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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: June 1, 2018

SUBJECT: Transfluthrin: Human Health Risk Assessment for Proposed Use of a New Active Ingredient in Indoor and Outdoor Residential Settings

PC Code: 129140
Decision No.: 520689
Petition No.: NA
Risk Assessment Type: Single Chemical
TXR No.: NA
MRID No.: NA

DP Barcode: D435696
Registration No.: EPA File Symbol 91879-R
Regulatory Action: Section 3, New Active Ingredient
Case No.: NA
CAS No.: 118712-89-3
40 CFR: NA

FROM: Krystle Yozzo, Ph.D., Biologist
Gerad Thornton, Environmental Protection Specialist
Michael A. Doherty, Ph.D., Chemist
Risk Assessment Branch II
Health Effects Division (HED, 7509P)

THROUGH: RARC Reviewers

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

TO: Kable Davis, Product Manager Team Leader (Team 3)
Catherine Aubee, Branch Chief
Invertebrate-Vertebrate Branch 1
Registration Division (7505P)

Table of Contents

The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. Bayer Environmental Science has requested registration of the new active ingredient (ai) transfluthrin in an impregnated textile passive diffusion device, for use as an area repellent in semi-enclosed and enclosed spaces in residential settings. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that may result from the proposed uses of the pyrethroid insecticide, transfluthrin.

A summary of the findings and an assessment of human health risk resulting from the proposed uses of transfluthrin are provided in this document. This risk assessment includes hazard characterization, residential exposure assessment, and a consideration of the impact of transfluthrin on the pyrethroid cumulative risk assessment (CRA). There are currently no registered or proposed food uses for transfluthrin, and drinking water exposure is not expected from the proposed use. Therefore, dietary assessments for transfluthrin have not been conducted, and an aggregate risk assessment is not required.

1.0 Executive Summary

Transfluthrin {(2,3,5,6-tetrafluorophenyl)methyl (1*R*,3*S*)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate}is a Type I synthetic pyrethroid insecticide. Transfluthrin is being proposed for use as an area repellent in semi-enclosed and enclosed spaces in residential settings. The proposed product is formulated as an impregnated textile passive diffusion device, called a personal insect repellent kit (PIRK), containing 15.6% transfluthrin (w/w).

Exposure Profile

Based on the proposed use of the passive diffusion device, only residential post-application inhalation exposures are expected for adults (all use sites), children 3 to <6 years (for use in garages/barns) and children 1 to <2 years (for use in tents, RV/campers, and outdoor areas such as patios, porches, etc.). The end-use product is formulated as an impregnated textile, and there are no special exposure-related activities associated with handling/placing the product, or with residential vs. occupational exposure scenarios. Therefore, the residential post-application inhalation assessment is assumed to be protective for any potential residential or occupational handler, or occupational post-application inhalation exposures. Negligible dermal exposure is expected as the label specifies that for maximum efficiency the product should not be moved after it is placed or hung. Additionally, no hazard was identified for dermal exposure; therefore, an assessment of dermal exposure and risk is not needed. Given the proposed use pattern on the label, incidental oral exposure to children <6 years of age (i.e., the applicable lifestage for this type of exposure) is expected to be negligible as the product must be placed at least 5 feet above the ground. For the proposed new use, only a short-term post-application inhalation assessment was conducted based on hazard and exposure considerations.

Hazard Characterization

Transfluthrin has been evaluated for a variety of toxic effects in experimental toxicity studies. There are no outstanding studies according to 40 CFR Part 158 data requirements for a non-food-use pesticide registration. In addition, numerous studies from the scientific literature that describe the pharmacodynamic and pharmacokinetic profile of the pyrethroids in general have been considered in this assessment. After reviewing the extensive body of peer-reviewed literature on pyrethroids, the agency has no residual uncertainties regarding age-related sensitivity for women of child bearing age, as well as for all adult populations and children ≥6 years of age. Additionally, no evidence of increased quantitative or qualitative susceptibility was seen in the pyrethroid scientific literature related to pharmacodynamics. The Food Quality Protection Act (FQPA) does not apply because transfluthrin is a non-food use chemical; however, the agency will apply an additional 3X safety factor for children <6 years of age based on the increased quantitative susceptibility seen in studies on pyrethroid pharmacokinetics.

Neurotoxic effects (tremors) consistent with Type I pyrethroids were observed following oral gavage and inhalation exposures. No neurotoxic effects were observed throughout the database following dietary (oral feeding) or dermal exposure. Liver toxicity was also observed in parental animals in the two-generation reproduction study at doses higher than doses eliciting neurotoxic effects in the database.

The No Observed Adverse Effect Levels (NOAELs) and Lowest Observed Adverse Effect Levels (LOAELs) established from transfluthrin single-dose and repeat-dosing studies show that repeat exposures do not result in lower NOAELs. Thus, for purposes of endpoint selection and risk assessment, only single-day exposures have been considered.

Based on the proposed use pattern, dermal exposure is expected to be negligible. Furthermore, even though there was quantitative susceptibility in the developmental neurotoxicity study (DNT) and the dermal toxicity study does not assess developmental effects, a dermal point of departure (POD) would not be needed even if higher dermal exposure were expected because 1) no systemic toxicity, including neurotoxicity, was observed up to the limit dose tested in the dermal toxicity test (1000 mg/kg/day), and 2) the use of an estimated 5% DAF based on other pyrethroids to convert an oral LOAEL of 55 mg/kg/day from the rat developmental toxicity study results in a dermal equivalent dose above the limit dose of 1000 mg/kg/day (55/0.05 = 1100 mg/kg/day).

The 90-day inhalation study was selected for short-term inhalation exposure based on clinical signs of toxicity (ungroomed and bristling coat, tremors, and hyperactivity) in both sexes observed at the lowest observed adverse effects concentration (LOAEC) of 0.2202 mg/L (no observed adverse effects concentration, NOAEC = 0.0467 mg/L).

The transfluthrin POD from the inhalation study (NOAEC = 0.0467 mg/L) was used to calculate human equivalent concentrations (HECs) for residential post-application scenarios. For assessing post-application exposure from the use of the proposed product in tents, HEC calculations assumed 8 and 13 hr/day for adults and children, respectively; and for use in RVs/campers, HEC calculations assumed 16 and 18 hr/day for adults and children, respectively. For assessing post-application exposure from the use of the product in barns/garages, HEC calculations assumed 2 and 4 hr/day for children and adults, respectively; and outdoor post-application HEC calculations

assumed 2.3 hr/day for both adults and children, to match the exposure time assumptions in the residential post-application assessment. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the HEC calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X. A 3X uncertainty factor (UF_S) for sensitivity is being applied to children <6 years old based on the increased quantitative susceptibility seen in studies on pyrethroid pharmacokinetics (PKs) and the increased quantitative juvenile susceptibility observed in high dose studies in the literature. Therefore, the level of concern (LOC), based on the combined uncertainty and safety factors, is a margin of exposure (MOE) of 100 for children <6 years old, and 30 for children ≥6 years old and adults.

Residential Post-application Exposure and Risk Assessment

There are no risk estimates of concern for any lifestage, with inhalation MOEs ranging from 190 to 150,000 (LOC = 100 for children <6 years of age; LOC = 30 for adults and children ≥6 years of age).

Cumulative Risk Assessment

The agency completed a CRA for the pyrethroids in 2011. In conducting this risk assessment for transfluthrin, HED has completed a qualitative analysis of the proposed transfluthrin use and has determined that it will not contribute significantly or change the overall findings presented in the pyrethroid cumulative risk assessment.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations[1]."

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include the Outdoor Residential Exposure Task Force (ORETF) database and the Residential SOPs (Outdoor Fogging/Misting Systems), are 1) subject to ethics review pursuant to 40 CFR 26; 2) have received that review; and 3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the agency website[2].

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

[2] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

2.0 HED Conclusions

HED has evaluated the toxicity and exposure databases for the new active ingredient, transfluthrin, and has conducted a human health risk assessment of the proposed uses. Based on this assessment, there are no risk estimates of concern for any lifestages, with inhalation MOEs ranging from 190 to 150,000 (LOC = 100 for children <6 years of age; LOC = 30 for adults and children ≥6 years of age).

2.1 Data Deficiencies

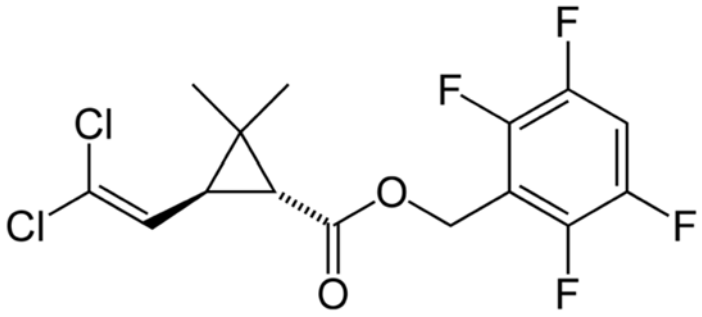
There are no data deficiencies associated with the toxicology, residue chemistry, or exposure databases for transfluthrin.

2.2 Label Recommendations

None

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Transfluthrin Nomenclature.	
Parent Compound	
Common name	Transfluthrin
Company experimental name	NAK 4455
IUPAC name	2,3,5,6-tetrafluorobenzyl (1*R*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate
CAS name	(2,3,5,6-tetrafluorophenyl)methyl (1*R*,3*S*)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
CAS registry number	118712-89-3
Molecular wt.	371.15

3.2 Physical/Chemical Characteristics

Appendix B summarizes the physical and chemical properties of transfluthrin. Based on the available data, transfluthrin has a moderate vapor pressure ($9x10^{-4}$ Pa), and based on how the

end-use product works, exposure to this chemical in the vapor phase is expected to occur. The octanol/water partitioning coefficient is high, indicating that transfluthrin has the potential to accumulate in fatty tissues. Transfluthrin has very low water solubility and is not expected to occur in environmental water systems at appreciable levels.

3.3 Pesticide Use Pattern

The proposed use of transfluthrin is as a personal insect repellent kit, described as a transfluthrin-impregnated textile that passively diffuses volatilized transfluthrin into the air space surrounding the device, which acts to repel insects. Each device is impregnated with 1.5 g of transfluthrin, with a stated useful life of 21 days; the label indicates that one device can be used to treat a room volume of up to 12'x12'x8' (i.e., 1152 ft^3 or 33 m^3). The device may be hung or placed approximately 5 feet above the ground in a variety of enclosed or semi-enclosed spaces.

Table 3.3. Summary of Directions for Use of Transfluthrin

Formulation [EPA File Symbol]	Use Site	Application Rate	Application Method	Use Directions and Limitations
Transfluthrin-impregnated textile [91879-R]	Enclosed or semi-enclosed areas: Tents, stables (i.e., barns), RVs, campers, port-a-potties, garages, outdoor space under canopied areas, patios, porches, campsites	1 device/33 m^3 1.5 g/33 m^3	Passive diffusion, effective for 21 days	Hang from the loop or place on a table. Hang product approximately 5 feet above the floor or the ground surface. Device must be deployed continuously for maximum effectiveness. Not for use in farm structure or buildings housing food-producing animals or poultry.

3.4 Anticipated Exposure Pathways

Humans may be exposed to transfluthrin via inhalation as the device slowly diffuses transfluthrin into the air. Negligible dermal exposure is expected as the label specifies that for maximum efficiency the product should not be moved after it is placed or hung. Exposure to handlers is expected to be negligible and any potential contact with the device is expected to be minimal. Incidental oral exposures are also expected to be negligible for children <6 years of age. There is potential for post-application inhalation exposure, and assessment of post-application inhalation exposure is considered to be protective for any potential handler inhalation exposure.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water

consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it is also being considered whenever appropriate. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Transfluthrin is a member of the pyrethroid class of chemicals. Pyrethroids have historically been classified into two groups, Type I and Type II, based upon chemical structure and toxicological effect. Type I pyrethroids, which lack an alpha-cyano moiety, induce, in rats, a syndrome consisting of aggressive sparring, altered sensitivity to external stimuli, hyperthermia, and fine tremors progressing to whole-body tremors and prostration (T-syndrome). Type II pyrethroids, which contain an alpha-cyano moiety, produce in rats a syndrome that includes pawing, burrowing, salivation, hypothermia, and coarse tremors leading to choreoathetosis (CS-syndrome) (Verschoyle and Aldridge 1980; Lawrence and Casida 1982). Transfluthrin is considered a Type I pyrethroid. The adverse outcome pathway (AOP, based on the Bradford-Hill criteria) shared by pyrethroids involves the ability to interact with voltage-gated sodium channels (VGSCs) in the central and peripheral nervous systems, leading to changes in neuron firing and, ultimately, neurotoxicity (Figure 4.0). The agency has determined that pyrethroids and naturally occurring pyrethrins share a common mechanism of toxicity.

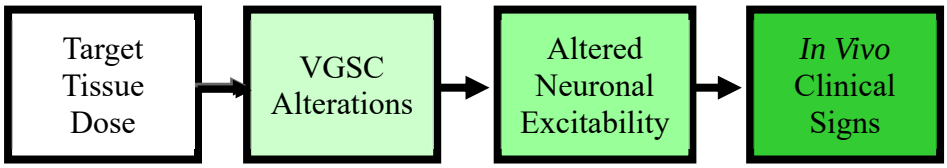


Figure 4.0. Adverse outcome pathway for pyrethroids

4.1 Toxicology Studies Available for Analysis

The toxicological database for transfluthrin is adequate for selecting toxicity endpoints and PODs for the purpose of human health risk assessment based on the proposed non-food use pattern. An immunotoxicity study is not available for transfluthrin; however, the Hazard and Science Policy Council (HASPOC) concluded, based on a weight of evidence approach, that an immunotoxicity study is not anticipated to provide a lower POD or result in a more sensitive

endpoint than those already used in the risk assessment; therefore, an immunotoxicity study is not needed for transfluthrin (TXR# 0056830, U. Habiba, 11/13/2013). Additionally, a subchronic neurotoxicity (SCN) study is not available for transfluthrin. HASPOC concluded, based on a weight of evidence approach, that an SCN is not needed since pyrethroids characteristically do not show increased potency following repeated dosing due to rapid absorption, metabolism, and elimination (TXR# 0057710, M. Wilson, 04/05/2018), and this finding is supported for transfluthrin based on the submitted studies.

