UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

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SUBJECT: Re-Evaluation of the FQPA Safety Factor for Pyrethroids: Updated Literature and CAPHRA Program Data Review

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This document is a review of the data available for pyrethroids both in the available public literature was well as submissions to EPA regarding the Food Quality Protection Act (FQPA) Safety Factor (SF). A draft was published in EPA's website in July of 2019; a revised document may be prepared after review of public comments.

USEPA Office of Pesticide Programs' Re-Evaluation of the FQPA Safety Factor for Pyrethroids: Updated Literature and CAPHRA Program Data Review

July 1, 2019

Previously, EPA's Office of Pesticide Programs (OPP) used a 3X FQPA Safety Factor based on concerns for pharmacokinetic differences between adults and children (E. Scollon, D381210, 06/27/2011). OPP has re-evaluated the need for an FQPA Safety Factor for human health risk assessments for pyrethroid pesticides. Consistent with EPA's 2014 Guidance for Applying Quantitative Data to Develop Data Derived Extrapolation Factors (DDEF) for Interspecies and Intraspecies Extrapolation[1], the Agency considers the FQPA safety factor as having two components: with 3X assigned to pharmacokinetics (PK) and 3X to pharmacodynamic (PD) differences. The previous conclusion that the PD contribution to the FQPA factor is 1X remains the same. Based on a review of the available guideline and literature studies as well as data from the Council for the Advancement of Pyrethroid Human Risk Assessment (CAPHRA) program, the Agency concludes that the PK contribution to the FQPA factor is also 1X for adults, including women of child-bearing age, and children. Therefore, the total FQPA safety factor for pyrethroids can be reduced to 1X for all populations.

[1] https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf

Chemical	PC Code	CAS No.
Allethrin	004001	584-79-2
Bioallethrin	004003	28057-48-9
S-Bioallethrin	004004	28434-00-6
D-Allethrin	004005	84030-86-4
Esbiothrin	004007	84030-86-4
Bifenthrin	128825	82657-04-3
Cyclethrin	004052	97-11-0
Cyfluthrin	128831	68359-37-5
Cyfluthrin, beta-	118831	68359-37-5
Cyhalothrin	128867	68085-85-8
Cyhalothrin, lambda-	128897	91465-08-6
Cyhalothrin, gamma-	128807	76703-62-3
Cypermethrin	109702	52315-07-8
Cypermethrin, alpha-	209600	67375-30-8
Cypermethrin, beta-	118831	65731-84-2
Cypermethrin, zeta-	129064	52315-07-8
Cyphenothrin	129013	39515-40-7
Deltamethrin	097805	52918-63-5
Esfenvalerate	109303	66230-04-4
Fenvalerate	109301	51630-58-1
Fenfluthrin	109705	69409-94-5
Fenpropathrin	127901	39515-41-8
Imiprothrin	004006	72963-72-5
Metofluthrin	109709	240494-70-6
Permethrin	109701	52645-53-1
Prallethrin	128722	23031-36-9
Pyrethrins (not synthetic)	069001	8003-34-7
Resmethrin	097801	10453-86-8
Sumithrin (phenothrin)	069005	26002-80-2
Tau-fluvalinate	109302	102851-06-9
Tefluthrin	128912	79538-32-2
Tetramethrin	069003	7696-12-0
Tralomethrin	121501	66841-25-6
Transfluthrin	129140	118712-89-3

Re-Evaluation of the FQPA Safety Factor for Pyrethroids: Updated Literature and CAPHRA Program Data Review

1. Background

Naturally occurring pyrethrin and synthetic pyrethroid[2] pesticides constitute a class of insecticides used to control a variety of pests. The typical pyrethroid structure includes a chrysanthemic acid linked to an aromatic alcohol through an ester linkage (Figure 1). Structural modifications such as the addition of halogens to the chrysanthemic acid and aromatic alcohol moieties and the addition of the α-cyano group have increased photostability, insecticidal potency, and in some incidences, stereoisomerism of the pyrethroids. As a point of reference, pyrethroids lacking the α-cyano group are referred to as Type I and those with the α-cyano group are referred to as Type II pyrethroids.

