1.8 ± 1.4 and 1.6 ± 1.6 , respectively. As such, the standard deviations for each dose group were equal or greater than the respective means and the incidence of counts shows a weak gradation in response.

The DNT is unique in that it provides quantifiable measurements of learning and memory, acoustic startle response, and brain morphometrics. However, EPA's review of the available DNTs indicates that these parameters are not sensitive indicators of pyrethroid toxicity. Rather, the offspring LOAELs in five of six studies were based on decreased body weight and body weight gain. Some DNTs do demonstrate occasional neurotoxic effects (grooming counts, vocalizations, and tremors) but these effects do not consistently appear for the pyrethroids tested. Furthermore, with the exception of bifenthrin, the adverse effects observed in the DNT are not consistent with pyrethroid neurotoxicity. Additionally, the effects noted in the DNTs were also observed in other guideline studies (reproduction, acute neurotoxicity, special FOB, subchronic neurotoxicity, etc.) at similar or lower doses compared to the DNTs. Thus, these DNT studies provide little unique information on the hazard potential of these pesticides.

Sensitivity

As discussed briefly below, sufficient evidence exists to suggest pups may be more susceptible to pyrethroid toxicity than adults (i.e. sensitivity). However, this sensitivity is not consistently evident in the available DNTs. In four DNT studies (bifenthrin, deltamethrin, fenpropathrin, and lambda-cyhalothrin), adverse effects were observed in pups at doses that were equal to or greater than doses which caused adverse effects in dams (i.e., there was no evidence of increased sensitivity in the offspring for these four). In two of the six studies (beta-cyfluthrin and zeta-cypermethrin), effects in pups were noted at lower doses than in the dams.

- For *beta-cyfluthrin*, there are four multigeneration reproduction studies available. Similar to the results of the beta-cyfluthrin DNT, three of the studies indicate pups are more sensitive than the dams based on body weight changes. In the fourth study, there were no toxic effects in the parents or offspring. In addition, decreased brain weight was observed at the pup LOAEL in the DNT, despite the absence of maternal toxicity at this dose. The brain and body weight changes in the DNT were observed at similar doses causing body weight changes in the reproduction studies. Furthermore, tremors were not observed in the DNT but were noted in the pups in two of the reproduction studies at the LOAELs. Thus, the DNT did not provide new information on the toxic potential of beta-cyfluthrin when compared to the other guideline studies.
- For *zeta-cypermethrin*, there are three multigeneration reproduction studies available. In these studies, pup weight effects were seen at doses comparable to dams; whereas, pup weight effects seen in the DNT study were observed at lower doses than those that caused the same effect in the dams, and therefore were considered evidence of increased susceptibility. Decreases in pup weight gains were observed at 25, 27, and 37.5 mg/kg/day in the reproduction studies. Pup weights were reduced in the DNT study at 17.3 mg/kg/day, a dose similar to the dose at which these effects were seen in the reproduction studies. Maternal weights were also decreased in all of the studies at these same doses. Maternal weight effects were typically <10% different from respective controls, while pup weight effects varied from 5 to 21% below control values among all studies, including the DNT. The effect on maternal weight was not considered adverse in the DNT, and therefore, the decreased pup weight was categorized as increased sensitivity. While the DNT is the only zeta-cypermethrin study to indicate increased sensitivity in the pups, the results from the DNT and reproduction studies, which did not indicate increased susceptibility, are actually very similar. In this instance, the DNT did not provide new information on the toxic potential of zeta-cypermethrin when compared to the other guideline studies.

Therefore, while the beta-cyfluthrin and zeta-cypermethrin DNT studies did indicate some potential increased sensitivity in the offspring based on body weight changes, similar effects were also observed in multigeneration reproduction studies for these two pyrethroids. Moreover, the reproductive toxicity studies for beta-cyfluthrin noted tremors in pups that were not observed in the DNT. When taken together, the results of all six DNT studies provided no new information on the hazard of these pyrethroids or the potential for sensitivity in pups beyond what was already understood from other guideline toxicity studies. It is also important to note that the findings of the DNTs are not consistent with literature studies suggesting that juveniles may indeed be more sensitive than adults. These literature studies are discussed in detail in Shafer et al. (2005) and are summarized briefly below.

Critical Effects Selected for Risk Assessment:

Points of departure and critical effects used in risk assessments for the pyrethrins and pyrethroids are provided in Table 1. Neurotoxicity consistent with the pyrethroid MOA is more commonly observed in acute neurotoxicity studies in rats and/or acute and chronic studies in dogs and therefore these studies frequently provide the most sensitive endpoints for this class. Neurotoxic effects have been selected by OPP as regulatory endpoints to derive reference doses (RfDs) or population adjusted doses (PADs) for use in single chemical risk assessments. None of the six DNTs have been used for endpoint and dose selection for dietary risk assessments. Only one DNT study was used to identify a point of departure (PoD) for the short- and intermediate-term incidental oral and dermal endpoint (children only) (i.e. zeta-cypermethrin) based on decreased body weight and body weight gain in pups.

The studies used for selection of PoDs, acute neurotoxicity in rats and/or dog studies, administer pyrethroids in a bolus dose. Acute neurotoxicity studies are administered via oral gavage and the dog studies may either be administered via capsule or in the food. Although mixing the pyrethroid with food in the chronic dog studies may appear similar to subchronic or chronic rat feeding studies, because dogs tend to consume their meals quickly over a few minutes, the chemical is ingested over a very short period of time. In contrast, during dietary administration, rats will eat over several hours, resulting in a much longer period of feeding. Therefore, the dose span for the acute neurotoxicity study in rats and dog studies covers only a few seconds to minutes, while the dose is consumed over several hours in rat feeding studies.

As discussed in the *Mode of Action* section, pyrethroids are rapidly absorbed, distributed and cleared from the body and neurotoxicity is correlated with peak concentrations. Therefore, the gavage and bolus feeding patterns result in greater internal doses (i.e., amount of pyrethroid reaching the target site) compared to rodent dietary administration, resulting in lower PoDs. For risk assessment, PoDs were based on neurotoxic endpoints from acute and bolus studies and are protective of neurotoxic effects observed in the dietary administration DNT studies.