The available toxicity studies include the following:

- 28-day dermal toxicity study in rabbits
- 28-day inhalation toxicity study in rats
- 90-day inhalation toxicity in rats
- Developmental toxicity studies (oral) in rats and rabbits
- Two-generation reproduction study (oral) in rats
- Battery of genotoxicity studies
- Neurotoxicity studies in rats (acute [ACN] and developmental [DNT])

In addition, numerous studies from the scientific literature conducted over several decades describe the pharmacodynamic and pharmacokinetic profile of pyrethroids as a chemical class; this scientific literature has been recently reviewed by several groups (Soderlund et al. 2002; Shafer et al., 2005; Wolansky and Harrill 2008).

4.2 Toxicological Effects

Transfluthrin has been evaluated for a variety of toxic effects in experimental toxicity studies. Neurotoxic effects (tremors) consistent with Type I pyrethroids were observed following oral gavage dosing. No neurotoxic effects were observed throughout the database following dietary exposure. This is consistent with other pyrethroids. Since rats feed continuously, pyrethroids administered via the diet are metabolized and excreted from the system relatively quickly, and the overall systemic concentration in the rat remains low. Therefore, an internal dose sufficient to disrupt the sodium channels may not be achieved via dietary exposure. In fact, following dietary administration of transfluthrin, decreased hepatic triglyceride concentration, increased liver and/or kidney weights, and microscopic renal findings were observed in parental rats, but no neurotoxic effects were observed. In contrast, bolus/gavage studies, which included the DNT and ACN studies in rats, result in greater maximal plasma concentrations immediately after dosing, and subsequently in neurotoxic effects. Additionally, the systemic toxicity observed during the feeding studies occurred at slightly higher measured doses (87.8 mg/kg/day) compared to neurotoxic effects observed following bolus/gavage dosing (55 mg/kg/day). Neurotoxicity was also present after 28- and 90-day inhalation exposures, with clinical signs of ungroomed and bristling coat with slightly reduced motility and tremors being observed in both exposure durations.

No evidence of increased quantitative or qualitative susceptibility was noted in the core developmental toxicity or reproduction studies for transfluthrin; however, there was increased quantitative susceptibility in the DNT study, in which decreased pup body weight occurred at

doses lower than those at which maternal toxicity was observed. There was no evidence of developmental toxicity up to the highest dose tested in the rat and rabbit developmental toxicity studies or in the two-generation reproduction study in rats. Maternal effects in the developmental toxicity studies included tremors in rats and mortality (one doe) in rabbits at approximately the same dose in both species (~50 mg/kg/day). Maternal effects in the two-generation reproductive toxicity study in rats included decreased hepatic triglyceride concentration in females, increased liver and/or kidney weights in males and females, and microscopic renal findings in males and females at the highest dose tested (79.1/87.8 mg/kg/day [M/F]).

Transfluthrin did not result in any systemic toxicity following dermal exposure for 28-days up to the limit dose of 1000 mg/kg bw/day, which is consistent with the low dermal absorption observed for most pyrethroids (around 5%). Skin redness; scaling, encrustation, swelling, and red patches, as well as increased skin fold thickness, were observed in males and females at 200 mg/kg/day; however, for conventional pesticides, HED does not select endpoints based on irritation effects.

Transfluthrin has low acute toxicity, being classified as Category III or IV in the acute oral, dermal, inhalation, and eye/dermal irritation studies. Transfluthrin is not a dermal sensitizer.

4.3 Pyrethroid Pharmacokinetic (PK) and Pharmacodynamic (PD) Profile

OPP is making best use of the extensive scientific knowledge about the AOP on pyrethroids in the risk assessments for this class of pesticides. In this way, information on a subset of pyrethroids can be used to help interpret and understand the toxicological profile for other members of the class. In that regard, a group of pesticide registrants and product formulators known as the Council for the Advancement of Pyrethroid Human Risk Assessment (CAPHRA) has been conducting multiple experiments with permethrin and deltamethrin as model Type I and Type II compounds, respectively, in order to develop an initial extensive database of *in vitro* and *in vivo* toxicology studies and highly refined physiologically-based pharmacokinetic (PBPK) models. The CAPHRA presented its most recent experimental data and proposed path forward to the FIFRA Science Advisory Panel (SAP) on May 19, 2015 (USEPA 2015). Based on the comments from the SAP, the CAPHRA has continued to pursue its research efforts and submitted additional data. However, the data available from the CAPHRA were not useful for deriving PODs or for species extrapolation, so the CAPHRA data are under review but have not been included in the current risk assessment.

In addition to the efforts of the CAPHRA, the extensive body of scientific literature on the pyrethroids provides insight into the contributions of PK and PD to the general toxicity profile of this class of chemicals. This information also provides valuable insight into the potential age-related differences in toxicity for the pyrethroids. This scientific literature has been reviewed by several groups (Soderlund et al. 2002; Shafer et al. 2005; Wolansky and Harrill 2008) and the following sections of the risk assessment discuss the specific issues related to pyrethroid PK, pyrethroid PD, and age-related differences in pyrethroid toxicity. Furthermore, the agency will be updating its literature review for pyrethroids as described below prior to completion of the revised risk assessments.

In recent years, the National Academies' National Research Council (NRC) has encouraged the agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific risk assessments to inform regulatory decision making (NRC 2011, 2014). The NRC defines systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies" (NRC 2014). According to the NRC, systematic reviews "have several common elements: transparent and explicitly documented methods, consistent and critical evaluation of all relevant literature, application of a standardized approach for grading the strength of evidence, and clear and consistent summative language." EPA's Office of Chemical Safety and Pollution Prevention is currently developing systematic review policies and procedures, and is working to develop a systematic review for the pyrethroids.

4.3.1 Pharmacokinetics (PK)

PK can be defined as what the body does to the chemical; in this case, how pyrethroids are distributed and eliminated following exposure. Specific to pyrethroids, PK refers to the process(es) that determine(s) the concentration of the pyrethroids reaching sodium channels. The underlying PK of pyrethroids is an important determination of their toxicity because the concentration of pyrethroid at the sodium channel relates to the extent of toxicity; greater pyrethroid concentration translates as increased neurotoxicity. Physiological processes that significantly contribute to the PK include metabolism, protein binding, and partitioning. Carboxylesterases and cytochrome P450 enzymes are the two major enzyme families responsible for the metabolism of pyrethroids. It is the ontogeny of these enzymes that accounts for the age-related sensitivity observed after pyrethroid exposures, as described below in more detail. In terms of partitioning, pyrethroids tend to distribute into fat. However, pyrethroid residues in fatty tissue are not available to interact with the VGSCs in vital tissues and, therefore, do not contribute to overall toxicity.

Age-dependent PK differences have been identified for several pyrethroids; that is, there are differences in the ability of adults and juveniles to metabolize pyrethroids. The enzymes that metabolize and detoxify pyrethroids are present in rats and humans at birth (Koukouritaki et al. 2004; Yang et al. 2009). As a result, both juveniles and adults are able to tolerate low doses of pyrethroids when the internal dose, or the amount of pyrethroid at the sodium channel, is low. However, the expression, and therefore activity, of these enzymes increases with age, conveying in adults a greater capacity than juveniles to detoxify pyrethroids (Anand et al. 2006; de Zwart et al. 2008; Yang et al. 2009). For example, the rate of *in vitro* metabolism of deltamethrin by plasma carboxylesterases, plus hepatic carboxylesterases and cytochrome P450s (microsomes) is at least 6 times as high post-natal day (PND) 90 rats as for PND 10 rats (Anand et al. 2006). In humans, expression of hepatic carboxylesterases is significantly lower in infants <3 weeks old but then increase to near adult levels (Hines et al. 2016). Similar information is also available for the major human P450s involved in pyrethroid metabolism (CYP2C8, CYP2C19, and CYP3A4). CYP2C19 levels are approximately 80% of adult values from >5 months to 10 years, CYP3A4 reaches near adult levels by 1-2 years, and CYP2C8 levels are comparable to adult levels after 6 months of age (Koukouritaki et al. 2004; Stevens et al. 2003; Song et al. 2015). As a consequence, higher internal doses (i.e., those associated with high doses in experimental

toxicology studies) 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. As a matter of perspective, the anticipated exposures from typical dietary or residential activities are not expected to overwhelm the premature metabolic systems in juveniles.

To better understand the role of PK and reduce uncertainty associated with extrapolating across species (i.e., rat to human) and life stages, the agency developed PBPK models designed to predict pyrethroid concentration in tissues following *in vivo* exposure. The agency has determined that the important PK properties relevant to the metabolism and distribution of pyrethroids in the body are sufficiently similar for members of this class such that using a 'generic' or family model structure for this class is scientifically appropriate. In other words, because of the similarities in the PK profiles of pyrethroids, a single model structure is able to predict the tissue dose based on the PK of every member of the class. The family modeling approach was primarily developed based on PBPK modeling performed with deltamethrin and was presented to, and supported by, the Federal Insecticide, Fungicide, and Rodenticide Scientific Advisory Panel (FIFRA SAP) (USEPA 2007).

The initial deltamethrin PBPK model presented to the SAP was developed in the adult male Sprague Dawley (SD) rat (Mirfazaelian et al. 2006). The deltamethrin PBPK model was further refined based on oral bioavailability and disposition studies in rats and included estimates for target tissue concentrations in humans (Godin et al. 2010). The initial PBPK model was also extended by accounting for age-dependent changes in physiological and biochemical parameters (Tornero-Velez et al. 2010) to address juvenile sensitivity in rats. This model predicts that, 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. For example, the internal dose from an administered dose of 1 mg/kg in the adult is equivalent to the internal dose from an administered dose of 0.26 mg/kg (≈1 mg/kg÷3.8mg/kg) in the 10-day old rat and to an administered dose of 0.4 mg/kg (≈1 mg/kg÷2.5mg/kg) in the 21-day old rat. As a result, the agency concludes that juvenile rats are three times as sensitive as adult rats with respect to pyrethroid PK. At this time, the agency considers that the differences in the PK profile observed in the rat are relevant to humans. Therefore, for food use pyrethroids the PK contribution to the Food Quality Protection Act Safety Factor (SF) is 3X for children less than 6 years old and 1X for children 6 years of age or older and for adults. Further information regarding the decision to retain the FQPA Safety Factor and the choice of age groups it applies to can be found in the Re-Evaluation of the FQPA Safety Factor of Pyrethroid Pesticides memo (D381210, E. Scollon, 06/27/2011). Although, the FQPA SF does not apply to transfluthrin since there are no food uses, HED has applied a 3X factor to account for the susceptibility of children less than 6 years of age.

4.3.2 Pharmacodynamics (PD)

PD can be defined as the changes that chemicals cause to the body, in this case, how pyrethroids interact with the sodium channels. Substantial evidence from in vitro and in vivo studies support the AOP illustrated in Figure 4.0 above and the disruption of sodium channels by pyrethroids as an early key event (Lund and Narahashi 1982; Salgado et al. 1989; Song and Narahashi 1996; Tabarean and Narahashi 1998; Soderlund et al. 2002). As a new active ingredient, there are no

recent studies for transfluthrin that provide information on how transfluthrin interacts with the sodium channels. However, there are several recent studies which provide information on a variety of other pyrethroids. Choi and Soderlund (2006) examined interactions of several pyrethroids with mammalian VGSCs expressed in *Xenopus* oocytes. With respect to altered neuronal excitability, Type I pyrethroids cause slight prolongations of the sodium current tails (e.g. ~20 ms), often resulting in long trains of action potentials. In contrast, Type II pyrethroids significantly prolong sodium current tails (e.g. 200ms to minutes) typically resulting in increased resting membrane potential and ultimately causing depolarization dependent action potential block. Cao et. al. (2011a) measured Na influx in primary cultures of mammalian (mouse) neurons and demonstrated that pyrethroids caused increases in Na influx in this model; this confirms the ability of pyrethroids to interact with VGSC in intact mammalian neurons. An additional study by Cao et. al. (2011b) demonstrated that the interaction of pyrethroids with VGSC caused changes in neuronal excitability that resulted in calcium influx into intact mouse neurons.

HED would prefer to use an early key event in the AOP for pyrethroids in selection of points of departure, such as sodium channel modification. However, *in vivo* techniques used to detect VGSC alteration and altered neuronal excitability are not practical for use in risk assessment at this time, and approaches for extrapolating *in vitro* findings to *in vivo* measures are not yet developed. As such, the agency is focusing its efforts for all pyrethroids in hazard characterization and identification on the apical endpoint (i.e., changes in neurobehavior in laboratory animals). Neurotoxicity resulting from pyrethroids is generally characterized by tremors, hyper- or hypothermia, heightened response to stimuli, salivation, reduced locomotor activity, or convulsions (Soderlund et al. 2002; Wolansky and Harrill 2008; Weiner et al. 2009). In addition, results from a study by Wolansky et al. (2006) indicated that motor activity is a sensitive and robust measure of neurotoxicity for this class of compounds. The changes in motor activity observed were not specific to either of the syndromes described for pyrethroids and were observed with both Type I and Type II pyrethroids.