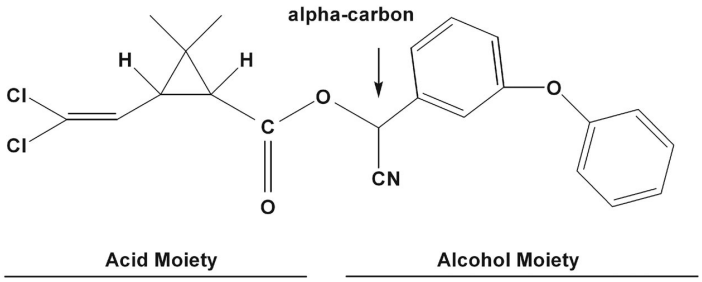

Figure 1. The typical structure of a pyrethroid pesticide, as illustrated by cypermethrin, includes an acid and an alcohol moiety. Type II pyrethroids also contain an α-cyano group.

Pyrethroid pesticides have a common mammalian mode of action: interaction with voltage-gated sodium channels (VGSCs) (USEPA, 2009). This interaction results in disruption of membrane excitability in the nervous system, leading to neurotoxicity. Two specific toxicity syndromes have been observed in rats following pyrethroid exposure: T- (fine tremors) and CS-syndromes (choreoathetosis and salivation). The T-syndrome is associated with Type I pyrethroids and characterized by aggressive sparring, increased sensitivity to external stimuli and fine whole-body tremors. The CS-syndrome is associated with Type II pyrethroids and characterized by initial pawing and burrowing, salivation, and choreoathetosis. A few pyrethroids, including esfenvalerate and fenpropathrin, elicit symptoms that are a combination of the T- and CS-syndromes.

In human health risk assessment, the Agency commonly applies default uncertainty factors to estimate potential human health risks based on animal toxicity study results (interspecies extrapolation), and to account for human variability (intraspecies extrapolation). In addition, the Food Quality Protection Act (FQPA) (1996) instructs EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, **an additional tenfold margin of safety** for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account **potential pre- and post-natal toxicity and**

[2] Herein, the naturally occurring pyrethrins and synthetic pyrethroids are called "pyrethroids"

completeness of data with respect to exposure and toxicity to infants and children." Section 408 (b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Consistent with EPA's 2014 Guidance for Applying Quantitative Data to Develop Data Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation[3], when sufficient scientific information is available to delineate the key differences between animals and humans, or across human populations (e.g., mode of action, metabolism rates), DDEFs can replace the use of default uncertainty factors of 3X for PK and 3X for PD. The PK component depicts the process of chemicals being absorbed into, distributed to, metabolized within, and excreted from the body, and thus, PK processes influence the target tissue dose of a chemical that enters the body. The PD component determines how a chemical mechanistically brings about target tissue responses at a given target tissue dose.

The Agency also considers the FQPA safety factor of 10X to have two components: with 3X assigned to PK and 3X to PD associated with differences between adults and juveniles that impact lifestage sensitivity. In the case of the pyrethroids, these pesticides share the same mode of action and a similar pattern of toxicity. The parent pyrethroid is the toxicologically active compound and metabolism results in detoxification. Also, the rapid absorption, distribution, and clearance of pyrethroids from the body results in the onset of toxicity and recovery within a few hours of exposure is shared across the class of pesticides. As such, robust information is available for this class to support a DDEF approach to the FQPA SF. Moreover, these similarities support the use of a single FQPA factor for the entire pyrethroid class. The purpose of this document is to provide a reevaluation the FQPA safety factor for pyrethroids based on updated information.

2. 2011 Evaluation of the FQPA SF for Pyrethroids

In 2010, as part of registration review[4] and new use registrations under the Pesticide Registration Improvement Act (PRIA), OPP performed a comprehensive evaluation of data pertinent to assessing the health risks of pyrethroid exposures to children. This review included reproductive, developmental, and developmental neurotoxicity (DNT) animal guideline studies submitted by registrants, as well as studies from the open literature (E. Scollon, D371723, 01/20/2010). The Agency also evaluated information on PK (i.e., time course of absorption, distribution, metabolism, and excretion of pyrethroids) and PD (i.e., sequence of events at the molecular/cellular levels leading to a toxic response) to determine whether there are any quantitative differences in how young animals respond to pyrethroids versus adult animals.