Key Literature Studies on Juvenile Sensitivity:

Data from studies published in the open literature suggest that juveniles may be more sensitive than adults to direct administration of pyrethroids. Possible sources of the increased sensitivity in pups include age-related pharmacokinetic (PK) and pharmacodynamic (PD) differences. With respect to differences in pharmacokinetic properties, potential sensitivity of young animals is likely attributable to incomplete maturation of the enzyme systems that detoxify pyrethroids, particularly the carboxylesterases and cytochrome P450s. Consequently, pyrethroid concentrations in the target tissue (e.g., brain) may be higher in young animals than in adults given the same administered dose. Sheets et al. (1994) examined the effects of deltamethrin on auditory startle response in PND 21 and PND 72 rats. At 4 mg/kg, there was no difference in the startle response between these two age groups. However, deltamethrin brain concentrations were approximately 2-fold higher in the PND 21 compared to the PND 72 rats suggesting a possible functional difference. In examining the lethality of deltamethrin on PND 11, 21, and 72 rats, the LD50 was lowest in the PND 11 rats (5.1 mg/kg) and increased as the rats aged; in PND 21 rats the LD50 (median lethal dose) was 11 mg/kg, and in PND 72 rats it was 81 mg/kg. The deltamethrin brain concentrations were similar between weanlings receiving an LD50 dose of 11 mg/kg and adults receiving an LD50 dose of 81 mg/kg. Therefore, although the younger pups received a much lower dose of deltamethrin compared to the adults, brain concentrations were similar between the two age groups. The comparable brain concentrations despite large differences in dose supports the conclusion that age-dependent pharmacokinetics plays a major role in increased pup sensitivity to acute deltamethrin toxicity (Sheets et al., 1994).

Similarly, Cantalamessa (1993) treated juvenile (PND 8, 16 and 21) and adult rats with cypermethrin and permethrin and found an inverse relationship between toxicity and age; the

pyrethroids were most toxic to the youngest animals. Furthermore, Cantalamessa (1993) pretreated juvenile and adult rats with either tri-o-tolyl phosphate (TOTP), an esterase inhibitor, or piperonyl butoxide (PB), a monooxygenase inhibitor. Pretreatment with either TOTP or PB had no effect on juvenile mortality. In adults, pretreatment with TOTP caused a significant increase in cypermethrin and permethrin mortality while pretreatment with PB had no effect. Cantalamessa (1993) concluded that lack of response in the pretreated neonate rat is likely due to incomplete development of the ester hydrolysis detoxification pathway in young animals.

The data from Sheets et al. (1994) and Cantalamessa (1993) are consistent with more recent *in vitro* data. Anand et al. (2006) demonstrated the *in vitro* metabolism of deltamethrin by plasma carboxyesterases, hepatic carboxyesterases, and hepatic microsomes were 6, 35, and 7 times higher for PND 90 rats than PND 10 rats. However, the Sheets et al. (1994, 2000) and Cantalamessa (1993) studies used high doses, often at or near lethality. It is unknown whether such sensitivity would occur at lower doses more relevant for human health risk assessment. For example, following a single dose with deltamethrin at 0.4, 2, or 10 mg/kg in adult rats, brain concentrations were 5-fold greater in the 2 and 10 mg/kg groups compared to the 0.4 mg/kg group after 2 hours (Kim et al., 2008). Furthermore, while half-life values for tissues were very similar for the 2 and 10 mg/kg doses, ranging from 10 hours in the blood to 200 hours in the fat, half-life values were not generated for any tissue in 0.4 mg/kg dose due to the rapid metabolism and elimination. Therefore, exposure to pyrethroids at lower environmental concentrations is not likely to lead to accumulation and is more similar to a series of acute exposures than to a chronic exposure. EPA is currently developing a deltamethrin physiologically-based pharmacokinetic (PBPK) model to evaluate differences in tissue dosimetry for rats ranging from PND 10 to PND 90 based on available time course data of doses that ranged from 0.4 to 10 mg/kg. This model predicts an approximately 3-fold increase in deltamethrin brain concentration in juvenile rats compared to adults.

With respect to pharmacodynamics, disruption of voltage-gated sodium channel (VGSC) is a key event in pyrethroid neurotoxicity. Multiple isoforms of the VGSC exist and are expressed in a tissue, region and developmentally specific fashion. Evidence is unclear about whether there are differences in sensitivity between the VGSC isoforms since the isoform of the sodium channel differs between fetal and post-natal rats. The developmentally expressed isoforms of the VGSC transition to the adult isoforms between birth and PND 6-10 in rodents. Recent studies indicate that one rodent VGSC isoform that is highly expressed primarily during embryonic periods may be more sensitive than one isoform that is highly expressed in the adult nervous system, but this sensitivity may be concentration dependant (Meacham et al., 2008). In addition, the developmentally expressed isoform of human VGSCs may be less sensitive than are the VGSCs expressed in adult or juvenile rats (Tan and Soderlund, 2009). The data in Tan and Soderlund (2009) suggest that one human VGSC isoform is less sensitive than its analog in rats with respect to pharmacodynamic characteristics. However, additional studies with the other isoforms widely expressed in nervous tissue are necessary before a general conclusion can be made regarding species-specific pharmacodynamic differences. More information is available in a review by Shafer et al. (2005) on developmental neurotoxicity and sensitivity in juveniles to pyrethroids.

Based on this information, the Agency finds there is sufficient evidence to assume increased susceptibility of juveniles to pyrethroid toxicity due to age-dependent pharmacokinetic mechanisms. The currently available DNT studies do not provide any additional information beyond the standard reproductive guideline studies in this regard, and none of DNT studies include direct dosing to the young prior to weaning, for which there is greater evidence of sensitivity differences.