In contrast to the age-related PK differences identified in the 2011 analysis, PD contributions to pyrethroid toxicity are not age-dependent, even though there are several variations of sodium channels, called isoforms, which are differentially expressed by tissue and age. Because of the nature of the interaction of pyrethroids with sodium channels, it is difficult to obtain dynamic information *in vivo.* To date, a readily useable biomarker of *in vivo* pyrethroid interaction with sodium channels has not been identified, making it impractical to determine the isoform combinations that are present and being acted upon by pyrethroids. Therefore, much of the information available to the agency to characterize the PD relationship between pyrethroids and sodium channels has been derived from *in vitro* studies using frog oocytes or neuronal cells cultured in defined media. These *in vitro* techniques do not provide a direct quantitative measure of *in vivo* pyrethroid activity. However, these techniques consistently and qualitatively demonstrate that sodium channel isoforms expressed in juveniles are not more sensitive to pyrethroid perturbation compared to isoforms expressed in adults and that, pharmacodynamically, the rat is a conservative model for humans. For example, Meacham et al. (2008), expressed adult and juvenile isoforms of rat sodium channels in frog oocytes and compared their sensitivity following exposure to deltamethrin. The isoforms had comparable responses at environmentally relevant concentrations (<500 nM) of deltamethrin, suggesting a

lack of PD difference between juveniles and adults at low exposure levels. In addition, in a direct comparison of a homologous rat and human VGSC isoform $NaV_{1.3}$, the rat isoform was 4-fold more sensitive than the equivalent human sodium channel to the pyrethroid tefluthrin (Tan and Soderlund 2009). This observation suggests that the rat is a highly-sensitive model, and extrapolations from the rat would be protective of human health. The occurrence and ontogeny of VGSCs in humans is not as well characterized compared to those of the rat. However, based on the comparable function and distribution of sodium channels between the species, the rat is an appropriate surrogate for the evaluation of human PD (Goldin et al. 2000; Goldin 2002). As a result, the agency concludes that juvenile rats are not more sensitive than adults with respect to pyrethroid pharmaco-dynamics based on sodium channel data. Therefore, the PD contribution to the FQPA factor will be 1X.

4.3.3 Critical Duration of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. For transfluthrin, neurotoxicity is the most sensitive endpoint with effects such as tremors observed within 1 hour following oral gavage dosing in the developmental toxicity study in rats. These observations are consistent with the toxicity profiles for other pyrethroids which are marked by rapid absorption, metabolism, and elimination, with a time to peak effect for neurobehavioral effects ranging from 4 to 8 hours (Wolansky and Harrill 2008; Weiner et al. 2009; Scollon et al. 2011). The combination of rapid absorption, metabolism, and elimination precludes accumulation and increased potency following repeated dosing. Therefore, for most pyrethroids, the acute toxicity studies typically result in neurotoxicity at lower doses. In general, rat dietary studies tend to have higher NOAELs/LOAELs for pyrethroids since as rats feed continuously pyrethroids are metabolized and excreted from the system relatively quickly and the overall systemic concentration in the rat remains low. In contrast, bolus/gavage dosing results in greater maximal plasma concentrations immediately after dosing. This is also true for transfluthrin, as feeding studies did not result in neurotoxic effects in the rat; however, neurotoxicity was observed in gavage studies.

Table 4.3.3. Transfluthrin NOAEL and LOAEL Values versus Treatment Time for Signs of Neurotoxicity in Adult Rats

Study	Duration	Study findings	
		NOAEL (mg/kg/day)	LOAEL (mg/kg/day)
Acute Neurotoxicity (Sprague Dawley Rat) (1 ml/kg gavage volume[a])	Acute	78.6	100
Developmental Toxicity (Sprague Dawley Rat) (10 mL/kg gavage volume[b])	Repeated (10 days)	25	55
Developmental Neurotoxicity (Wistar Rat) (dietary administration)	Repeated (~35 days)	534	Not established
Two-Generation Reproduction Toxicity (Han Wistar Rat) (dietary administration)	Chronic	15.5[c]	79.1

[a] vehicle: corn oil

[b] vehicle: 5% aqueous Emulphor EL-719

[c] lower NOAEL compared to the developmental toxicity study is due to dose-spacing; parental LOAEL in two-generation reproduction toxicity study is based on non-neurotoxic endpoints.

4.4 Consideration of Susceptibility of Infants and Children[3]

FQPA does not apply because transfluthrin is a non-food use chemical. However, HED considered the potential for susceptibility of infants and children, and has concluded: 1) the toxicity database is complete for a non-food use chemical, including adequate studies to assess the potential susceptibility in the young (including a DNT study); 2) there is no indication of quantitative or qualitative susceptibility in the rat or rabbit core guideline developmental toxicity or in the rat two generation reproduction studies; 3) the endpoints and doses chosen for risk assessment are protective of the quantitative susceptibility observed in the DNT; 4) clear NOAELs were identified for the developmental/offspring effects observed in all developmental and reproduction studies; and 5) the endpoints and doses chosen for risk assessment are protective of the neurotoxicity observed in these studies.

After reviewing the extensive body of peer-reviewed literature on pyrethroids, the agency has no residual uncertainties regarding age-related sensitivity for women of child bearing age as well as for all adult populations and children ≥6 years of age, based on the absence of pre-natal sensitivity observed in 76 guideline studies for 24 pyrethroids and the scientific literature. Additionally, no evidence of increased quantitative or qualitative susceptibility was seen in the pyrethroid scientific literature related to PD. Even though the use pattern for transfluthrin is non-food, the agency is applying a 3X uncertainty factor to protect for exposure to children <6 years old based on the increased quantitative susceptibility seen in studies on pyrethroid PKs and the increased quantitative juvenile susceptibility observed in high dose studies in the literature. The residential exposure assessment uses conservative assumptions, ensuring that exposure and risk will not be underestimated.

4.4.1 Completeness of the Toxicology Database

The toxicology database for transfluthrin is complete for consideration of the non-food use pattern, and there are no residual uncertainties with regard to assessment of pre- and/or postnatal susceptibility. Acceptable developmental toxicity studies in rats and rabbits are available for transfluthrin, in addition to an acceptable two-generation reproduction study in rats. While the database is considered to be complete with respect to the guideline toxicity studies, EPA lacks additional data to address the potential for juvenile sensitivity to all pyrethroids, including transfluthrin. As noted previously, additional research efforts are underway to address juvenile sensitivity for the pyrethroids including transfluthrin.

4.4.2 Evidence of Neurotoxicity

As with other pyrethroids, neurotoxicity was observed across the toxicology database for transfluthrin, in the inhalation studies and in the oral studies with gavage/bolus dosing. However, there is a low degree of concern for the potential neurotoxic effects of transfluthrin since clear NOAELs were identified for the neurotoxic effects and the selected endpoints are protective of the observed effects.

[3] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

No evidence of increased quantitative or qualitative susceptibility was observed in rat and rabbit core guideline developmental toxicity and rat reproduction studies; however, there was increased quantitative susceptibility in the DNT study, where decreased pup body weight occurred at doses lower than maternal toxicity. However, the degree of concern for the susceptibility is low because the decreased pup body weight was seen at a relatively high dose (>500 mg/kg/day), the effect is well characterized with defined NOAEL/LOAEL values, and the PODs selected for risk assessment are protective of the increased susceptibility.

The agency has reviewed existing pyrethroid data and concluded that the DNT is not a particularly sensitive study for comparing the sensitivity of young and adult animals to pyrethroids (USEPA 2010). High dose studies in the scientific literature indicated that younger animals were more susceptible to the toxicity of pyrethroids. For example, Sheets et al. (1994) found increased brain deltamethrin levels in young rats (PND 11 and 21) relative to adult rats (PND 72). These age-related differences in toxicity are principally due to age-dependent pharmacokinetics; the activity of enzymes associated with the metabolism of pyrethroids increase with age (Anand et. al. 2006). In addition, ORD has recently developed an age-dependent PBPK model deltamethrin (Tornero-Velez et. al. 2010) which predicts a 3–fold increase of pyrethroid in neuronal tissue in younger animals compared to adults. There are several studies (*in vitro* and *in vivo*) that indicate pharmacodynamic contributions to pyrethroid toxicity are not age-dependent. Examination of specific VGSCs have demonstrated that there is a lack of increased sensitivity in either juvenile specific isoforms (Meacham et. al. 2008) or in human isoforms compared to rat variants (Tan and Soderlund 2009). As a result, the agency is applying a 3X uncertainty factor to protect for exposure to children <6 years of age.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database based on: 1) the proposed use is a non-food use, and 2) adequate exposure data are available to assess the occupational and residential exposure resulting from the proposed uses. HED used the residential SOPs in order to complete the residential exposure assessment.

4.5 Toxicity Endpoint and Point of Departure Selections

Acute and Chronic Dietary: Transfluthrin is proposed for non-food uses only and exposure from drinking water will not occur; therefore, dietary PODs have not been selected.

Incidental Oral (Short-term): The rat developmental toxicity study was selected for incidental oral exposure based on tremors that occurred 1-hour post dose at the LOAEL of 55 mg/kg/day (NOAEL = 25 mg/kg/day). This study is appropriate for the route (oral) and duration of exposure since the effects were observed within 1-hour post dosing and is protective of all offspring effects in the reproduction and developmental studies. Based on the proposed use pattern, incidental oral exposures are not expected; however, this endpoint has been selected for potential future uses that may result in incidental oral exposures.

Dermal (Short-term): Based on the proposed use pattern with negligible dermal exposure expected, a dermal endpoint has not been selected. Furthermore, even though there was quantitative susceptibility in the DNT and the dermal toxicity study does not assess developmental effects, no dermal hazard is expected because 1) no systemic toxicity, including neurotoxicity, was observed up to the highest dose tested in the dermal toxicity test (1000 mg/kg/day), and 2) the use of an estimated 5% DAF based on other pyrethroids to convert an oral LOAEL of 55 mg/kg/day from the rat developmental toxicity study results in a dermal equivalent dose above the limit dose of 1000 mg/kg/day (55/0.05 = 1100 mg/kg/day); therefore, a dermal endpoint would not be needed even if higher dermal exposures were expected.

Inhalation (Short-term): The 90-day inhalation study was selected for short-term inhalation exposure based on clinical signs of toxicity (ungroomed and bristling coat, tremors, and hyperactivity) in both sexes at the LOAEC of 0.2202 mg/L (NOAEC = 0.0467 mg/L). The LOAEC in this study is similar to the LOAEC (0.168 mg/L) from the 28-day study; HED considers the difference in LOAECs between the two studies to be an artifact of dose-spacing.

The methods and dosimetry equations described in EPA's reference concentration (RfC) guidance (1994) are suited for calculating HECs based on the inhalation toxicity POD (NOAEL, LOAEL, or BMDL) for use in MOE calculations. Since the inhalation toxicity study was administered as an aerosol, the regional-deposited-dose ratio (RDDR) can be used to estimate the different dose fractions deposited along the respiratory tract. The RDDR is also based on interspecies differences in ventilation and respiratory-tract surface areas. Thus, the RDDR can be used to adjust an observed inhalation exposure of an animal to the equivalent inhalation exposure for a human that would result in same toxic effect. For the subchronic inhalation toxicity study with transfluthrin, the RDDR was estimated at 2.99 based on systemic effects observed at the LOAEC of 0.2202 mg/L (NOAEC = 0.0467 mg/L), with a mass median aerodynamic diameter (MMAD) of 1.23, geometric standard deviation (GSD) of 1.39, and the default rat body weight of 217 g.

The transfluthrin POD from the inhalation study (NOAEC = 0.0467 mg/L) was used to calculate human equivalent concentrations (HECs) for residential post-application scenarios. For assessing post-application exposure from the use of the proposed product in tents, HEC calculations assumed 8 and 13 hr/day for adults and children, respectively; and for use in RVs/campers, HEC calculations assumed 16 and 18 hr/day for adults and children, respectively. For assessing post-application exposure from the use of the product in barns/garages, HEC calculations assumed 2 and 4 hr/day for children and adults, respectively; and outdoor post-application HEC calculations assumed 2.3 hr/day for both adults and children, to match the exposure time assumptions in the residential post-application assessment.

The HEC calculations are summarized in Table 4.5.3.b; for inhalation risk assessment, the standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X for all age groups due to the HEC calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X. The uncertainty factor for sensitivity of children <6 years (UF_s) can be reduced to 3X. Therefore, the LOC is 100 for children <6 years old and 30 for adults and children ≥6 years old.

While the proposed new use could be considered to result in intermediate- or long-term exposure, the single dose and repeat dosing transfluthrin studies show that repeat exposures do not result in lower PODs (i.e. there is no evidence of increasing toxicity with an increased duration of exposure). Therefore, for transfluthrin, a short-term assessment was conducted, and it is considered to be protective of scenarios in which exposure occurs for longer durations.

4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment

Incidental/short-term oral and inhalation exposures can be combined since the same study/effects were selected to evaluate both routes; however, oral exposure is not expected based on the proposed use pattern. Furthermore, a dermal endpoint was not selected; therefore, there are no exposures from other routes to combine with inhalation exposure.

4.5.2 Cancer Classification and Risk Assessment Recommendation

Carcinogenicity studies are not required for non-food use pesticides, and there are no cancer studies available for transfluthrin; therefore, a cancer classification has not been determined. Chronic toxicity data are conditionally required for non-food use chemicals when significant chronic exposure is likely, the pesticide is applied directly to the skin or to wearing apparel, or specific toxicity triggers are observed including concerns for mutagenicity, structural similarity to known carcinogens, or the presence of morphological effects which may be precursors to neoplastic changes. HED has determined that transfluthrin does not meet these criteria; therefore, chronic toxicity studies are not required. To address the limited potential for longer-duration exposures, risks estimated using endpoints derived from subchronic studies are considered protective for these potential exposures.

Transfluthrin is not expected to pose a cancer risk at anticipated dermal and inhalation exposures because:

- Transfluthrin is negative for mutagenicity in the full mutagenicity battery, so it is not expected to have mutagenic mode of carcinogenicity and therefore short-term points of departure would be protective of any potential cancer effects.
- Transfluthrin is a type 1 pyrethroid compound having short half-life in the body (4 to 6 hours) and does not accumulate in the body.
- The transfluthrin database does not show any specific target organ toxicity

Based on the above considerations, HED concluded that it is not necessary to conduct a cancer risk assessment at this time. HED will re-consider this determination if there is a significant change in the use pattern.