PD can be defined as the changes that chemicals cause to the body; in this case, how pyrethroids interact with the sodium channels. There are several variations of sodium channels, called isoforms, which have been shown to be differentially expressed by tissue and age in rats. Therefore, it is reasonable to hypothesize that there may be differences in the age-dependent toxicity of pyrethroids related to age-specific populations of sodium channel isoforms.

[3] https://www.epa.gov/sites/production/files/2015-01/documents/ddef-final.pdf
[4] http://www.epa.gov/oppsrrd1/registration_review/

In 2011, the Agency reviewed available data to characterize the PD relationship between pyrethroids and sodium channels (E. Scollon, D381210, 06/27/2011). Studies identified at the time consisted of *in vitro* studies using frog oocytes or nervous cells artificially grown in media. While these data did not provide direct quantitative measure of *in vivo* pyrethroid activity, they consistently and qualitatively demonstrated that juvenile sodium channels are not more sensitive to pyrethroid perturbation compared to adults and that, pharmacodynamically, the rat is a conservative model for humans. Therefore, the Agency concluded that the default pyrethroid 3X FQPA safety factor for PD could be reduced to 1X for humans at all ages.

PK can be defined as what the body does to chemicals; in this case, how pyrethroids are absorbed, distributed, metabolized, and excreted following exposure. Differences in the ability of the adults and juveniles to metabolize pyrethroids, or age-dependent PK, are largely responsible for the juvenile susceptibility previously noted in rats. No such susceptibility has been found in developmental or reproductive toxicity studies reviewed by EPA (E. Scollon, D381210, 06/27/2011). Furthermore, fetal exposure and exposures to children below 6 months of age are expected to be negligible because pyrethroid levels in food and drinking water are generally low and there is no or low potential for contact with treated surfaces. Therefore, EPA's concern and the focus of this evaluation is humans between 6 months and 6 years old.

In 2011, the Agency reviewed physiologically based pharmacokinetic (PBPK) models developed to describe the PK of a few pyrethroids, including deltamethrin, in rats at multiple ages (Scollon, 2011; Godin, 2010; Mirfazaelian, 2006). At the time, no similar age-dependent human PBPK models were available for these pyrethroids. The rat PBPK model predicted increased deltamethrin concentrations in 10- and 21-day old rats compared to 90-day old adults given the same administered dose. A 10-day old rat is a close approximation to the most sensitive human population, children from birth to <6 years old. Therefore, the Agency retained the default pyrethroid 3X FQPA safety factor for PK for children <6 years old.

Although the available guideline studies do not indicate that juveniles are more susceptible to pyrethroid toxicity than adults, several literature studies demonstrate increased juvenile sensitivity following treatment with high doses of pyrethroids. However, the Agency considered these literature studies were not sufficiently robust for use in risk assessment and concluded that additional data were needed to adequately characterize potentially relevant juvenile susceptibility. To address this data gap, the Agency requested proposals for study designs/protocols that could identify and quantify potential juvenile sensitivity (USEPA-OPP, 2010). Based on this request, CAPHRA was formed by pyrethroid and pyrethrin registrants in 2011 to develop a research program with the aim of addressing the data gaps identified by EPA to evaluate potential differential sensitivity of pyrethroids between juveniles and adults.

3. Available Information for the 2019 Reevaluation

New information considered for this evaluation includes research conducted by CAPHRA as well as systematic review of the pyrethroid open literature.

3.1 Research Conducted by CAPHRA

The fundamental scientific question that CAPHRA worked to address is whether children are more sensitive than adults to the acute neurotoxic effects resulting from pyrethroid exposure. Thus, their research program has evaluated both PD and PK factors that are associated with pyrethroid neurotoxicity to determine if these factors possibly lead to age-related sensitivity to pyrethroid neurotoxicity in humans. The program included three phases: (1) phase I established baseline data and understanding of PD and PK using two chemicals (deltamethrin and permethrin); (2) phase II extrapolated findings from the first phase to five other pyrethroids; (3) phase III generated data needed to extend the knowledge gained from the previous two phases to the remaining pyrethroids in the class. A Science Advisory Panel (SAP) reviewed the proposal and some of the initial research (USEPA, 2010) and a peer-review panel evaluated the resulting PBPK model.