Weight of the Evidence:

It has been established that pyrethroids share a common mechanism of action: interaction with the voltage-gated sodium channels leading to neurotoxicity. As previously discussed, differences between Type I and II compounds in their interactions with VGSC produce different effects on membrane excitability (repetitive firing for Type Is and depolarization-dependent action potential block for Type IIs). These differences in action at the cellular level are the basis for acute toxicity characterized by either fine tremors (T-syndrome/Type I pyrethroids) or choreoathetosis and salivation (CS-syndrome/Type II pyrethroids), although not all steps between cellular changes in excitability and behavior are well understood.

The ability to evaluate this mechanism of toxicity using Agency Guideline studies is paramount to producing an effective and relevant risk assessment. Several factors weigh into the ability of the DNT to effectively contribute to this decision, including the pharmacokinetics of pyrethroids and implications for toxicity and potential juvenile sensitivity to acute pyrethroid toxicity.

The pharmacokinetic properties of pyrethroids lead to rapid absorption and elimination. Since neurotoxicity is correlated to peak concentrations in tissue, signs of acute neurotoxicity progress rapidly. A general time course typifying the progression in mammalian species includes signs of toxicity appearing within 1 hour of sub-lethal oral exposure, peaking within 4-8 hours, and recovering in 12-48 hours.

Consistent with this pattern of toxicity, studies that administer the pyrethroids in a bolus dose more frequently provide the most sensitive endpoints. In dietary administration studies like the DNT study, rats are exposed to the pesticide over several hours of feeding. This is in contrast to a bolus dose in gavage studies where the entire dose is given at one time. In the dietary studies, the total *administered dose* of the pyrethroid consumed may be equal to or even higher than the gavage dose. However, it is the *internal dose* at the target tissues which is related to the magnitude of toxicity. Due to the rapid metabolism and clearance in the dietary studies, pyrethroids do not reach a peak level at the target tissues as high as in gavage studies and thus the degree of toxicity in dietary studies is far less than that for gavage studies. As a result, acute gavage studies tend to be far more sensitive than dietary studies for pyrethroids.

Chemicals with a small window of time-to-peak-effect such as the pyrethroids are difficult to evaluate using dietary studies such as the DNT. This difficulty stems from the following: 1) the DNT does not consider a time-to-peak-effect and therefore may miss the window of peak toxicity, and 2) the dietary administration results in lower internal doses compared to gavage studies. In the more robust studies the Agency has to evaluate pyrethroid toxicity, the Wolansky et al. (2006) acute motor activity study and the Pyrethroid Working Group (PWG) modified Functional Observational Battery (FOB) study, the investigators carefully determined the time-to-peak-effect following an acute dose. While the PWG FOB study was not designed to determine threshold effects, studies that were, such as the Wolansky et al. (2006) motor activity study and Sheets et al. (1994), resulted in lower effective doses compared to guideline studies. For example, the Wolansky et al. (2006) study indicated a no-effect level of 1 mg/kg for deltamethrin and the Sheets et al. (1994) study produced an ED50 (effective dose 50%) of 4 mg/kg based on auditory startle response. The no-effect level in the deltamethrin DNT is higher, at 6.8 mg/kg/day.

Until more evidence becomes available, the Agency currently assumes juveniles have an increased susceptibility to acute pyrethroid toxicity based on literature direct-dosing studies such as Sheets et al. (1994), Cantalamessa (1993), and Anand et al. (2006). Based on the Agency's analysis of available DNT studies, the role of pharmacokinetics, and the lack of a chemical-specific time-to-peak-effect window in the DNT study, the DNT is not likely to be able to identify or characterize increased juvenile susceptibility.

In addition to the pharmacokinetic issues related to the feeding study design, there is a high degree of variability commonly observed in DNT studies. It is not unusual for standard deviations

to exceed the mean value for many measurements in the DNT. This variability has been described in Tyl et al. (2008) and complicates the review and interpretation of these studies.

The six DNTs are valuable in that they allow the Agency to better focus our inquiry regarding neurotoxic effects of pyrethroids in juveniles on effects relevant to the mechanism of action and pharmacokinetics. This focus would not be possible in the absence of the six DNT results. Although they are useful in terms of weight-of-evidence considerations, the pyrethroid DNT studies have not made a significant impact in determining the points of departure for use in risk assessment for these pesticides. Instead, clinical signs of neurotoxicity and body weight effects observed in other guideline studies provide the critical endpoints.

Conclusions

Based on the scientific evidence summarized in this document, the Agency believes that conducting additional DNT studies on pyrethroids will not contribute new information which is relevant for risk assessment, since EPA believes the available data will appropriately characterize potential relevant results of conducting a DNT for any pyrethroid. Thus, EPA is hopeful that the registrants with DNT requirements will choose to cite the existing database to satisfy the DNT requirement rather than devoting new substantial resources (animal use, laboratory time, EPA review resources, etc.) associated with conducting and evaluating new DNT studies. However, scientific evidence does indicate a continued concern for possible differential sensitivity with direct dosing in juveniles compared with adults. Thus, there is a need for additional information to inform these concerns.

As observed with organophosphates and *N*-methyl carbamate pesticides, the DNT is not a particularly sensitive study for evaluating comparative sensitivity of young animals to adults for pyrethroids. This is further evidenced by the Sheets et al. (1994) study which demonstrates a greater sensitivity of pups compared to adults for lethal doses of deltamethrin; sensitivity which was not observed in the deltamethrin DNT. The importance of focused experimentation on pyrethroid-specific effects related to the MOA and pharmacokinetic characteristics of pyrethroids has also been shown in the modified FOB study supported by the Pyrethroid Working Group.

The Agency is currently evaluating what additional experimentation on pyrethroid-specific effects related to the MOA and pharmacokinetic characteristics and comparative sensitivity between juveniles and adults may be necessary. The Agency will continue to communicate with the pyrethroid registrants and other stake-holders as additional action is needed.