4.5.3 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.3.a Summary of Toxicological Doses and Endpoints for Transfluthrin for Use in Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (All Populations)	Based on the proposed use pattern (non-food use), acute dietary exposure is not expected and an endpoint has not been selected.			
Chronic Dietary (All Populations)	Based on the proposed use pattern (non-food use), chronic dietary exposure is not expected and an endpoint has not been selected.			
Incidental Oral Short-Term (1-30 days)	Based on the proposed use pattern, incidental oral exposure is not expected and an endpoint has not been selected.			
Dermal Short-Term	No dermal hazard is expected -no systemic toxicity, including neurotoxicity, was observed at the highest dose tested in the dermal toxicity test (1000 mg/kg/day). In addition, the use of a 5% DAF to convert an oral LOAEL of 55 mg/kg/day from the rat developmental toxicity study results in a dermal equivalent dose above the limit dose of 1000 mg/kg/day (55/0.05 = 1100 mg/kg/day).			
Inhalation Short-Term (1-30 days) Children ≥6 years old and adults	NOAEC = 0.0467 mg/L (See table 4.5.3.b for HEC calculation)	UF_A = 3x UF_H = 10x	Children ≥6 and adults: LOC for MOE =30	**90-day Inhalation Toxicity (Rat)** MRID 49617856 LOAEC = 0.2202 mg/L based on clinical signs of toxicity (ungroomed and bristling coat, tremors, and hyperactivity) in both sexes
Inhalation Short-Term (1-30 days) Children <6 years old	NOAEC = 0.0467 mg/L (See table 4.5.3.b for HEC calculation)	UF_A = 3x UF_H = 10x UF_S = 3x	Children <6: LOC for MOE = 100	**90-day Inhalation Toxicity (Rat)** MRID 49617856 LOAEC = 0.2202 mg/L based on clinical signs of toxicity (ungroomed and bristling coat, tremors, and hyperactivity) in both sexes
Cancer (oral, dermal, inhalation)	Classification: not determined. Carcinogenicity studies are not required for non-food use pesticides.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_S = sensitivity among children <6. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

Table 4.5.3.b Summary of Post-Application Inhalation HEC/HED values for Transfluthrin						
Population	**Scenario**	**Human Daily Duration (hours)**	**Toxicity duration adjustment[a]**		**HEC[b]**	
			Daily	**Weekly**	**mg/L**	**mg/m^3**
Residential	Barns/garages - children	2	NA	NA	0.140	139.633
	Outdoor – adults and children	2.3				
	Barns/garages - adults	4				

Table 4.5.3.b Summary of Post-Application Inhalation HEC/HED values for Transfluthrin						
Population	Scenario	Human Daily Duration (hours)	Toxicity duration adjustment[a]		HEC[b]	
			Daily	Weekly	mg/L	mg/m^3
	Tent - adults	8	0.75	0.71	0.075	74.803
	Tent - children	13	0.46	0.71	0.046	46.033
	RVs/campers - adults	16	0.38	0.71	0.037	37.402
	RVs/campers - children	18	0.33	0.71	0.033	33.246

NA = not applicable (the expected duration of the exposure scenario is less than the duration in the available inhalation toxicity studies; downward adjustments are not permitted).

[a] Toxicity duration adjustment from 6 hours/day, 5 days/week in the 90-day route-specific inhalation study. For example, an indoor post-application scenario assumed at 16 hours per day, 7 days per week has a daily adjustment of 0.38 (6 hrs/16 hrs) and a weekly adjustment of 0.71 (5 days/7 days). Outdoor post-application, including barns and garages, were not adjusted as all exposure durations are less than the 6 hours (i.e., shorter than the duration of the rat inhalation toxicity study).

[b] HEC =human-equivalent concentration; HEC = rat POD x daily duration adjustment x weekly daily duration adjustment x RDDR. (systemic RDDR = 2.99; MMAD = 1.23, GSD = 1.39; default rat body weight = 217 g).

5.0 Dietary Exposure and Risk Assessment

HED has not conducted a dietary risk assessment. There are no uses at this time that will result in exposure to transfluthrin via residues in food or drinking water.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

6.1 Residential Handler Exposure and Risk Estimates

The proposed product label specifies that the product is to be placed and removed without touching the product itself; the product includes a string allowing for it to be hung/placed. Additionally, no dermal hazard was identified in the toxicity studies, and therefore a dermal assessment is not needed. For these reasons, a residential dermal handler assessment was not conducted. Furthermore, handling the product is not expected to result in greater exposure than that which occurs after the product is put in place; therefore, the post-application inhalation assessment (Section 6.2) is considered protective of handler inhalation exposure. A separate inhalation assessment for handlers was not conducted.

6.2 Residential Post-Application Exposure and Risk Estimates

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[4]. While not the only lifestages potentially exposed for these post-application scenarios, the lifestages that are included in the quantitative assessment are protective for other lifestages.

Residential Post-application Exposure Data and Assumptions

[4] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs[4]. However, since the proposed use specifies use locations that are not directly addressed in the SOPs, assumptions have been made in order to address these uses. The following assumptions were made:

- Exposure Time
    - *RVs/Campers:* RVs and campers are assumed to have similar exposure time as other indoor residential sites (e.g., homes and apartments), for which the standard indoor SOP assumption of 16 and 18 hrs/day for adults and children, respectively, is used.
    - *Tents:* As no tent-specific exposure data are available, HED used data from the Exposure Factors Handbook (2011 Edition) to estimate the amount of time adults and children spend sleeping/napping. The data show that adults spend approximately 8 hrs/day sleeping, and children, 1 to < 2 years of age spend approximately 13 hrs/day sleeping/napping. HED has determined using 8 and 13 hrs/day is a conservative estimate for time spent in a tent since these values represent the time spent sleeping/napping under more typical environments (i.e., in a home).
    - *Barns/Garages:* Time spent in garages is assumed to be comparable to time spent in barns, and the standard barn SOP assumption of 4 and 2 hrs/day for adults and children, respectively, has been used.
    - *Port-a-potties:* Exposure to a treated port-a-potty is expected to be minimal given the relatively short amount of time expected that adults and children will spend in this use site; therefore, this scenario was not quantitatively assessed.
    - *Outdoors:* All other sites (i.e., patios, campsites, etc.) are treated as outdoor use sites, for which the standard outdoor SOP assumption of 2.3 hrs/day is used.
- Air Flow/Air Exchange
    - *RVs/Campers:* RVs and campers are assumed to have a similar air exchange rate to other indoor residential sites, and the standard indoor SOP assumption of 0.45 air exchanges per hour is used.
    - *Tents:* The barn air exchange value, 4 air exchanges per hour, from the 2012 Residential SOPs is a reasonable surrogate for tents. This conclusion is supported by the study "Experimental study on indoor air thermal equilibrium model of the tent" published in the *International Journal of Low-Carbon Technologies* (L. Zhang, et al. March 2017. Volume 12, Issue 1, Pages 36-42). The study experimentally determined air exchange values by measuring ventilation rates in a model tent. The ventilation rates ranged from 4 to 7 times per hour, which is comparable to the barn air exchange rates of 4 to 8 times per hour; therefore, the animal barn SOP inputs were assumed to be a reasonable range for risk assessment.
    - *Barns/Garages:* Garages are assumed to be similar to barns, and the standard barn SOP assumption of 4 air exchanges per hour is used.
    - *Outdoors:* All other sites (i.e., patios, campsites, etc.) are treated as outdoor residential sites. The 2012 residential SOPs provide an air flow based on a minimal wind speed and cross-section of the treated volume. The value for the air flow was adjusted from the standard SOP assumption of 4,000 m^3/hr to 3,211

m^3/hr, accounting for the difference in the cross-sectional area of the treated volume specified on the proposed label (8 x 12 feet or 8.9 m^2 vs 11 m^2 in SOP). The air flow can be converted to an air exchange rate (see Appendix A for algorithm), where an airflow of 3,211 m^3/hr yields an air exchange rate of 97.3 air exchanges per hour.

- Treated Volume
  - RVs/Campers/Barns/Garages/Outdoors: The label specified maximum volume of 33 m^3 per product is used in the assessment.
  - Tents: Although tents are made in a variety of sizes, a smaller volume was assumed in order to be protective for commercially available tents. HED has assumed the smallest, most likely used, tent size for adults and children is a four-person tent. The volumes for these tents, calculated from dimensions provided in the product specifications for several different tent models, ranged from 7 to 9 m^3. The lower end of the range, 7 m^3, was used in the assessment to result in a more health protective risk estimate.

- *Application Information:* The proposed new use application information may be found in Table 3.3.

- *Exposure Duration:* While the proposed new use could be considered an intermediate- or long-term exposure, the single dose and repeat dosing transfluthrin toxicity studies show that repeat exposures do not result in lower PODs (i.e. there is no evidence of increasing toxicity with an increased duration of exposure). Therefore, for transfluthrin, a short-term assessment was conducted, and is protective of scenarios in which exposure occurs for longer durations.

- *Efficiency of Vaporization:* Vaporization efficiency is the percentage of active ingredient in the product that becomes available for inhalation exposure through evaporation over the useful life of the product. Once the end-use product is deployed, it is likely that not all of the active ingredient in the product will be available for inhalation exposure.

  In support of the proposed use, Bayer Environmental Science has provided a study: "Study of the Degradation and Evaporation Behaviour of Transfluthrin in/on Representative Indoor Surfaces" (MRID 50509401) and its raw data (MRID 50309401). A liquid solution containing radiolabeled transfluthrin was applied to various substrates (carpet, glass, wallpaper, wood, varnish, and PVC floor coverings). After 0, 10, 21, and 90 days, the remaining amount of transfluthrin was determined. The study authors noted that the application solution was inhomogeneous, preventing accurate quantification of the amount of transfluthrin that evaporates (or vaporizes) off of an indoor surface. This concern was accepted by the study author as the aim of the experiment was to identify potential degradation of transfluthrin and not to quantify the amount evaporated or degraded. However, the study did demonstrate that only a fraction of transfluthrin applied to a surface will evaporate.

  Given that the radiolabeled solution of transfluthrin used in the study was inhomogeneous and that the study authors were unable to accurately quantify the amount of transfluthrin

applied to each surface, HED has assumed that 100% of the transfluthrin found in the end-use product will evaporate over the course of the product's label-specified life of 21 days. However, HED notes that additional product-specific data on the evaporation of transfluthrin from the end-use product would help to further refine these risk estimates.

Residential Post-application Non-Cancer Concentration and Risk Algorithms

Typically, post-application inhalation risk is calculated using an exposure algorithm based on the well-mixed box model (see Appendix D in the 2012 Residential SOP). However, as the inhalation endpoint selected for assessing risk comes from a route-specific inhalation toxicity study, HED has determined risk estimates should instead be calculated by comparing the modeled air concentration an individual would be exposed to over the exposure time (i.e., a time-weighted average [TWA] air concentration) to a human equivalent concentration (HEC) calculated from the NOAEC selected from the toxicity study. The algorithm used to estimate the residential post-application time-weighted average concentration is derived from equation D.7 in the 2012 Residential SOPs[5] and can be found in Appendix D.

Additionally, in order to model air concentration, airflow was calculated using either the wind speed and cross-sectional area of the treated volume or the air exchange rate and the treated volume. These equations may be found in Appendix D.

A summary of the residential inhalation post-application exposure and risk estimates for transfluthrin is presented in Table 6.2.1

[5] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Table 6.2.1. Residential Inhalation Post-application Non-cancer Exposure and Risk Estimates for Transfluthrin.

Lifestage	Post-application Exposure Scenario[2]		Emission rate[3] (mg ai/hr)	Air Exchange[4] ACH (exchanges /hr)	Airflow[4] Q (m^3/hr)	Vap. Efficiency[5] (%)	Exposure Time (hrs/day)	Volume of Treated space (m^3)	Concentration[6] (mg/m^3)	MOEs[7]
	Use Site	Route of Exposure								
Adult (LOC = 30)	Outdoor	Inhalation	2.98	97.3	3,211	100	2.3	33	9.23E-04	150,000
	Garages/Barns		2.98	4	132	100	4	33	2.11E-02	6,600
	Tents		2.98	4	28	100	8	7	1.03E-01	730
	RV/Camper		2.98	0.45	14.85	100	16	33	1.73E-01	220
Children (LOC = 100; 3 to <6 years old)[1]	Garages/Barns		2.98	4	132	100	2	33	2.11E-02	7,100
Children (LOC = 100; 1 to <2 years old)[4]	Outdoor		2.98	97.3	3,211	100	2.3	33	9.23E-04	150,000
	Tents		2.98	4	28	100	13	7	1.04E-01	440
	RV/Camper		2.98	0.45	14.85	100	18	33	1.76E-01	190

1 While exposure may occur for children 1 to <2 years of age in barns/garages, children 3 to <6 years old are considered the index lifestage for this exposure scenario, according to the 2012 Residential SOPs (Outdoor Fogging/Misting Systems).

2 Based on proposed label (EPA File Symbol No. 91879-R).

3 The emission rate (mg ai/hr) = Amount ai in product (1500 mg ai/product) * Number of products (1 product) / Useful life (504 hrs). The useful life is based on label information (21 days = 504 hours).

4 Air Flow, Q (m3/hr) = Air Exchange (# of exchanges/hr) * Room Volume (m3), or Air Flow, Q (m3/hr) = minimum air velocity (0.1 m/s) * cross sectional area (8.9 m2) * conversion factor (3600 s/hr).

5 The vaporization efficiency is a standard assumption from the Residential 2012 SOPs (CCTM).

6 The exposure concentration (mg/m^3) algorithm models the potential concentration over an individual's exposure time (i.e., time-weighted average concentration). It is derived from equation D.7 provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).

7 MOE = HEC (mg/m^3) ÷ TWA Air Concentration (mg/m^3).

6.3 Combined Residential Risk Estimates (Multiple Exposure Scenarios)

Since only inhalation exposure is expected based on the proposed use pattern, there are no other applicable exposure routes to combine.

7.0 Aggregate Exposure/Risk Characterization

At this time, the only expected exposures to transfluthrin are from residential sources. Therefore, aggregate exposure and risk estimates are equal to the residential estimates in Section 6.

8.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Per the Residential SOPs, a quantitative residential post-application inhalation exposure assessment was performed, and is considered protective for bystander post-application inhalation exposure.

9.0 Non-Occupational Spray Drift Exposure and Risk Estimates

The proposed use of transfluthrin is not expected to result in spray drift and, therefore, does not need to be assessed.

10.0 Cumulative Exposure/Risk Characterization

The agency is required to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The agency has determined that the pyrethroids and pyrethrins share a common mechanism of toxicity (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). As explained in that document, the members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. In 2011, after establishing a common mechanism grouping for the pyrethroids and pyrethrins, the agency conducted a cumulative risk assessment (CRA) which is available at http://www.regulations.gov; EPA-HQ-OPP-2011-0746. In that document, the agency concluded that cumulative exposures to pyrethroids (based on pesticidal uses registered at the time the assessment was conducted) did not present risks of concern. For information regarding EPA's efforts to evaluate the risk of exposure to this class of chemicals, refer to https://www.epa.gov/ingredients-used-pesticide-products/pyrethrins-and-pyrethroids.