3.1.1 PD Data Provided by CAPHRA

For PD, CAPHRA used an Adverse Outcome Pathway (AOP) for pyrethroid neurotoxicity to guide the design of targeted studies to investigate whether there is an age-related difference in the interaction of pyrethroids with the VGSCs in juveniles that makes them more sensitive to the same target tissue dose in adults. These targeted studies include (a) examining the *in vitro* effects of pyrethroids on mammalian cells transfected with the human VGSCs; (b) examining the *in vitro* effects of pyrethroids on tetrodotoxin-sensitive, voltage-sensitive sodium channels in juvenile and adult rat brain neurolemma fragments; and (c) examining the *in vivo* effects on acoustic startle response and clinical observations in juvenile and adult rats.

***a. In vitro* effects of pyrethroids on mammalian cells transfected with VGSCs**

The effects of 9 pyrethroids (cypermethrin, bifenthrin, pyrethrum, prallethrin, permethrin, esfenvalerate, deltamethrin, tefluthrin, and allethrin) on human sodium channels commonly found in the young and adult central nervous system were examined *in vitro* (MRID 49916401). Several deficiencies were noted in this study, which make the results difficult to interpret, including: lack of methodology details such as experiment temperatures (some pyrethroid effects are known to be temperature-dependent) or how the pyrethroids were solubilized; also, researchers could not confirm the transfection of the β1 subunits. Furthermore, this study did not show differences in sodium channel sensitivity for most of the pyrethroids tested. These results differ from published studies showing that deltamethrin affects human sodium (Nav1.1) channel currents (James, 2017). The differing results together with the identified deficiencies decrease confidence in this study. Therefore, this study is not considered informative regarding age-related pharmacodynamic differences for the pyrethroids.

***b.* Neurolemma Study**

Neurolemma preparations from juvenile and adult rat brains were microtransplanted into Xenopus oocytes to compare age-specific concentration-dependent response curves (CDRCs) from sodium channels (MRID 50409303, TXR 0057772, D444188, D448281, K. Yozzo, 04/23/2019). The effects of treatment with permethrin and deltamethrin on native VGSC neurolemma preparations were compared. However, several deficiencies (see data evaluation report [DER] for details) undermine confidence in this study, including: large variability in the

data and concerns with the appropriateness of the statistical analyses. Given these concerns, this neurolemma study is considered insufficiently reliable to provide additional insight on the issue of pharmacodynamic differences for the pyrethroids.

c. In vivo Acoustic Startle Response Studies in Rats

Acoustic startle response (ASR) studies are used to demonstrate the direction, magnitude, and time-course of effects of pyrethroids on neurological function in adult rats. However, the SAP concluded in 2010 that ASR is not the best measure for juvenile sensitivity to pyrethroids because this type of response varies with age (USEPA, 2010). Nonetheless, CAPHRA examined the suitability of ASR to measure acute neurotoxicity effects of deltamethrin (MRID 50409301) and permethrin (MRID 50409302) in adult and juvenile rats. EPA has conducted a full review and performed statistical analyses on these studies, details of which can be found in the respective DERs (TXR 0057772, D444188, D448281, K. Yozzo, 04/23/2019). A short summary is presented below.

Exposure to deltamethrin decreased the ASR in both juvenile and adult rats; however, juvenile rats were more sensitive to the neurotoxic effect of deltamethrin compared to adult rats. Motility, salivation and tremor rose above moderate at the highest dose only. Appropriate doses for post-natal day 15 (PND15) pups were not established in this study; deltamethrin induced significant dose-dependent decreases in ASR at all doses that did not dissipate or level-off by 8 h post-treatment. Therefore, a clear time to peak effect, post-treatment interval for testing, or no observed adverse effect level (NOAEL) were not established.

Exposure to permethrin increased ASR in adult rats starting at the mid-dose. Tremors were observed in juvenile (PND15) rats at all doses. The adverse effects (tremors) observed at all doses tested for the juvenile rats did not allow study authors to establish a clear time to peak effect, or post-treatment interval for testing. Also, the available data indicate that tremors interfered or confounded the results of the ASR testing in juveniles. Based on the results of the deltamethrin and permethrin ASR studies, a quantitative comparison between juveniles and adults is not appropriate using ASR data.