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Allethrin; S-Bioallethrin (004003, 004004) (Type I)	Acute Dietary, general population=0.03 (Acute Neurotoxicity study rats (30/90) [#] based on tremors, hunched posture, abnormal gait, decreased grip strength.	Chronic Dietary=0.008 6-Month dog (BMDL ₁₀ = 8) based on hepatocellular degeneration	Short-term Range-finding dog (20/63) based on elevated liver enzymes and increased liver weights. Intermediate-term 6-month dog (BMDL ₁₀ = 8) based on hepatocellular degeneration	Short-and intermediate-term, general population not required.	Short-, intermediate-, and long-term 28 day inhalation rat: (1.3/6.5) based on limb tremors, hunched posture, vocalizations during handling. <i>Residential and Occupational exposure.</i>	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Bifenthrin (128825) (Type I)	<p>Acute Dietary, general population=0.33</p> <p>Acute neurotoxicity in rats (32.8/70.3) based on observations of mortality (females only), clinical and FOB findings and differences in motor activity</p>	<p>Chronic Dietary=0.013</p> <p>1-year dog (1.3/2.7) based on observations of increased incidence of tremors in both sexes</p>	<p>Short-and intermediate-term</p> <p>90-day dog (2.2/4.4) based on increased incidence of tremors in both sexes</p>	<p>Short-, intermediate-, and long-term</p> <p>21-day dermal rat (47/93) based on staggered gait and exaggerated hind limb flexion</p> <p><i>Residential and Occupational exposure.</i></p>	<p>Short-and intermediate-term</p> <p>90-day dog (2.2/4.4) based on increased incidence of tremors in both sexes</p> <p>Long-term</p> <p>1-year dog (1.3/2.7) based on increased incidence of tremors in both sexes</p> <p><i>Residential and Occupational exposure.</i></p>	<p>Maternal (3.6/7.2) based on tremors, convulsions, increased grooming counts;</p> <p>Offspring (3.6/7.2) based on increased grooming counts</p>

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Cyfluthrin (128831) (Type II)	<p>Acute Dietary, general population=0.02</p> <p>Acute neurotoxicity in rats (2/10) based on gait incoordination, decreased activity, writhing, salivation and decreased motor activity</p>	<p>Chronic Dietary=0.024</p> <p>1-year dog (2.4/10.64) based on clinical signs, gait abnormalities, abnormal posture</p>	<p>Short-, intermediate-, and long-term</p> <p>90-day dog (2.4/13.9) based on vomiting, gait abnormalities, decreased body weight gain</p>	<p>Short-, intermediate-term</p> <p>90 day dog (2.4/13.9) based on vomiting, gait abnormalities, decreased body weight gain</p> <p>Long-term</p> <p>1-year dog (2.4/10.64) based on clinical signs, gait abnormalities, abnormal posture</p> <p><i>Residential and Occupational exposure.</i></p>	<p>Short-term</p> <p>28-day rat (0.07/0.73) based on decreases in body weight and decreased urinary pH in males</p> <p>Intermediate-and long-term (90-day inhalation rat (0.02/0.16) based on decreases in body weight in males and clinical signs in females</p> <p><i>Residential and Occupational exposure.</i></p>	N/A
Cyfluthrin, beta- (118831) (Type II)	Same as cyfluthrin	Same as cyfluthrin	Same as cyfluthrin	Same as cyfluthrin	Same as cyfluthrin	<p>Maternal (17.8/ND)</p> <p>Offspring (11/17.8) based on decreased BW/BWG & brain weight in females</p>

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Cyhalothrin (128867) (Type II)	<p>Acute Dietary, general population=0.005</p> <p>1-year dog; lambda cyhalothrin (0.5/ 3.5) based on ataxia observed from day 2.</p>	<p>Chronic Dietary=0.001</p> <p>1-year dog; lambda cyhalothrin (0.1/0.5) based on gait abnormalities.</p>	<p>Short- and intermediate-term</p> <p>1-year dog; lambda cyhalothrin (0.1/0.5) based on gait abnormalities.</p>	<p>Short-, intermediate-, and long-term</p> <p>21-day dermal rat; lambda cyhalothrin (10/50) based on neurotoxicity (reduced splay reflex and stability, and splayed gait), decreases in body weight gain.</p> <p><i>Residential and Occupational exposure.</i></p>	<p>Short-, intermediate-, and long-term</p> <p>21-day inhalation rat; lambda cyhalothrin (0.08/0.90) based on neurotoxicity (salivation, lacrymation, and splayed gait), decreases in body weight gain, punctuate foci in the cornea, changes in urinalysis, and decrease in cholesterol.</p> <p><i>Residential and Occupational exposure.</i></p>	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Cyhalothrin, lambda- (128897) (Type II)	Same as cyhalothrin	Same as cyhalothrin	Same as cyhalothrin	Same as cyhalothrin	Same as cyhalothrin	<p>Maternal (4.3/10) based on decreased BW/BWG & FC;</p> <p>Offspring Although toxicity seen at 10 mg/kg/day, definitive NOAEL/LOAEL not determined due to deficiencies.</p>
Cyhalothrin, gamma- (128807) (Type II)	<p>Acute Dietary, general population=0.002</p> <p>1-year dog; lambda cyhalothrin (0.25/3.5) based on ataxia observed from day 2.</p>	Same as cyhalothrin	Same as cyhalothrin	Same as cyhalothrin	Same as cyhalothrin	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Cypermethrin (109702) (Type II)	<p>Acute Dietary, general population=0.1</p> <p>Acute neurotoxicity in rats (10/50) based on soiled fur, abnormal posture, splayed hindlimbs, impaired gait, and convulsions.</p>	<p>Chronic Dietary=0.06</p> <p>1-year dog (6/18.1) based on decreased BW/BWG in females; mortality, tremors, irregular gait, and salivation in males.</p>	<p>Short- and intermediate-term</p> <p>Developmental Neurotoxicity (7.40/17.30) based on decreased BW.</p>	<p>Short- and intermediate-term, general population not required</p> <p>Long-term, general population</p> <p>1-year dog (6/18.1) based on decreased BW/BWG in females; mortality, tremors, irregular gait, and salivation in males.</p> <p>Short- and intermediate-term children</p> <p>Developmental Neurotoxicity (7.40/17.30) based on decreased BW.</p>	<p>Short-, intermediate and long-term</p> <p>21-day rat inhalation (0.01/0.05 mg/L) based on decreases in BW and salivation.</p> <p><i>Residential and Occupational exposure.</i></p>	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Cypermethrin, zeta- (129064) (Type II)	Same as cypermethrin	Same as cypermethrin	Same as cypermethrin	Same as cypermethrin	Same as cypermethrin	Maternal (7.3/ND); Offspring (7.4/17.3) based on decreased BW/BWG.
Cyphenothrin (129013) (Type II)	N/A	N/A	Short- and intermediate-term 90-day dog (10/30) based emesis, tremors, and reddish/pale mucosa	Short- and intermediate-term 90-day dog (10/30) based emesis, tremors, and reddish/pale mucosa <i>Residential and Occupational</i>	Short- and intermediate-term 90-day dog (10/30) based emesis, tremors, and reddish/pale mucosa <i>Residential and Occupational</i>	N/A
Deltamethrin (097805) (Type II)	Acute Dietary, All populations=0.01 Wolansky et al., 2006: (1/3) based on reduced motor activity.	Chronic Dietary=0.01 Wolansky et al., 2006: (1/3) based on reduced motor activity.	Short-, intermediate-term, all populations Wolansky et al., 2006: (1/3) based on reduced motor activity.	Short-, intermediate- and long-term, all populations Wolansky et al., 2006: (1/3) based on reduced motor activity. <i>Residential and Occupational exposure.</i>	Short-, intermediate- and long-term, all populations Wolansky et al., 2006: (1/3) based on reduced motor activity. <i>Residential and Occupational exposure.</i>	Maternal (6.8/16.1) based on decreased BW/BWG and FC; Offspring (6.8/16.1) based on decreased BW/BWG, vocalizations, and decreased fixed brain weight.