Since the 2011 CRA, for each new pyrethroid and pyrethrin use, the agency has conducted a screen to evaluate any potential impacts on the CRA prior to registration of that use. For the proposed new transfluthrin residential uses, the agency has conducted an additional screen, taking into account all previously approved uses and these proposed new uses. The agency considers both the exposure to and the toxicology of the chemical in assessing risk. The agency concludes that transfluthrin will not significantly impact the findings of the 2011 CRA since all pyrethroid residential uses that do not fall under the four main pyrethroid residential use scenarios – turf, pets, gardens, and indoors (i.e., broadcast, fogger, and crack and crevice

applications) are considered minor contributors to the pyrethroid CRA based on amount of use and exposure potential and are not included in the pyrethroid CRA; as the proposed use is a personal insect repellent system it would be considered a minor contributor to the pyrethroid CRA and does not need to be included in the screening-level assessment. Therefore, the agency concludes that current cumulative risk estimates will not change with the registration of the transfluthrin personal insect repellent.

11.0 Occupational Exposure/Risk Characterization

While it is possible for both occupational handlers and post-application workers to use the proposed end-use product, as for residential product use, dermal exposure is expected to be negligible. The proposed label specifies that the product is to be placed and removed without touching the treated surface of the product, and the product will include a string allowing for it to be hung/placed. Additionally, no dermal hazard was identified in the toxicity studies, and therefore a dermal assessment is not needed. Furthermore, inhalation exposure is also expected to be minimal for occupational handlers, as the device slowly diffuses transfluthrin into the air over the course of the label-specified useful life of 21 days, and occupational handlers are not expected to remain in the premises following placement of the product. Thus, the residential post-application inhalation assessment (Section 6.2), which showed no risks of concern for adults, is considered protective for occupational inhalation exposures.

12.0 References

Anand, S. S., J. V. Bruckner, W. T. Haines, S. Muralidhara, J. W. Fisher and S. Padilla (2006). "Characterization of deltamethrin metabolism by rat plasma and liver microsomes." Toxicol Appl Pharmacol 212(2): 156-166.

Cao, Z., T. J. Shafer, K. M. Crofton, C. Gennings and T. F. Murray (2011a). "Additivity of Pyrethroid actions on sodium influx in cerebrocortical neurons in primary culture." Environ Health Perspect. 119(9): 1239-1246.

Cao, Z., T. J. Shafer and T. F. Murry (2011b). "Mechanisms of pyrethroid insecticide-induced stimulation of calcium influx in neocortical neurons." J Pharmacol Exper Ther 336(1): 197-205.

Choi, J. S. and D. M. Soderlund (2006). "Structure-activity relationships for the action of 11 pyrethroid insecticides on rat Nav1.8 sodium channels expressed in Xenopus oocytes." Toxicology and Applied Pharmacology 211(3): 233-244.

Godin, S. J., M. J. DeVito, M. F. Hughes, D. G. Ross, E. J. Scollon, J. M. Starr, R. W. Setzer, R. B. Conolly and R. Tornero-Velez (2010). "Physiologically based pharmacokinetic modeling of deltamethrin: Development of a rat and human diffusion-limited model." Toxicol Sci 115(2): 330-343.

Goldin, A. L., R. L. Barchi, J. H. Caldwell, F. Hofmann, J. R. Howe, J. C. Hunter, R. G. Kallen, G. Mandel, M. H. Meisler, Y. B. Netter, M. Noda, M. M. Tamkun, S. G. Waxman, J. N. Wood and W. A. Catterall (2000). "Nomenclature of voltage-gated sodium channels." Neuron 28(2): 365-368.

Goldin, A. L. (2002). "Evolution of voltage-gated Na+ channels." J Exp Biol 205(5): 575-584.

Hines, R. N., P. M. Simpson and D.G. McCarver. (2016). “Age-dependent human hepatic carboxylesterase 1 (CES1) and carboxylesterase 2 (CES2) postnatal ontogeny.” Drug Metabl Dispos 44(7): 959-966.

Koukouritaki, S. B., J. R. Manro, S. A. Marsh, J. C. Stevens, A. E. Rettie, D. G. McCarver and R. N. Hines (2004). "Developmental expression of human hepatic CYP2C9 and CYP2C19." J Pharmacol Exp Ther 308(3): 965-974.

Lawrence, L. and J. Casida (1982). "Pyrethroid toxicology: Mouse intracerebral sturcture-toxicity relationships." Pestic Biochem Physiol 18: 9-14.

Lund, A. and T. Narahashi (1982). "Dose-dependent interaction of the pyrethroid isomers with sodium channels of squid axon membranes." Neurotoxicology 3(1): 11-24.

NRC (National Research Council). 2011. Review of the Environmental Protection Agency's draft IRIS assessment of formaldehyde. National Academies Press, Washington, DC. http://www.nap.edu/catalog/13142.html

NRC (National Research Council). 2014. Review of EPA's Integrated Risk Information System (IRIS) process. The National Academies Press, Washington, DC. http://www.nap.edu/catalog.php?record_id=18764

Meacham, C. A., P. D. Brodfuehrer, J. A. Watkins and T. J. Shafer (2008). "Developmentally-regulated sodium channel subunits are differentially sensitive to [alpha]-cyano containing pyrethroids." Toxicology and Applied Pharmacology 231: 273-81.

Mirfazaelian, A., K. B. Kim, S. S. Anand, H. J. Kim, R. Tornero-Velez, J. V. Bruckner and J. W. Fisher (2006). "Development of a physiologically based pharmacokinetic model for deltamethrin in the adult male Sprague-Dawley rat." Toxicol Sci 93(2): 432-442.

Salgado, V., M. Herman and T. Narahashi (1989). "Interactions of the pyrethroid fenvalerate with nerve membrane sodium channels: Temperature dependence and mechanism of depolarization." Neurotoxicology 10(1): 1-14.

Scollon, E. J., J. M. Starr, K. M. Crofton, M. J. Wolansky, M. J. DeVito and M. F. Hughes (2011). "Correlation of tissue concentrations of the pyrethroid bifenthrin with neurotoxicity in the rat." Toxicology 290: 1-6.

Shafer, T. J., D. Meyer and K. M. Crofton (2005). "Developmental neurotoxicity of pyrethroid insecticides: critical review and future needs." Environ Health Persp 113(2): 123-136.

Sheets, L. P., J. D. Doherty, M. W. Law, L. W. Reiter and K. M. Crofton (1994). "Age-dependent differences in the susceptibility of rats to deltamethrin." Toxicol Appl Pharmacol 126(1): 186-190.

Soderlund, D., J. Clark, L. Sheets, L. Mullin, V. Piccirillo, D. Sargent, J. Stevens and M. Weiner (2002). "Mechanisms of pyrethroid neurotoxicity: implications for cumulative risk assessment." Toxicology 171(1): 3-59.

Song, J. H. and T. Narahashi (1996). "Modulation of sodium channels of rat cerebellar purkinje neurons by the pyrethroid tetramethrin." Journal of Pharmacology and Experimental Therapeutics 277: 445-453.

Song, G., X. Sun, R. Hines, D. McCarver, B. Lake, T. Osimitz, M. Creek, H. Clewell, and M. Yoon (2015). "Age-Dependent Changes in Human Hepatic CYP2C8 and 1A2 Expression" Presented at the Society of Toxicology Annual Meeting, San Diega, CA, March 22-26, 2015.

Stevens, J. C., R. N. Hines, C. Gu, S. B. Koukouritaki, J. R. Manro, P. J. Tandler, and M. J. Zaya (2003). "Developmental Expression of the Major Human Hepatic CYP3A Enzymes" J Pharmacol Exp Ther 307(2): 573-582.

Tabarean, I. V. and T. Narahashi (1998). "Potent modulation of tetrodotoxin-sensitive and tetrodotoxin-resistant sodium channels by the Type II pyrethroid deltamethrin." J Pharmacol Exp Ther 284(3): 958-965.

Tan, J. and D. M. Soderlund (2009). "Human and rat Nav1.3 voltage-gated sodium channels differ in inactivation properties and sensitivity to the pyrethroid insecticide tefluthrin." Neurotoxicology 30(1): 81-89.

Tornero-Velez, R., A. Mirfazaelian, K.-B. Kim, S. S. Anand, H. J. Kim, W. T. Haines, B. James V and J. W. Fisher (2010). "Evaluation of deltamethrin kinetics and dosimetry in the maturing rat using a PBPK model." Toxicol Appl Pharmacol 244: 208-217.

TXR# 0056830, Synthetic Pyrethroids: Update to the August 12, 2013 Hazard and Science Policy Council (HASPOC) Memo: Recommendations on Data Requirement for Immunotoxicity Studies for Synthetic Pyrethroid Pesticides. U. Habiba, 11/13/2013.

TXR# 0057710, Transfluthrin: Summary of Hazard and Science Policy Council (HASPOC) Meeting on January 25, 2018: Recommendations on the Need for a Subchronic Neurotoxicity Study (SCN) and Immunotoxicity Study Waiver Requests. M. Wilson, 04/05/20018.

USEPA (2007). “Meeting Minutes: FIFRA SAP Meeting on assessing approaches for the development of PBPK models of pyrethroid pesticides.” Document ID: EPA-HQ-OPP-2007-0388-0049.

USEPA (2011). "Pyrethroid Cumulative Risk Assessment, D394567, 10/04/11."

USPEA (2010). “Meeting Minutes: FIFRA SAP Meeting on Scientific Issues Associated with the Comparative Adult and Juvenile Sensitivity Toxicity Protocols for Pyrethroids.” Docket No. EPA-HQ-OPP-2010-0378.

USEPA (2015). “Meeting Minutes: FIFRA SAP Meeting on Scientific Uncertainties Associated with Research to Evaluate the Potential for Juvenile Sensitivity to Pyrethroids.” Document ID: EPA-HQ-OPP-2015-0130-0019.

Verschoyle, R. D. and W. N. Aldridge (1980). "Structure-activity relationships of some pyrethroids in rats." Arch Toxicol 45(4): 325-329.

Weiner, M. L., M. Nemec, L. Sheets, D. Sargent and C. Breckenridge (2009). "Comparative functional observational battery study of twelve commercial pyrethroid insecticides in male rats following acute oral exposure." Neurotoxicology 30 Suppl 1: S1-16.

Wolansky, M., C. Gennings and K. Crofton (2006). "Relative potencies for acute effects of pyrethroids on motor function in rats." Toxicol Sci 89(1): 271-277.

Wolansky, M. J. and J. A. Harrill (2008). "Neurobehavioral toxicology of pyrethroid insecticides in adult animals: A critical review." Neurotoxicol Teratol 30(2): 55-78.

Yang, D., R. E. Pearce, X. Wang, R. Gaedigk, Y. J. Wan and B. Yan (2009). "Human carboxylesterases HCE1 and HCE2: Ontogenic expression, inter-individual variability and differential hydrolysis of oseltamivir, aspirin, deltamethrin and permethrin." Biochem Pharmacol **77** (2): 238-247.

Zhang, L., Y. Yu, L. Xu, W. Zhang, Q. Shen (2017). "Experimental study on indoor air thermal equilibrium model of the tent." International Journal of Low-Carbon Technologies 12(1): 36–42, https://doi.org/10.1093/ijlct/ctw005.

de Zwart, L., M. Scholten, J. G. Monbaliu, P. P. Annaert, J. M. Van Houdt, I. Van den Wyngaert, L. M. De Schaepdrijver, G. P. Bailey, T. P. Coogan, W. C. Coussement, and G. S. Mannens (2008). "The ontogeny of drug metabolizing enzymes and transporters in the rat." Reprod Toxicol 26(3-4): 220-230.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for non-food for transfluthrin are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1. Toxicology Data Requirements for Conventional Pesticides (Non-Food Use): Transfluthrin

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	---	---
870.3150	Oral Subchronic (nonrodent)	---	---
870.3200	21/28-Day Dermal	no	yes
870.3250	90-Day Dermal	---	---
870.3465	90-Day Inhalation	yes	yes[1]
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	---	---
870.4100b	Chronic Toxicity (nonrodent)	---	---
870.4200a	Oncogenicity (rat)	---	---
870.4200b	Oncogenicity (mouse)	---	---
870.4300	Chronic/Oncogenicity	---	---
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Mammalian Erythrocyte Micronucleus	no	yes
870.5550	Mutagenicity—Unscheduled DNA Synthesis	no	yes
870.5915	Mutagenicity—*In Vivo* Sister Chromatid Exchange	no	---
870.6100a	Acute Delayed Neurotox. (hen)	no	---
870.6100b	90-Day Neurotoxicity (hen)	no	---
870.6200a	Acute Neurotox. Screening Battery (rat)	yes	---[2]
870.6200b	90 Day Neurotox. Screening Battery (rat)	yes	no[3]
870.6300	Develop. Neuro	yes	yes
870.7485	General Metabolism	---	---
870.7600	Dermal Penetration	---	---
870.7800	Immunotoxicity	yes	no[4]

[1] – conducted a 4-week and 13-week study in place of the 90-day study

[2] – conducted a non-guideline ACN

[3] – A subchronic neurotoxicity study is not required for the currently registered use patterns. See HASPOC memo (TXR# 0057710, M. Wilson, 04/05/2018) for details.

[4] – An immunotoxicity study is not required for the pyrethroid chemical class. See HASPOC memo (TXR# 0056830, U. Habiba, 11/13/2013) for details.

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile - Transfluthrin technical				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral - rat	49617850	LD_{50} > 5000 mg/kg	IV
870.1200	Acute dermal - rat	49617851	LD_{50} > 5000 mg/kg	IV
870.1300	Acute inhalation - rat	49617852	LC_{50} > 0.5126 mg/L	III
870.2400	Acute eye irritation - rabbit	49617853	Non-irritant	III[1]
870.2500	Acute dermal irritation - rabbit	49617853	Non-irritant	IV
870.2600	Skin sensitization - guinea pig	49617854	Non-Sensitizer	N/A

[1] Normally assignment would be to toxicity category IV. Since the test material can be in the form of needles (with possibility of mechanical irritation) at room temperature, technical transfluthrin is assigned to toxicity category III for eye irritation.