3.1.2. PK Data Provided by CAPHRA

To address the potential PK sensitivity for juveniles, CAPHRA centered their research strategies on developing a generic, life stage PBPK model for humans for pyrethroids, which can be parameterized for individual pyrethroids. The ultimate goal was to use the individual PBPK models to predict dose metrics in target tissues, which is the maximal concentration (Cmax) in plasma, for juveniles and adults, followed by calculating a data-derived FQPA safety factor for the entire class of pyrethroids. In phase I, life-stage PBPK models for rats were developed for deltamethrin and permethrin as both chemicals have extensive body of data for parameterizing models and evaluating the predictive capability of these models. These data include *in vivo* time-concentration data for male Sprague-Dawley rats (PND15, PND21, and adults) for up to 24 hours following oral administration (MRID 49840710, 49840709, 49840708, 49884601, 49840703, 49840704, 49884604, 49884603, 49884602), *in vivo* tissue/plasma partition coefficients (MRIDs 49840705, 49840706, and 49916407), *in vitro* absorption rates (MRIDs 49817604, 49821808, 49821809), *in vitro* protein binding data (MRIDs 49817601, 49817605,

49840701, 49817602), and *in vitro* enzyme expression data (MRIDs 49916404 and 49916405) (See Appendix for study summaries).

The key findings from rat PBPK modeling analysis for deltamethrin and permethrin were that (1) one generic PBPK model structure parameterized with chemical-specific metabolism rates is appropriate for simulating plasma Cmax for deltamethrin and permethrin; (2) an *in vitro* to *in vivo* extrapolation (IVIVE) approach implemented to estimate *in vivo* metabolic clearance from *in vitro* measurements based on microsomes and cytosol requires an empirical factor to describe "restrictive clearance" *in vivo*, but a single value for the empirical factor is appropriate for both deltamethrin and permethrin; and (3) the life stage model that incorporates metabolic ontogeny data is capable of predicting plasma Cmax in juvenile and adult rats. After demonstrating the rat models have the capability to simulate oral exposures to deltamethrin and permethrin, the same model structure and parameterization approaches (e.g., IVIVE, enzyme ontogeny) were used to develop human life stage PBPK models, based on *in vitro*-measured metabolic clearance rates for humans (MRIDs 50600302, 50600304) and enzyme ontogeny data, for predicting distributions of plasma Cmax in juveniles and adults.

The modeling analysis in phase I was reviewed by an external panel that consisted of 10 members between July and October 2018. The peer reviewers addressed approximately 20 charge questions in five areas: model representation, coding, evaluation, documentation, and applications. Their findings were summarized in a report (MRID 50309104) submitted to EPA in November 2018; the panel concluded that significant modifications must be made to the documentation before the models can be considered appropriate. Following external peer-review of the PBPK models for deltamethrin and permethrin, CAPHRA provided their responses to the peer review comments and revised documentations and model code for the deltamethrin and permethrin models in a submission dated June 10, 2019 (MRID 50879601). In addition, this CAPHRA report included analyses and results from phase II of their research program.

The read across approach that used the deltamethrin model as a generic modeling platform for pyrethroids and replacing metabolic clearance rates with *in vitro*-measured rates for individual pyrethroids, proved to be appropriate for cis- and trans-permethrin in phase I. Thus, in phase II, the same read across approach was applied to five additional pyrethroids (esfenvalerate, bifenthrin, cyphenothrin, cyfluthrin and cyhalothrin) to develop individual PBPK models using *in vitro* metabolic clearance rates measured for each chemical (MRIDs 50600303, 50600308, 50600305, 50600301; TXR 0057772, D444188, D448281, K. Yozzo, 04/23/2019). The performance of these models was evaluated by comparing model simulations with *in vivo* time-concentration data measured in PND15 and PND90 rats for each of the five pyrethroids. The difference between observed and simulated plasma Cmax was generally within two-fold. Similar to the analysis conducted in phase I, these five rat PBPK models were scaled up to humans, using *in vitro*-measured metabolic clearance rates and enzyme ontogeny data, for calculating data-derived FQPA safety factors. Data-derived FQPA safety factors calculated using the five models ranged between 0.66-1.16 (MRID 50879601). After peer-review and revision of the PBPK model, OPP concludes that this model is adequate for calculating a data-derived FQPA safety factor for the entire class of pyrethroids.