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Esfenvalerate (109303) (mixed)	Acute Dietary, general population=0.002 Acute neurotoxicity study in rats (1.75/1.90) based on tremors.	Chronic Dietary=0.002 Acute neurotoxicity study in rats (1.75/1.90) based on tremors.	Short-, intermediate-term Acute neurotoxicity study in rats (1.75/1.90) based on tremors.	Short-, intermediate- and long-term, 21-day dermal (25/125) based on abnormal hindlimb gait. <i>Residential and Occupational exposure.</i>	Short-, intermediate, and long-term Acute neurotoxicity study in rats (1.75/1.90) based on tremors. <i>Residential and Occupational exposure.</i>	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Fenpropathrin (127901) (mixed)	<p>Acute Dietary, general population=0.06</p> <p>Developmental rat (6/10) based on ataxia, sensitivity to extreme stimuli, spastic jumping and tremors.</p>	<p>Chronic Dietary=0.025</p> <p>1-year dog (2.5/6.25) based on tremors and ataxia.</p>	N/A	<p>Short-, intermediate-, and long term</p> <p>Reproduction rat (3/8.9) based on clinical signs and mortality.</p> <p><i>Occupational exposure only.</i></p>	<p>Short-, intermediate-, and long term</p> <p>Reproduction rat (3/8.9) based on clinical signs and mortality.</p> <p><i>Occupational exposure only.</i></p>	<p>Maternal (8-16/19-40) (gestation-lactation) based on tremors;</p> <p>Offspring NOAEL/LOAEL= (8-16/19-40) (gestation-lactation) based on small pup size, decreased BW/BWG, increased maximum & average startle response amplitude (females), and decreased brain weight (males).</p>
Fenvalerate (109301) (Type II)	same as esfenvalerate	same as esfenvalerate	same as esfenvalerate	same as esfenvalerate	same as esfenvalerate	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Tau-fluvalinate (109302) (Type II)	<p>Acute Dietary, general population=0.005</p> <p>Chronic rat and subchronic neurotoxicity (0.5/1) based on excessive salivation, lacrimation, pawing, hyper/hypo activity, abnormal stance, and ruffling.</p>	<p>Chronic Dietary, general population=0.005</p> <p>Chronic rat and subchronic neurotoxicity (0.5/1) based on excessive salivation, lacrimation, pawing, hyper/hypo activity, abnormal stance, and ruffling.</p>	N/A	N/A	<p>Short-, intermediate-, and long term</p> <p>Chronic rat and subchronic neurotoxicity (0.5/1) based on excessive salivation, lacrimation, pawing, hyper/hypo activity, abnormal stance, and ruffling.</p> <p><i>Occupational exposure only.</i></p>	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Imiprothrin (004006) (Type II)	N/A	N/A	N/A	N/A	<p>Short-, intermediate-, and long-term</p> <p>28 day inhalation rat (0.022/0.186 mg/L) based on increased incidence of clinical signs indicating effects on the nervous system, decreases in BWG, hemolytic anemia, increase in relative liver weights, dark liver, increase in absolute and relative salivary gland weights and hyperplasia of acinous cells.</p>	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Metofluthrin (109709) (Type I)	N/A	N/A	Short-term Developmental rat (15/30) based on tremors in adults.	N/A	Short-term 28 day inhalation rat (0.099/0.196 mg/L) based on mortality, tremors, ataxia, hypersensitivity, gait changes, lateral position, convulsions, and hypothermia in both sexes. <i>Occupational exposure only.</i>	N/A
Permethrin (109701) (Type I)	Acute Dietary, general population=0.025 Acute neurotoxicity in rats (25/75) based on aggression, abnormal/decreased movement and increased body temperature.	Chronic Dietary=0.025 Acute neurotoxicity in rats (25/75) based on aggression, abnormal/decreased movement and increased body temperature.	Short- and intermediate-term Acute neurotoxicity in rats (25/75) based on aggression, abnormal/decreased movement and increased body temperature.	Short-, intermediate- and long-term 21-day dermal (500/ND) <i>Residential and Occupational exposure.</i>	Short-, intermediate- and long-term 15 day inhalation rat (0.042/ 0.583 mg/L) based on tremors and hypersensitivity. <i>Residential and Occupational exposure.</i>	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Prallethrin (128722) (Type II)	Acute Dietary, general population=0.05 1-year dog (5/10) based on tremors week 1.	Chronic dietary=0.05 1-year dog (5/10) based on trembling, rapid eye, blinking, and hunched posture.	Short- and intermediate-term 1-year dog (5/10) based on trembling, rapid eye, blinking, and hunched posture.	Short-, intermediate- and long-term 21-day dermal (30/150) based on fixation, abnormal gait, tremors, sensitivity to external stimuli, vocalization, twitching and writhing, and spasms. <i>Residential and Occupational exposure.</i>	Short-, intermediate- and long-term 28 day inhalation rat (0.0010/0.0044 mg/L) based on irregular respiration, decreased spontaneous activity, nasal discharge, salivation, and incontinence. <i>Residential and Occupational exposure.</i>	Range finding completed.