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Transfluthrin		
Study Type	**MRID No.**	**Results**
870.3200 28-Day Dermal (Rabbit)	49617855 (1990) Acceptable/Guideline 0, 20, 200, 1000 mg/kg bw/day (nominal concentrations – analytical chemistry was not conducted)	Systemic LOAEL = cannot be established. NOAEL = 1000 mg/kg bw/day. Dermal LOAEL = 200 mg/kg bw/day based on skin redness; scaling, encrustation, swelling, and red patches; and increased skin fold thickness in males and females. NOAEL = 20 mg/kg bw/day.
870.3465 28-day Inhalation	49617849 (1989) Acceptable/Non-guideline 0, 0.0015, 0.0066, 0.037, and 0.168 mg/L (Nominal concentration = 0, 0.015, 0.060, 0.250, or 1.000 mg/L [equivalent to 0, 15, 60, 250, and 1000 mg/m^3])	LOAEC = 0.168 mg/L based on clinical signs (ungroomed and bristling coat with slightly reduced motility). NOAEC = 0.037 mg/L.
870.3465 90-Day Inhalation (Wistar rat)	49617856 (1989) Acceptable/Guideline 0, 0.0049, 0.0467, or 0.2202 mg/L (Nominal concentrations = 0, 0.040, 0.250, 1.000 mg/L; 0, 40, 250, 1000 mg/m^3)	LOAEC = 0.2202 mg/L based on clinical signs of toxicity (ungroomed and bristling coat, tremors, and hyperactivity) in both sexes. NOAEC = 0.0467 mg/L.
870.3700a Prenatal Developmental Toxicity (Sprague Dawley)	49617858 (1988) Acceptable/Guideline 0, 25, 55, or 125 mg/kg bw/day (dose volume 10 mL/kg)	Maternal LOAEL = 55 mg/kg bw/day based on tremors that occurred within 1-h post-dose. NOAEL = 25 mg/kg bw/day. Developmental LOAEL = cannot be established. NOAEL = 125 mg/kg bw/day.
870.3700b Prenatal Developmental Toxicity (Himalayan rabbit)	49617859 (1989) Acceptable/Guideline	Maternal LOAEL = 50 mg/kg bw/day based on mortality. NOAEL = 15 mg/kg bw/day.

	0, 15, 50, 150 mg/kg bw/day (nominal concentration; dose volume 5 ml/kg bw)	Developmental LOAEL = cannot be established. NOAEL = 150 mg/kg bw/day.
870.3800 Two-Generation Reproduction Toxicity (Han Wistar)	49617860 (1988) Acceptable/Guideline 0, 20, 200, 1000 ppm (0/0, 1.4/1.7, 15.5/17, 79.1/87.8 mg/kg bw/day [M/F])	Parental LOAEL = 79.1/87.8 mg/kg bw/day (M/F) based on decreased hepatic triglyceride concentration in F1 females, increased liver and/or kidney weights in P males and females, and microscopic renal findings in the P and F1 animals. NOAEL = 15.5/17 mg/kg bw/day (M/F). Offspring LOAEL = cannot be established. NOAEL = 79.1/87.8 mg/kg bw/day (M/F). Reproductive LOAEL = cannot be established. NOAEL = 79.1/87.8 mg/kg bw/day (M/F).
870.5100 Gene Mutation – *Salmonella*/microsome	49617861 (1987) Acceptable/Guideline Trial 1: 0, 20, 100, 500, 2500, and 12,500 µg/plate (±S9) Trial 2: 0, 775, 1550, 3100, 6200, and 12,400 µg/plate (±S9) Trial 3:0, 775, 1550, 3100, 6200, and 12,400 µg/plate (+S9)	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay.
870.5300 Gene Mutation – HGPRT with CHO cells	49617863 (1989) Acceptable/Guideline Preliminary cytotoxicity Non-activated conditions: 0, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, and 100 µg/mL Activated conditions: 0, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, and 100 µg/mL Mutagenicity assay Non-activated conditions: 0, 25, 50, 75, 90, and 100 µg/mL Activated conditions: 0, 25, 50, 75, 90, and 100 µg/mL	No increase in mutant frequency under the conditions of the study. Cytotoxicity was observed at 100 µg/mL (-S9) and ≥50 µg/mL (+S9).
870.5375 *In Vitro* Chromosomal Aberration Assay in Human Peripheral Blood Lymphocytes	49617864 (1990) Acceptable/Guideline Trial 1: 0, 50, 100, and 200 µg/mL (±S9) Trial 2: 0, 120, 160, and 200 µg/mL (−S9) 21 h exposure with no recovery period	There was no evidence of chromosome aberrations induced over background in the presence or absence of S9 activation. Cytotoxicity was observed at >500 µg/mL (±S9).
870.5395	49617865 (1988) Acceptable/Guideline	There was no significant increase in the frequency of micronucleated polychromatic

In Vivo Mammalian Cytogenetics (Mice)	Pilot studies: 250, 375, 500, 750, 1000, and 2500 mg/kg Main study: 375 mg/kg	erythrocytes in bone marrow after any treatment time. Mortality was observed in 7/40 mice at 375 mg/kg. Clinical signs were observed at ≥375 mg/kg (roughened fur, lateral position, twitching, spasms, leaping spasms, dribbling, and shivering).
870.5395 Micronucleus Assay in Mice	49617866 (2012) Acceptable/Guideline 0/0,62.5/109.38, 125/218.75, and 250/437.5 mg/kg (M/F)	There was no significant increase in the frequency of MPCEs in bone marrow after any treatment time. 1 female at 437.5 mg/kg died. No clinical signs were observed.
870.5550 UDS in Mammalian Cells	49617862 (1992) Acceptable/Guideline Range-Finding Study: 0, 7.8, 15.6, 31.25, 62.5, 125, 250, 500, 1000, and 2000 µg/mL UDS Assay: 0, 1, 5, 25, 50, 100, 250, and 500 µg/mL	There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts], was induced.
870.6200 Acute neurotoxicity (ACN) (Sprague Dawley)	49617870 (2015) Acceptable/Non-guideline 0, 25.7, 52.2, 78.6, 100, and 127 mg/kg bw	LOAEL = 100 mg/kg bw based on clonic convulsions and tremors (males). NOAEL = 78.6 mg/kg bw.
870.6300 Developmental neurotoxicity (DNT) (Wistar)	50130601 (2007) Acceptable/Guideline 0, 42.1, 161, or 534 mg/kg/day	<u>Maternal</u> LOAEL = cannot be established. NOAEL = 534 mg/kg/day. <u>Developmental</u> LOAEL = 534 mg/kg/day based on decreased pup body weight in males and females (>5%) NOAEL = 161 mg/kg/day.

A.3 Hazard Identification and Endpoint Selection

A.3.1 Acute Reference Dose (aRfD) - Females age 13-49

Non-food use. Exposure from food is not expected.

A.3.2 Acute Reference Dose (aRfD) - General Population

Non-food use. Exposure from food is not expected.

A.3.3 Chronic Reference Dose (cRfD)

Non-food use. Exposure from food is not expected.

A.3.4 Incidental Oral Exposure (Short-Term)

Based on the proposed use pattern, an incidental oral endpoint has not been selected.

A.3.5 Dermal Exposure (Short-Term)

Based on the proposed use pattern with negligible dermal exposure expected, a dermal endpoint has not been selected. Furthermore, even though there was quantitative susceptibility in the DNT and the dermal toxicity study does not assess developmental effects, no dermal hazard is expected because 1) no systemic toxicity, including neurotoxicity, was observed up to the highest dose tested in the dermal toxicity test (1000 mg/kg/day), and 2) the use of an estimated 5% DAF based on other pyrethroids to convert an oral LOAEL of 55 mg/kg/day from the rat DNT results in a dermal equivalent dose above the limit dose of 1000 mg/kg/day (55/0.05 = 1100 mg/kg/day); therefore, a dermal endpoint would not be needed even if higher dermal exposures were expected.

A.3.6 Inhalation Exposure (Short-Term)

Study Selected: 90-day Inhalation study (rat)
MRID No.: 49617856
Executive Summary: See Appendix A, Guideline § 870.3465
Dose and Endpoint for Risk Assessment: NOAEC = 0.0467 mg/L; LOAEC = 0.2202 mg/L based on clinical signs in both sexes
Comments about Study/Endpoint/Uncertainty Factors: This study is appropriate for the route (oral) and duration of exposure and is protective of all offspring effects in the reproduction and developmental studies. The intraspecies uncertainty factor remains at 10X. The sensitivity among children <6 years old factor (UF_s) can be reduced to 3X. Therefore, the LOC is 100 for children <6 years old and 30 for children ≥6 years old and adults.

A.4 Executive Summaries

A.4.1 Subchronic Toxicity

870.3200 21/28-Day Dermal Toxicity – Rabbit

In a subchronic dermal toxicity study (MRID 49617855), transfluthrin (95.0% a.i., Lot # 250987) was applied to the shaved skin of five or ten New Zealand rabbits/sex/dose at dose levels of nominal concentrations 0, 20, 200, or 1000 mg/kg bw (vehicle control, 1%, 10%, and 50% formulation, respectively) 6 h/day, 5 days/week for three weeks. The test compound was formulated before each treatment with Cremophor EL (2% v.v) in a sterile physiological saline solution. No analytical chemistry was conducted. Five rabbits/sex/dose from the control and 1000 mg/kg bw groups were observed during a recovery period of two weeks following the end of treatment.

There were no adverse, treatment-related effects on mortality, clinical signs, body weights or body weight changes, food consumption, hematology, clinical chemistry, organ weights, or gross and microscopic pathology.

In the 200 mg/kg bw animals, slight skin redness (Grade 1) occurred in females on Day 4, with further scaling observed at Days 7-8, and red or swollen patches occurring during the periods of Days 13-19 or Days 20-22. Increased skin fold thickness was observed in the males, with

increases to 4.1-4.2 mm from Day 3 to Day 21, and in the females, with increases to 3.4-3.5 mm on Days 3 and 8, with a subsequent decreasing trend back to 3.2 mm by Days 14-21.

In the 1000 mg/kg bw animals, skin redness (Grade 1) was observed for males on Days 2-5, with no further findings through Day 23. In females, skin redness (Grade 1) was observed on Day 3, with no further findings through Day 23. Skin findings such as scaling, encrustation, swelling, and red patches were observed in 8/10 males and 9/10 females between Days 3 and 23/24. Skin fold thickness was increased in the males up to 3.6-3.8 mm from Day 3 to Day 16, with a final increase to 4.0 mm on Day 21. The females also had an increased skin fold thickness of 3.4 mm on Day 3, and a subsequent decreasing trend back to 3.1 mm by Day 21 similar to control. Lastly, necrosis was observed in 1 male and 6 females.

No treatment-related changes in skin redness or skin fold thickness were observed in the 20 mg/kg bw animals.

The LOAEL for systemic toxicity was not determined. The NOAEL for systemic toxicity was 1000 mg/kg bw (the limit dose). The LOAEL for dermal toxicity was 200 mg/kg bw based on skin redness; scaling, encrustation, swelling, and red patches; and increased skin fold thickness in males and females. The NOAEL for dermal toxicity was 20 mg/kg bw.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements for a 21/28-day dermal toxicity study according to OECD 410. The study was conducted in 1988, prior to implementation of the current harmonized OCSPP 870.3200 guidelines.

870.3465 90-Day Inhalation – Rat

In a subchronic inhalation toxicity study (MRID 49617856), groups of ten Wistar [Bor:WISW (SPF-Cpb)] rats/sex/concentration were exposed to transfluthrin (NAK 4455; 95% a.i.; batch # 250 987) by nose-only inhalation at nominal concentrations of 0, 0.040, 0.250, or 1.000 mg/L (equivalent to 0, 40, 250, and 1000 mg/m^3) for 6 h/day, 5 days/week for at least 13 weeks. An additional ten rats/sex/concentration were exposed to transfluthrin at 0 or 1.000 mg/L for 13 weeks, and then allowed to recover unexposed for four weeks. The rats were exposed for a total of 64-67 days. Measured concentrations averaged 0.0049, 0.0467, or 0.2202 mg/L (equivalent to 4.9, 46.7, or 220.2 mg/m^3). The mass median aerodynamic diameter (MMAD) (low to high dose, respectively) was 1.09, 1.13, 1.23, and 1.13 µm, and the geometric standard deviation (GSD) was 1.35, 1.36, 1.39, and 1.35. All surviving animals were euthanized at the end of exposure.

There were no effects of treatment observed on mortality, body weights or body weight gains, food consumption, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, pulmonary function tests, organ weights, or gross or microscopic examinations.

On Day 1, four females (#127, #130, #133, and #138) died during exposure to a nominal concentration of 1.500 mg/L (measured concentration 0.3389 mg/L). These rats were replaced and were not discussed further. On Day 2, the nominal concentration was reduced to 1.000 mg/L for the duration of the study. During Week 12, a 1.000 mg/L female (#127) died during

exposure. The cause of death was considered to be suffocation, and not treatment-related. All other animals survived to scheduled euthanasia.

Beginning during the first week of exposure, all 1.000 mg/L (measured concentration 0.2202 mg/L) rats were observed with bristling and ungroomed (soiled) coats, tremors, and increased activity, continuing to the last day of exposure. These clinical signs were not present prior to exposure on the following day. A gradual decline in severity was noted beginning on Week 2 and continuing through the exposure period, with slight to moderate hyperactivity considered to be the primary clinical sign.

Gross pathological and histopathological examination of the respiratory tract did not identify evidence of portal of entry toxicity, consistent with the lack of observed clinical signs or mortality. There were also no effects to body weight, food consumption, urinalyses, clinical chemistry, or haematological parameters, and no observed organ damage.

The LOAEC is 1.000 mg/L (equivalent to 1000 mg/m^3; measured concentration 0.2202 mg/L), based on clinical signs of toxicity (ungroomed and bristling coat, tremors, and hyperactivity) in both sexes. The NOAEC is 0.250 mg/L (equivalent to 250 mg/m^3; measured concentration 0.0467 mg/L).

This subchronic inhalation toxicity study is classified **acceptable / guideline** and satisfies the guideline requirements (OCSPP 870.3465; OECD 413) for a subchronic inhalation toxicity study in the rat.

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 49617858), transfluthrin (94.5% a.i.; Batch # 130187) in 5% (v/v) aqueous Emulphor EL-719 was administered daily by oral gavage to 28 presumed pregnant Sprague Dawley [Crl:(CD) BR] rats/dose group at dose levels of 0, 25, 55, or 125 mg/kg bw/day (dose volume 10 mL/kg; 5% aqueous Emulphor vehicle) during gestation days (GD) 6-15. On GD 20, all maternal rats were euthanized; each dam's uterus and ovaries were removed via cesarean section, and the contents examined. The fetuses were examined for external, visceral, and skeletal malformations and variations.

There were no treatment-related effects on maternal body weight or body weight gain, food consumption, gross pathology, liver weights or liver to body weight ratios, or any cesarean section parameters.

At 55 mg/kg bw/day, tremors occurred post-dosing in three of 28 dams (11%). The tremors generally occurred within 1-h post-dosing, were transient, and had ceased prior to the afternoon observations. No mortality was observed.

At 125 mg/kg bw/day, all dams survived to scheduled termination, except for a single animal that was found dead on Day 8. Tremors occurred post-dosing, as described for the 55 mg/kg

bw/day animals, in the majority of the dams (23/28; 82%). The single dam that died had tremors on Days 6 and 7.

The maternal LOAEL was 55 mg/kg bw/day based on tremors that occurred within 1-h post-dose. The maternal NOAEL was 25 mg/kg bw/day.

There were no abortions, premature deliveries, complete litter resorptions, or dead fetuses. Furthermore, there were no treatment-related effects on the numbers of corpora lutea, implantations, litters, live fetuses, resorptions, sex ratio, or post-implantation loss. There were no treatment-related effects on fetal weights, and no treatment-related external, visceral, or skeletal malformations or variations.

The developmental LOAEL was not observed. The developmental NOAEL was 125 mg/kg bw/day.

This study is classified **acceptable/guideline** and satisfies the guideline requirements (OCSPP 870.3700a; OECD 414) for a developmental toxicity study in rats.

870.3700b Prenatal Developmental Toxicity Study – Rabbit

In a developmental toxicity study (MRID 49617859), transfluthrin (94.5% a.i.; Lot # 250987) in 0.5% aqueous Cremophor EL was administered daily by oral gavage in a dose volume of 5 mL/kg to 15 inseminated Himalayan rabbits/dose group at dose levels of 0, 15, 50, or 150 mg/kg bw/day during gestation days (GD) 6-18. Appearance and behavior were observed at least once daily from GD 0-29. On GD 29, all maternal rabbits were euthanized; each doe's uterus and ovaries were removed by cesarean section and the contents examined. The fetuses were examined for external, visceral, and skeletal malformations and variations.

No treatment-related effects on body weights and body weight gains (unadjusted or adjusted for gravid uterine weights), or pregnancy rate, were observed. Food consumption was not determined.

At 50 mg/kg bw/day, one doe was found dead on GD 18. This female exhibited tremors and prostration on Day 18 prior to death. Autopsy findings included swollen liver with lobulation and pale-colored lungs with patchy lobulation.

At 150 mg/kg bw/day, one doe was found dead on GD 19. This female exhibited severe spasms and prostration on Day 18, followed by death on Day 19. There were no abnormal organ findings for the 150 mg/kg bw/day doe.

The maternal LOAEL was 50 mg/kg bw/day based on mortality. The maternal NOAEL was 15 mg/kg bw/day.

There was only a single, complete litter resorption in the 50 mg/kg bw/day group, and the incidence of fetal deaths was unaffected by treatment. There were no treatment-related differences in intrauterine survival (including post-implantation loss, live litter size, and fetal sex

ratios); mean numbers of corpora lutea, implantation sites, and mean litter proportions of pre-implantation loss; numbers of litters, early resorptions, late resorptions, or live fetuses per doe; or sex ratio. Fetal body weights were not affected by treatment. Finally, there were no treatment-related external, visceral, or skeletal malformations or variations.

The developmental NOAEL was 150 mg/kg bw/day. The developmental LOAEL was not determined.

This study is classified **acceptable/guideline** and satisfies the guideline requirement (OCSPP 870.3700b; OECD 414) for a developmental toxicity study in rabbits. The study was conducted in 1988, prior to implementation of the current harmonized OCSPP 870.3700 guidelines.

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

In a two-generation reproduction toxicity study (MRID 49617860), transfluthrin (NAK 4455 technical; 94.5% a.i.; Batch # Mischpartie 250987) was administered to 30 (P generation) or 26 (F1 generation) Han Wistar (Kfm:WIST) rats/sex/dose group in the diet at concentrations of 0, 20, 200 or 1000 ppm (0/0, 1.4/1.7, 15.5/17, 79.1/87.8 mg/kg bw/day [M/F]) for two successive generations with two litters per generation. The P generation animals were fed the test diets for an 84-day period prior to mating to produce the F1a litters. After weaning of the F1a litters, the P generation animals were re-bred to produce the F1b litters. On post-natal day (PND) 21, 1 pup/sex/litter from the F1b litters was selected and fed the same test diet concentration as their dam. These F1 parents were fed the test diets for 105 days prior to mating to produce the F2a litters. After weaning of the F2a litters, the F1 generation animals were re-bred to produce the F2b litters.

There were no treatment-related effects on mortality or clinical signs; body weights or body weight gains in males (P and F1 generations) and females (P and F1 generations); food consumption; serum clinical chemistry evaluations; hepatic cytochrome P-450 content, or cholinesterase or *N*-demethylase activity; terminal body weights; organ weights of the P and F1 generation animals (except for liver and kidney weights in the P generation 1000 ppm males); macroscopic evaluations of all parental animals; or microscopic findings in 20 and 200 ppm animals.

In the 1000 ppm animals, decreases in mean body weights (↓5-6%) of the F1 females were noted between Days 29-43, and on Days 57, 64, 78, and 85 of the pre-mating period; however, this decrease was not considered toxicologically adverse because it is not greater than 10% and there was no effect on overall body weight gain (BWG). Liver triglyceride concentrations were decreased in the F1 generation females. Non-significant decreases in liver triglyceride concentrations also were noted in the P and F1 generation males, but no effect was observed in P generation females.

Mean absolute liver and relative (to body weight) liver weights were increased in the P males by 12% and 12%, respectively, and mean absolute kidney and relative kidney weights also were

increased in the P males by 10% and 9%, respectively. In addition, there was a slight increase (↑5%) in the mean relative (to body weight*)* kidney weight in the P females.

Treatment-related increases in incidence and severity (minimal or slight) of tubular pigment were observed in the P males (14/29 treated vs. 0/30 control) and females (23/30 treated vs. 2/29 control). The pigment was considered to be lipofuschin, but was not positively identified. Treatment-related increases in the incidence of basophilic tubules also were noted for the P males (13/29 treated vs. 4/30 control). Treatment-related increases in incidence and severity (minimal or slight) of tubular pigment also were observed in the F1 males (5/26 treated vs. 0/26 control) and females (20/26 treated vs. 8/26 control), as well as an increased incidence of basophilic tubules in the F1 males (19/26 treated vs. 13/26 control). Increased incidences of pelvic calcinosis in the F1 females (14/26 treated vs. 8/26 control) and tubular casts in males (21/26 treated vs. 14/26 control) also were observed. Increased incidences of tubular pigment, in addition to the other renal microscopic findings, may be indicative of an early stage of chronic progressive nephropathy, but a clear, dose-related effect was not supported at concentrations <1000 ppm.

The LOAEL for parental toxicity is 1000 ppm (79.1/87.8 mg/kg bw/day [M/F]) based on decreased hepatic triglyceride concentration in F1 females, increased liver and/or kidney weights in P males and females, and microscopic renal findings in the P and F1 animals. The NOAEL is 200 ppm (15.5/17 mg/kg bw/day [M/F]).

There were no treatment-related effects on the number of pups born alive or dead, litter size, pup survival, or pup sex ratio; body weights and body weight gains; pups; terminal body weights; organ weights; and macroscopic and microscopic findings of the F1 and F2 generation pups. Sexual maturation parameters (vaginal opening, preputial separation, and anogenital distance) were not assessed in the present study.

The NOAEL for offspring toxicity is 1000 ppm (79.1/87.8 mg/kg bw/day[M/F]). The LOAEL for offspring toxicity was not determined.

There were no effects of treatment at any dose level on reproduction parameters (e.g., fertility index, conception rate, gestation index, mean precoital time, duration of gestation, mean number of living and dead pups, postnatal loss, and breeding loss) in either generation. Mating was confirmed for all paired animals, but the conception index varied in a non-dose-related manner from 76.9% to 100%.

The NOAEL for reproductive toxicity is 1000 mg/kg (79.1/87.8 mg/kg bw/day [M/F]). The LOAEL for reproductive toxicity was not determined.

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OCSPP 870.3800; OECD 416) for a two-generation reproduction study in the rat. **Note:** when performed, the study conformed with US EPA Guideline: Reproductive and Fertility Effects, Subdivision F, Hazard Evaluation: Human and Domestic Animals, No. 83-4, November 1984; and OECD Guideline: Two-generation Reproduction Toxicity Study, Section 4, Health Effects, No. 416; May 1981.

A.4.4 Mutagenicity

Study	Results
870.5100, Bacterial Reverse Gene Mutation Assay MRID 49617861 Acceptable/Guideline	No mutagenic activity in bacteria (*Salmonella typhimurium*) under conditions of this assay. Trial 1: 0, 20, 100, 500, 2500, and 12,500 µg/plate (±S9). Trial 2: 0, 775, 1550, 3100, 6200, and 12,400 µg/plate (±S9). Trial 3: 0, 775, 1550, 3100, 6200, and 12,400 µg/plate (+S9).
870.5300 Gene Mutation – HGPRT with CHO cells MRID 49617863 Acceptable/Guideline	No increase in mutant frequency under the conditions of the study. Cytotoxicity was observed at 100 µg/mL (-S9) and ≥50 µg/mL (+S9). <u>Preliminary cytotoxicity</u> Non-activated conditions: 0, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, and 100 µg/mL. Activated conditions: 0, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, and 100 µg/mL. <u>Mutagenicity assay</u> Non-activated conditions: 0, 25, 50, 75, 90, and 100 µg/mL. Activated conditions: 0, 25, 50, 75, 90, and 100 µg/mL.
870.5375 *In Vitro* Chromosomal Aberration Assay in Human Peripheral Blood Lymphocytes MRID 49617864 Acceptable/Guideline	There was no evidence of chromosome aberrations induced over background in the presence or absence of S9 activation. Cytotoxicity was observed at >500 µg/mL (±S9). Trial 1: 0, 50, 100, and 200 µg/mL (±S9). Trial 2: 0, 120, 160, and 200 µg/mL (−S9). 21 h exposure with no recovery period
870.5395 *In Vivo* Mammalian Cytogenetics (Mice) MRID 49617865 Acceptable/Guideline	There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time. Mortality was observed in 7/40 mice at 375 mg/kg. Clinical signs were observed at ≥375 mg/kg (roughened fur, lateral position, twitching, spasms, leaping spasms, dribbling, and shivering).
870.5395 Micronucleus Assay (Mice) MRID 49617866 Acceptable/Guideline	There was no significant increase in the frequency of MPCEs in bone marrow after any treatment time. 1 female at 437.5 mg/kg died. No clinical signs were observed. <u>0/0, 62.5/109.38, 125/218.75, and 250/437.5 mg/kg (M/F).</u>
870.5550 UDS in Mammalian Cells MRID 49617862 Acceptable/Guideline	There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts], was induced. 0, 1, 5, 25, 50, 100, 250, and 500 µg/mL

A.4.5 Neurotoxicity

870.6300 Developmental Neurotoxicity Study

In a developmental neurotoxicity study (MRID 50130601), transfluthrin (99.1% a.i., EATFTJ005) was administered to 30 female Wistar rats/dose in diet at dose levels of 0, 500,

2000, and 7000 ppm (equivalent to 0, 42.1, 161, or 534 mg/kg/day) from gestation day (GD) 6 through lactation day (LD) 21 with adjustments during lactation to maintain a more consistent dosage throughout exposure. Diet was provided for *ad libitum* consumption throughout the study, except during the neurobehavioral testing. Litters were culled to yield as closely as possible with 4 males and 4 females on postnatal day (PND) 4. Subsets of offspring were subjected to evaluation of detailed clinical observations and a functional observational battery, ages for the onset of preputial separation or vaginal patency, body weight, motor activity, auditory startle habituation, learning and memory and an ophthalmic examination. Neuronal tissues were collected from 10/sex/dietary level on PND 21 (brain only) and at study termination (PND 75±5 days) for microscopic examination and morphometry.

Maternal toxicity: There were no treatment related effects on survival or clinical signs for females in the P-generation. There was a 10% decrease in body weight gain at 534 mg/kg/day during GD 0-20 but this was attributed to decreased food palatability. However, there was no treatment-related effects on absolute body weight. There was no effect on reproductive performance or fertility index.

The maternal LOAEL for transfluthrin was not established. The maternal NOAEL is 7000 ppm (equivalent to 534 mg/kg/day).

Offspring toxicity: There was no treatment-related effect on litter parameters, pup viability, or clinical observations. Offspring body weights were statistically decreased in the high-dose females and males (>5%) on PND 11, 17, and 21 for both sexes. There were no treatment-related effects on developmental landmarks for sexual maturation (e.g., the ages for onset of balanopreputial separation and vaginal patency) or developmental landmarks (onset for surface righting and pupil constriction).

There were no compound-related effects on the FOB or measures of motor or locomotor activity for either sex at any dietary level. Startle amplitude, latency, and habituation were not affected by treatment on any test occasion.

Absolute brain weight for non-perfused terminal males was not affected at any dietary level. There were no compound-related necropsy findings in animals that were either found dead or sacrificed on PND 21 or at study termination. For the micropathology brain measurements, the hippocampus thickness for the high-dose females (1.4 mm) was statistically decreased compared to the controls (8%) at PND 75 and was smaller than both the concurrent (1.56 mm) and historical (1.48-1.76 mm) controls; however, this decrease was not considered to be toxicologically relevant since there were no effects observed on learning and memory. There were no other effects of treatment on brain measurements.