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Pyrethrins (069001, 069004, 069006, 069012, 869001) (not synthetic)	Acute Dietary, general population=0.07 Acute neurotoxicity in rats (20/63) based on tremors.	Chronic Dietary=0.04 Chronic rat (4.37/43.9) based on an increased incidence of thyroid follicular cell hyperplasia in males.	Short-term Acute neurotoxicity in rats (20/63) based on tremors in females. Intermediate-term Reproduction in rat (6.4/65) based on decreased F1b pup weights during lactation.	Short-and intermediate-term, general population not required.	Short-, intermediate- and long-term 90-day inhalation rat (0.03/0.1 mg/L) based on tremors, labored breathing, hyperactivity, secretory signs, matted coat, and decreased BW/BWG.	N/A
Resmethrin (097801) (Type I)	N/A	Chronic dietary=0.35 Reproduction rat (35/ 70.8) based on decreased mating index, decreased viability index, and decreased pup weight.	Short- and intermediate-term Developmental rat (40/ 80) based on decreased body weight gain and food consumption.	Short-, intermediate-term, and long-term Developmental rabbit (30/100) based on skeletal variations, possible marginal increase in resorbed litters. <i>Residential and Occupational exposure.</i>	Short-, intermediate-, and long-term 90-day inhalation rat (ND/ 0.1 mg/L) based on decreased glucose levels in males, decreased body weight gain, and increased BUN. <i>Residential and Occupational exposure.</i>	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Sumithrin (d-phenothrin) (069005) (Type II)	<p>Acute Dietary, females 13-49=0.03</p> <p>Dev Rabbit (30/100) based on spina bifida</p>	<p>Chronic Dietary=0.007</p> <p>1-year dog (7.1/26.8) based on hepatocellular enlargement in the liver and focal degeneration in the adrenal cortex in both sexes</p>	<p>Short- and intermediate-term</p> <p>Reproduction rat (50/ 150) based decreased body weight, increased liver weight in parental animals, and an increase in spleen weight, decreased uterine weight in F1 adults, decreased body weight gain during lactation of F2b pups, decreased litter size of F1b litters at day 1, decreased absolute heart and kidney weight in F2b males, increased liver weight in male and female F2b pups.</p>	<p>Short-and intermediate-term, general population not required.</p>	<p>Short-, intermediate-term, all populations</p> <p>90-day inhalation rat (26.6/75) based on nasal histopathology.</p> <p><i>Residential and Occupational exposure.</i></p>	<p>N/A</p>

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Tefluthrin (128912) (Type I)	Acute Dietary, general population=0.005 1-year dog (0.5/2) based on tremors	Chronic Dietary=0.005 1-year dog (0.5/2) based on tremors	N/A	Short-, intermediate-term, and long-term 1-year dog (0.5/2) based on tremors	Short- and intermediate, and long-term not required.	N/A
Tetramethrin (069003) (Type I)	N/A	N/A	Short-term Reproduction rat (25/150) based on decreased body weight and food consumption, bile duct hyperplasia in F1 males	Short- and intermediate-term, general population not required.	Short-, intermediate-term 90-day inhalation rat (3.5/23.5) based on increased clinical signs, kidney and liver weights, decreased body weight, changes in hematology and urinalysis, liver hypertrophy and gross necropsy findings, hyaline droplets in kidney <i>Occupational exposure only.</i>	N/A

Table 1. Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments						
Pyrethroid name (PC Code) (Type I/II/mixed)	Acute RfD*	Chronic RfD*	Incidental Oral*	Dermal*	Inhalation*	Developmental Neurotoxicity Study (DNT)*
Tralomethrin (121501) (Type II)	Acute Dietary, general population=0.01 1-year dog (0.75/3) based on decreased BW, tremors, ptyalism. [0.75 raised to 1.0 at 14 weeks with no effects	Chronic Dietary=0.01 1-year dog (0.75/3) based on decreased BW, tremors, ptyalism. [0.75 raised to 1.0 at 14 weeks with no effects	N/A	Short-and intermediate-term, general population not required.	Not available	N/A

NOAEL – No Observed Adverse Effect Level; LOAEL – Lowest Observed Adverse Effect Level; BMDL₁₀ – Benchmark Dose Lower Confidence Level 10%; BW/BWG – Body Weight/Body Weight Gain; ND – Not Determined; N/A – Not Available

*Values in mg/kg/day unless otherwise noted

NOAEL/LOAEL

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Appendix 1.

List of MRIDs and citations for studies named in Table 1 “Points of Departure (PODs) for Pyrethroid and Pyrethrin Single Chemical Aggregate Risk Assessments”.

870.3100 Subchronic Rat

00072114 Dow Chemical Company (1944) Semichronic Oral Toxicity of p-Chlorophenyl p-Chlorobenzenesulfonate (K6451) to Female Rats: 130-day Dietary Feeding Study. (Unpublished study received Oct 24, 1955 under PP0050; CDL:090101-C)

44047101 McFarlane, M. (1996) S-Bioallethrin (Esbiol) Code: RU 16121: Rat 90-Day Dietary Repeat Dose Study: Lab Project Number: TOX 94423: TOX/95/254-5. Unpublished study prepared by AgrEvo UK Ltd. 354 p.

870.3150 Subchronic Dog

00141200 Serota, D.; Kundzins, W. (1984) 13-week Subchronic Oral Toxicity Study in Dogs with FMC 54800, Technical: Final Report: Project No. 104-217. Unpublished study prepared by Hazleton Laboratories America, Inc. 285 p.

41267801 Von Keutz, E. (1987) FCR 4545: Study of Subchronic Oral Toxicity to Dogs (13-Week Feeding Study): Project ID 98348. Unpublished study prepared by Bayer Ag. 259 p.

42717503 Nagata, R. (1987) Subacute (13-week) Oral Toxicity Study of S-2703F in Beagles: Final Report (EET-71-0074). Unpublished study prepared by Shin Nippon Biomedical Labs, Ltd. 522 p.

870.3200 21/28 Dermal Toxicity

41143801 Milburn, G. (1989) Permethrin: 21 Day Dermal Study in Rats: Report No. CTL/P/2445: Study No. LR0533. Unpublished study prepared by ICI Central Toxicology Laboratory. 305 p.

42653301 Milburn, G. (1989) Permethrin: 21 Day Dermal Study in Rats: Individual Animal Data Supplement: An Addendum: Lab Project Number: CTL/P/2445: LR0533. Unpublished study prepared by Zeneca Central Toxicology Lab. 249 p.

42999101 Bernier, L. (1993) A Study of the Subchronic (21-Day) Dermal Toxicity of S-4068SF in Albino Rats: Lab Project Number: 85131: FFT-31-0176. Unpublished study prepared by Bio-Research Laboratories, Ltd. 342 p.

44333802 Leah, A. (1989) Lambda-Cyhalothrin: 21-Day Dermal Toxicity to the Rat: (Final Report): Lab Project Number: CTL/P/2532: LR0526. Unpublished study prepared by ICI Central Toxicology Lab. 330 p.

45275401 Delker, D. (2000) Esfenvalerate Technical: Repeat Dose Dermal Toxicity: 21-Day Study in Rats: Lab Project Number: 12737: 1012: THA000428. Unpublished study prepared by E.I. du Pont de Nemours and Company. 570 p. {OPPTS 870.3200}

45280501 Watt, B.; Freeman, C. (2000) Bifenthrin Technical: 21-Day Repeated-Dose Dermal Toxicity Study in Rats: Lab Project Number: A2000-5162: P-3455: 182TSST00436. Unpublished study prepared by FMC Corp. 344 p. {OPPTS 870.3200}

870.3465 Subchronic Inhalation

00096713 Alexander, D.J.; Clark, G.C.; Jackson, G.C.; et al. (1980) Permethrin Technical: Inhalation Study in Rats: 15 X 6 Hour Exposures over a 3 Week Period: WLC 34/80323. Includes method CAL 1173 dated Sep 21, 1979. (Unpublished study received Mar 17, 1982 under 59-200; prepared by Huntingdon Research Centre, England, submitted by Burroughs Wellcome Co., Research Triangle Park, N.C.; CDL:247019-G)

00157793 Pauluhn, J. (1984) Study for Subchronic Inhalative Toxicity to the Rat for 13 Weeks: FCR 1272 (Cyfluthrin): Rept. No. 12436. Unpublished Mobay study no. 86443 prepared by Bayer AG Institute of Toxicology and Hanover Medical University. 170 p.

00158476 Coombs, D.; Hardy, C.; Clark, G.; et al. (1985) 90-Day Inhalation Toxicity Study in the Rat: Resmethrin: (SBP - 1382 Technical): SBP 6/84997. Unpublished study prepared by Huntingdon Research Centre. 333 p.

40082901 Pauluhn, J. (1987) Study of the Subchronic Inhalation Toxicity in Accordance with OECD Guideline No. 413: FCR 1272: Cyfluthrin: Addendum to Bayer Report No. 12436, Dated Feb. 1, 1984: Study No. T9015085. Unpublished Mobay Report No. 86443 prepared by Bayer AG. 157 p.

40239301 Pauluhn, J. (1983) Study of the Subchronic Inhalation Toxicity in Accordance with OECD Guideline No. 413: Baythroid: Supplemental Submission: Second Addendum to Bayer No. 12436. Unpublished study prepared by Bayer AG. 24 p.

41289201 Kenny, T.; Coombs, D.; Hardy, C. (1989) Sumithrin T.G.: 90-Day Inhalation Toxicity Study in the Rat (ET-91-0122) (Amended Version): Lab Project Number: SMO/314/89644. Unpublished study prepared by Huntingdon Research Centre Ltd. 273 p.

41321818 Kohda, H. (1986) Subacute Inhalation Toxicity of S-4068SF in Rats: (ETOC): Lab Study Nos. 380001; IH-84-09; Ref. No. FFT-60-0078. Unpublished study prepared by Sumitomo Chemical Co., Ltd. 329 p.

41387702 Hext, P. (1990) Lambda-Cyhalothrin Production Material: 21-day Sub-acute Inhalation Toxicity Study in the Rat: Lab Project Number: CTL/P/2772: MR0135. Unpublished study prepared by ICI Central Toxicology Laboratory. 102 p.

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42012101 Kawaguchi, S. (1991) Three-Month Inhalation Toxicity Study of Neo-Pynamin in Rats: Lab Project Number: 2189. Unpublished study prepared by Sumitomo Chem. Co. 1055 p.

42030907 Kohda, H. (1986) Subacute Inhalation Toxicity of S-4068SF in Rats: Lab Project Number: IH-84-09. Unpublished study prepared by Sumitomo Chemical Co., Inc. 334 p.

42478201 Newton, P. (1992) A Subchronic (3-Month) Inhalation Toxicity Study of Pyrethrum Extract in the Rat Via Whole-body Exposures: Final Report: Lab Project Number: 91-8335. Unpublished study prepared by Bio/dynamics Inc. 870 p.