The offspring LOAEL for transfluthrin is 7000 ppm (equivalent to 534 mg/kg/day) based on decreased pup body weight in males and females (>5%). The offspring NOAEL is 2000 ppm (equivalent to 161 mg/kg/day).

This study is classified acceptable and satisfies the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6); OECD 426 (draft). The study was

conducted with a few deviations to the guidelines outlined in the 1999 Data Call-In (DCI) Notice issued for several organophosphorus insecticides. The modifications include: (1) extend exposure to lactation / postnatal day 21 (rather than day 11) and (2) evaluate brains from 21-day-old (rather than 11-day-old) animals for morphometry and micropathology using (3) a sample size of 10 (rather than six) per sex per dietary level. These design elements are consistent with the draft OECD guideline for a Developmental Neurotoxicity Study (TG 426).

A.4.6 Special/Other Studies

Non-guideline 28-Day Inhalation – Rat

In a 28-day subchronic inhalation toxicity study (MRID 49617849), groups of ten Wistar [Bor:WISW (SPF-Cpb)] rats/sex/concentration were exposed to transfluthrin (NAK 4455; 94.5% a.i.; batch # 130187) by nose only inhalation at concentrations of 0, 0.015, 0.060, 0.250, or 1.000 mg/L (equivalent to 0, 15, 60, 250, and 1000 mg/m^3) for 6 h/day, 5 days/week for at least four weeks. The rats were exposed for a total of 21-23 days. Analytical concentrations averaged 0, 0.0015, 0.0066, 0.037, and 0.168 mg/L. The mass median aerodynamic diameter (MMAD) (low to high dose, respectively) was 1.57, 1.42, 1.37, 1.26, and 1.77 µm, and the geometric standard deviation (GSD) was 1.55, 1.50, 1.49, 1.45, and 1.59. All surviving animals were euthanized at the end of exposure. The test concentrations were selected based on the results of an acute (4 h) inhalation study and a range-finding subacute (5 days for 5 h/day) inhalation study that evaluated at concentrations up to 0.1479 mg/L.

No effects of treatment were observed on mortality, body weights, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, pulmonary function tests, organ weights, or gross or microscopic pathology.

All animals survived until scheduled euthanasia except one 1.000 mg/L (analytical concentration 0.168 mg/L) male that was euthanized moribund after it stopped breathing during the pulmonary function test. Slightly reduced motility during Weeks 1 and 2 and with ungroomed and bristling coat was noted for all males and females at 1.000 mg/L (analytical concentration 0.168 mg/L) throughout the exposure period.

The LOAEC is 1.000 mg/L (equivalent to 1000 mg/m^3; analytical concentration 0.168 mg/L), based on clinical signs of toxicity (ungroomed and bristling coat with slightly reduced motility) in both sexes. The NOAEC is 0.250 mg/L (equivalent to 250 mg/m^3; analytical concentration 0.037 mg/L).

This 28-day inhalation toxicity study in the rat is **acceptable / non-guideline** and satisfies the guideline requirement (OCSPP none; OECD 412) for a 28-day inhalation study in the rat.

Non-Guideline Analytical Method Validation and Stability Study

In a non-guideline, analytical method validation and stability study (MRID 49617869), an HPLC/UV method for the determination of transfluthrin (purity 97.7%, Lot # PLNS000112) concentrations in corn oil, including method specificity/selectivity, calibration reproducibility,

precision, accuracy, ruggedness, and transfluthrin stability/homogeneity in calibration standards and processed QC samples stored at room temperature was reported.

The selectivity/specificity of the method was confirmed in processed vehicle (corn oil) samples.

The RSD and RE values for each validation set of calibration standards met the acceptance criteria. The inter-session variability (RSD) of the back-calculated concentrations ranged from 1.1% to 3.9%. The inter-session mean concentrations had RE values that ranged from 2.3% to 0.91%. The RSD and RE values for each validation set of QC samples also met the acceptance criteria. The inter-session variability (RSD) of the calculated concentrations of each QC sample (precision) ranged from 1.8% to 4.3%. The inter-session mean concentrations of the QC samples had RE values (accuracy) that ranged from 0.035% to 5.6%. Based on the stated acceptance criteria, the reproducibility of the calibration data and the precision and accuracy of the transfluthrin assay were acceptable.

Assay ruggedness was successfully demonstrated for this method because a minimum of two of the thee validation sessions were conducted by different analysts, and all sessions met the required acceptance criteria.

Calibration standards prepared at 10.0 and 50.0 µg/mL were stored at room temperature for seven days prior to re-analysis to assess test substance stability. The mean post-storage concentrations ranged from 101% to 112% of the pre-storage values, which met the protocol-specified acceptance criteria for stability. Quality control samples prepared at nominal test substance concentrations of 1.00 and 200 mg/mL were also processed and analyzed. The processed samples were stored at room temperature for seven days prior to re-analysis to assess test substance stability. The mean post-storage concentrations ranged from 101% to 105% of the pre-storage values, which met the protocol-specified acceptance criteria for stability.

The homogeneity assessment of fresh formulations met the protocol-specified acceptance criteria for homogeneity, with RSD ranging from 0.90% to 1.2%, and the percentage of target concentrations ranging from 97.4-102%. The resuspension homogeneity assessments of the formulations after room temperature storage for 7 and 11 days also met the protocol-specified acceptance criteria for resuspension homogeneity. The RSD values ranged from 0.53% to 1.1% and the percentage of target concentrations ranged from 98.0% to 102% after seven days. The RSD values ranged from 1.1% to 1.5%, and the percentage of target concentrations ranged from 100% to 103% after eleven days. In addition, post-storage transfluthrin concentrations ranged from 101% to 103% of the pre-storage values, which met the previously stated protocol-specified acceptance criteria for stability.

This study is classified as **acceptable/non-guideline** and satisfies the stated purpose of analytical method validation and determination of stability of the test compound in a corn oil vehicle.

Non-Guideline Acute Neurotoxicity Study in Rats

In a non-guideline, acute neurotoxicity study (MRID 49617870), groups of 12 non-fasted male Crl:CD(SD) rats/dose group were administered a single oral dose of transfluthrin (97.7% a.i.; lot

PNLS000112) in corn oil at measured dose levels of 0, 25.7, 52.2, 78.6, 100, or 127 mg/kg bw with a dose volume of 1 mL/kg for all groups (nominal concentrations of 0, 25, 50, 75, 100, or 125 mg/kg bw). Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed for all animals at the time of peak effect (approximately 1 h post-dosing). After completion of neurobehavioral testing, all rats were euthanized and discarded without further examination. The stated purpose of this study was to establish a clear dose-response and a NOAEL for acute toxicity by evaluation with an FOB and motor activity testing for comparison with other pyrethroid insecticides.

All rats survived to scheduled euthanasia on Day 0. No effects of treatment were noted during the handling observations or on the physiological observations of the FOB assessments.

Treatment-related findings were observed during the Day 0 FOB assessments. During the home cage observations, clonic convulsions were noted in two 100 mg/kg rats and three 127 mg/kg rats, and slight to moderately-coarse tremors were seen in one 100 mg/kg rat and three 127 mg/kg rats. Additionally, at 127 mg/kg, the majority of the rats (11/12) were observed to be sitting or standing normally (8/12; $p<0.05$), alert (3/12), or rearing (1/12), and with eyelids wide open (10/12; $p<0.05$). During the open field observations, one 100 mg/kg rat and two 127 mg/kg rats were seen with clonic convulsions, and one 100 mg/kg rat and three 127 mg/kg rats were observed with slight to markedly-coarse tremors. These 127 mg/kg rats were also noted with slight to moderately-impaired mobility, gait anomalies, slight to considerable gait impairment, and no reaction to touch, startle, or tail-pinch stimuli. In the neuromuscular observations, Rotarod performance was decreased ($p<0.01$) in the 127 mg/kg rats (52.0 sec treated vs. 108.7 sec control).

On Day 0, total motor activity was increased ($p<0.05$) during subintervals 3, 4, 5, and 6, resulting in increased ($p<0.05$) cumulative total motor activity for the 127 mg/kg rats. However, ambulatory motor activity for all subintervals and cumulative counts was unaffected by treatment at 127 mg/kg. It was concluded that the increase in the total motor activity counts was a result of non-ambulatory movements, such as convulsions and tremors observed during the FOB.

There were no other effects of treatment noted on motor activity. Habituation was unaffected by treatment.

The LOAEL was 100 mg/kg bw, based on clonic convulsions and tremors observed during the FOB assessment in males. The NOAEL was 78.6 mg/kg bw.

This acute neurotoxicity study is classified as **acceptable / non-guideline** and satisfies the purpose for which it was intended.

Appendix B. Physical/Chemical Properties

Table B.1. Physical/Chemical Properties of Transfluthrin.		
Parameter	**Value**	**Reference**
Melting point (ºC)	32	1
pH	Not dispersible in water	2
Density (g/cm^3)	0.79	2
Water solubility (g/L at 20ºC)	0.000057	1
Solvent solubility (g/L at 25ºC)	Acetone Soluble Dichloromethane Soluble Ethyl acetate Soluble Heptane Soluble Methanol Soluble Octanol Soluble Xylene Soluble	3
Vapor pressure (Pa at 20ºC)	9 x 10 $^{-4}$	1
Dissociation constant, pK_a at 20ºC	None	1
Octanol/water partition coefficient, Log(K_{OW}) at 20ºC	5.46	1

[1] WHO Specifications and Evaluations for Public Health Pesticides. Transfluthrin, 2006
[2] D435699/D441760, A. Abromovitch, 12/12/2017
[3] Material Safety Data Sheet for transfluthrin technical material

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies, ethics review may have included review by the Human Studies Review Board. Descriptions of data sources as well as guidance on their use can be found at http://www.epa.gov/pesticides/science/handler-exposure-data.html and http://www.epa.gov/pesticides/science/post-app-exposure-data.html.

Appendix D. Summary of Residential Non-cancer Algorithms

Residential Non-cancer Post-application Algorithms

In order to best assess the proposed use of transfluthrin in the personal insect repellent kit, a mixed approach using data assumptions from the 2012 Residential SOP for Indoor Environments was used in conjunction with the algorithms and data assumptions from Outdoor Fogging/Misting Systems. The algorithms used in this assessment to model time-weighted average (TWA) air concentrations are found below and are derived from equation D.7 in the 2012 Residential SOPs:

$$C = \frac{\frac{V_E \times ER}{Q}\left[ET - \left(\frac{V}{Q}\right)\left(1 - e^{-\frac{Q}{V}(ET)}\right)\right]}{ET}$$

Where:

V_E = vaporization efficiency (%);
ER = emission rate (mg ai/hr);
ET = exposure time (hr/day);
V = volume of treated space (m^3); and
Q = airflow (m^3/hr).

The airflow through the treated space can be calculated as follows:

$$Q = AV \times CF1 \times CF2 \times A_{cross-section}$$

Where:

Q = airflow (m^3/hr);
AV = air velocity (m/s);
CF1 = time unit conversion factor (60 s/1 min);
CF2 = time unit conversion factor (60 min/1 hr); and
$A_{cross\text{-}section}$ = cross-section of outdoor space treated (m^2).

The airflow through the treated space can also be calculated as a function of both air changes per hour and the volume of the treated space. The equation listed in the 2012 Residential SOPs may be reworked (see Appendix D in the 2012 Residential SOPs, Vapor Emission for Surface Sprays for the original equation) to produce the following equation:

$$Q = ACH \times V$$

Where:

Q = airflow (m^3/hr);
ACH = air changes per hour (1/hr); and
V = volume of treated space (m^3).

The emission rate of the product can be calculated as follows:

$$ER = \frac{A \times N_P}{UL}$$

Where:

ER = emission rate (mg ai/hr);

A = amount of mg ai in product (mg ai/product);
N_P = number of products used (products); and
UL = useful life of product (hours).

The data assumptions used in this assessment are provided below and include assumptions from both the 2012 Residential SOP for Indoor Environments and for Outdoor Fogging/Misting Systems.

Table D.1: Outdoor Fogging/Misting Systems – Recommended Post-application Inhalation Exposure Factor Point Estimates

Algorithm Notation	Exposure Factor (units)		Point Estimate(s)
V_E	Vaporization efficiency (percent)		100%
A	Amount of ai in the product (mg)		Product-specific (1500 mg)
ER	Emission rate (mg ai/hr)		Calculated
UL	Useful life (hours)		Product-specific (21 days; 504 hours)
ET	Exposure time (hours)	Adults	2.3
		Children 1 < 2 years old	2.3
V	Volume of treated space (m^3)		Product-specific (33 for RVs/campers/barns/garages/outdoors and 7 for tents)
Q	Airflow through treated area (m^3/hr)		3,211 (adjusted from SOP value of 4,000 for difference in cross section area treated)
AV	Air velocity (m/s)		0.1
N_P	Number of products used (# products)		1 product per treated area
$A_{cross-section}$	Cross sectional area of area treated (m^2)		8.9

Table D.2: Indoor Environments – Recommended Post-application Inhalation Exposure Factor Point Estimates

Algorithm Notation	Exposure Factor (units)			Point Estimate(s)
ACH	Air changes per hour (hr^{-1})	RVs/Campers		0.45
		Barns/Garages		4
		Tents		4
V	Volume of treated space (m^3)	RVs/Campers, Barns/Garages		33
		Tents		7
	Exposure Time	Barns/Garages	Adults	2

Table D.2: Indoor Environments – Recommended Post-application Inhalation Exposure Factor Point Estimates				
Algorithm Notation	**Exposure Factor (units)**			**Point Estimate(s)**
ET	(hr/day)		Children 3 <6 years old	4
		Tents	Adults	8
			Children 1 <2 years old	13
		RVs/Campers	Adult	16
			Children 1 <2 years old	18
N_P	Number of products used (# products)			1 product per treated area
UL	Useful life (hours)			Product-specific (21 days)
ER	Emission rate (mg ai/hr)			Calculated
A	Amount of ai in the product (mg)			Product-specific (1500 mg)
V_E	Vaporization efficiency (percent)			100%