43750730 Kawaguchi, S. (1992) A 4-Week Inhalation Toxicity Study of S-41311 in Rats: Lab Project Number: 2485: SGT-20-0056: 200056. Unpublished study prepared by Sumitomo Chemical Co., Ltd. 459 p.

44517802 Coombs, D. (1997) ESBIOL: Rat 28-Day Repeat Dose Inhalation Toxicity Study: Lab Project Number: AGV 141/971017: TOX 96221. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 145 p.

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870.3700 Developmental Toxicity

00028453 Machi, R.A.; Kam, C.; Gallo, M.A.; et al. (1979) Teratologic Evaluation of SBP-1382 Technical in the Albino Rat: Snell Project # 2054-066. (Unpublished study received Jan 23, 1980 under 432- 487; prepared by Booz, Allen & Hamilton, Inc., submitted by Penick Corp., Lyndhurst, N.J.; CDL:241765-A; 241766; 241768; 241769; 241770)

0029002 Becci, P.J.; Knickerbocker, M.; Parent, R.A. (1979) Teratologic Evaluation of SBP-1382 Technical in Albino Rabbits: FDRL Laboratory No. 6288. (Unpublished study including letter dated Jan 14, 1980 from R.W. Fogleman to Maarten L. deVries, received Jan 23, 1980 under 432-487; prepared by Food and Drug Research Laboratories, Inc., submitted by Penick Corp., Lyndhurst, N.J.; CDL: 241800-A)

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41525903 Morseth, S. (1990) Rat Teratology Study with S-3206: Lab Project No.: 343-216. Unpublished study prepared by Hazleton Laboratories America, Inc. 304 p.

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870.3800 Reproduction and Fertility Effects

00163817 Cozens, D.; Barton, S.; Offer, J.; et al. (1986) Effect of S-3206 on Multigeneration of the Rat: SMO 164/85707. Unpublished study prepared by Huntingdon Research Centre. 468 p.

40276404 Tesh, J.; Willoughby, C.; Fowler, J. (1986) Sumithrin: Effects upon Reproductive Performance of Rats Treated Continuously throughout Two Successive Generations: (ET-61-0101): Laboratory Project ID: 85/SUM009/331. Unpublished study prepared by Life Science Research. 1449 p.

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870.4100 Chronic Toxicity (Dog)

00143130 Pence, D. (1984) Chronic Toxicity Study in Dogs: Project No. 343- 153. Unpublished study prepared by Hazleton Laboratories America, Inc. 514 p.

163065 Serota, D. (1985) 52-Week Chronic Oral Toxicity Study in Dogs: FMC 54800 Technical: Final Rept.: Project No. 104-219. Unpublished study prepared by Hazleton Laboratories America, Inc. 306 p.

40027902 Hext, P.; Brammer, A.; Chalmers, D.; et al. (1986) PP321: 1 Year Oral Dosing Study in Dogs: Report No. CTL/P/1316: [Includes Individual Animal Data Supplement of Report No. CTL/P.1316S]. Unpublished study prepared by Imperial Chemical Industries PLC, Central Toxicology Laboratory. 336 p.

40141308 Stonard, M. (1986) Tefluthrin: 1 Year Oral Dosing Study in Dogs: Laboratory Project ID: CTL/P/1575. Unpublished study prepared by ICI Central Toxicology Laboratory. 88 p.

40276401 Cox, R. (1987) Chronic Toxicity Study in Dogs with Sumithrin, T.G.: Final Report: HLA Study No. 343-173. Unpublished study prepared by Hazleton Laboratories America, Inc. 408 p.

42077002 Horner, S.; Buist, D.; Crook, D. et al. (1991) S-4068SF: Oral Toxicity Study in Beagle Dogs: Lab Project Number: SMO 292/ 89531. Unpublished study prepared by Huntingdon Research Centre Ltd. 315 p.

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44536801 Daly, I. (1995) A Chronic (12-Month) Oral Toxicity Study of FMC 30980 Technical in the Dog via Dietary Administration: Final Report: Lab Project Number: 92-3115: A93-3821: 92-8123. Unpublished study prepared by Pharmaco LSR, Inc. 876 p.

870.4300 Combined Chronic Toxicity/Carcinogenicity

41559501 Goldenthal, E. (1990) Evaluation of Pyrethrum Extract in a Two Year Dietary Toxicity and Oncogenicity Study in Rats: Lab Project No. 556-011. Unpublished study prepared by International Research and Development Corp. 2002 p.

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870.6200 Neurotoxicity Screening Battery

44401101 Sheets, L.; Gilmore, R.; Hamilton, B. (1997) An Acute Oral Neurotoxicity Screening Study with Technical Grade FCR 4545 in Fischer 344 Rats: Lab Project Number: 96-412-GO: 107755. Unpublished study prepared by Bayer Corp. 382 p.

44517801 Broadmeadow, A. (1997) ESBIOL: Rat Acute Oral Neurotoxicity Study: Lab Project Number: AGV133/970021: 96226: 970021. Unpublished study prepared by Huntingdon Life Sciences, Ltd. 327 p.

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44900601 Yoshida, M.; Watson, M. (1999) A 90-Day Subchronic Neurotoxicity Study in Rats with Tau-Fluvalinate: Lab Project Number: 7618-98-0114-TX-001: 2504. Unpublished study prepared by Ricerca, Inc. 632 p. {OPPTS 870.6200}

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45657401 McDaniel, K.; Moser, V. (1993) Utility of a Neurobehavioral Screening Battery for Differentiating the Effects of Two Pyrethroids, Permethrin and Cypermethrin. *Neurotoxicology and Teratology* 15:71-83. Non-guideline.

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870.6300 Developmental Neurotoxicity Study

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46814301 Gilmore, R.; Sheets, L.; Hoss, H. (2006) A Developmental Neurotoxicity Screening Study With Technical Grade Deltamethrin in Wistar Rats. Project Number: 04/D72/WO, 201469. Unpublished study prepared by Bayer Corp. 1074 p.

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