3.2 Systematic Review of Pyrethroid Open Literature

In 2017, OPP performed an updated literature search to generate a comprehensive list of publicly available pyrethroid citations (R. McGovern, D448870, 04/11/2019). A systematic review was performed on the 10,532 citation results to determine whether there were any studies that may be useful for risk assessment purposes. Two studies were identified and submitted for in-depth review and incorporation into chemical-specific risk assessments. Additionally, citations tagged as "*in vitro*" (271) were reviewed to determine whether new studies assessing age-related sensitivity as it relates to sodium channels could be located. However, no new studies relating to this topic were identified. A final search was performed in PubMed on 07/02/2018 for studies between 05/01/2017 and 07/01/2018 with the following search string:

(Pyrethroid OR Deltamethrin OR Bifenthrin OR Cyfluthrin OR Cypermethrin OR Cyphenothrin OR "d-Phenothrin" OR Esfenvalerate OR Fenpropathrin OR Imiprothrin OR Prallethrin OR Pyrethrin OR Tau-Fluvalinate OR Tetramethrin) AND (in vitro OR VGSC)
This search identified 67 citations but none of these studies were found to provide additional information on age-related sensitivity of sodium channels following abstract review.

A systematic review was also conducted for epidemiological studies investigating the association between pyrethroid exposure and human health effects (A. Aldridge, D450506, 4/30/2019). Overall, there was little substantive evidence to suggest a clear associative or causal relationship between exposure to pyrethroids and health outcomes in the studies identified.

In conclusion, systematic review of the open literature for pyrethroid epidemiological, *in vivo* and *in vitro* studies did not identify additional information to be used in the assessment of the FQPA safety factor for pyrethroids.

4. Results of the 2019 Reevaluation

4.1 Pharmacodynamic Considerations for the FQPA Safety Factor

The multiple deficiencies identified in the recently submitted studies preclude the use of these data to further characterize the PD properties of the pyrethroids. Also, the systematic review of the open pyrethroid literature did not identify additional studies that could be used to inform the PD properties of the pyrethroids. In the absence of new adequate data, the previous conclusions from the 2011 analysis that the rat is an appropriate surrogate for the evaluation of human PD and that juvenile rats are not more sensitive than adults with respect to pyrethroid PD remain the same. Therefore, the PD contribution for pyrethroids to the FQPA factor is 1X.

4.2 Pharmacokinetic Considerations for the FQPA Safety Factor

The EPA reviewed CAPHRA's reports describing their research strategies on developing a generic, human life stage PBPK model for pyrethroids, as well as the model code, and responses to peer review comments from the external panel that evaluated their phase I modeling approach in 2018. Based on this review, the EPA concludes that the PBPK modeling analysis, combined

with IVIVE and read-across approaches, are appropriate for estimating data-derived FQPA safety factors for the entire class of pyrethroids.

Based on a weight-of-the-evidence approach and considering all the available information, the EPA concludes that the PK contribution to the FQPA safety factor is 1X for all populations. This conclusion is based on the following: 1) there is reasonable concordance between Cmax in plasma predicted using rat life-stage PBPK models for deltamethrin, cis-permethrin, trans-permethrin, bifenthrin, esfenvalerate, cyphenothrin, cyhalothrin, and cyfluthrin, and those measured in PND15 and PND 90 rats; 2) human life stage PBPK models that incorporate enzyme ontogeny data for deltamethrin, cis-permethrin, trans-permethrin, bifenthrin, esfenvalerate, cyphenothrin, cyhalothrin, and cyfluthrin are used to estimate data-derived FQPA safety factors, which are all at or below 1X; 3) the read across approach for developing PBPK models for individual pyrethroids based on a single model structure and chemical-specific metabolic clearance rates measured in microsomes and cytosols has been evaluated for deltamethrin, cis-permethrin, trans-permethrin, bifenthrin, esfenvalerate, cyphenothrin, cyhalothrin, and cyfluthrin using *in vivo* time-concentration data collected in PND15 and PND90 rats, providing confidence in concluding that data-derived FQPA factor is also 1X for the remaining pyrethroids.

5. Conclusions

FFDCA section 408 requires the Agency to apply an additional 10X safety factor to account for the potential pre- and post-natal toxicity and completeness of the data with respect to infants and children unless, based on reliable data, EPA can conclude that another safety factor will be "safe." The Agency considered previous as well as newly available data on the two components of the FQPA safety factor (PD and PK). No new information of suitable quality was available on the age-related PD properties of the pyrethroids. Therefore, the previous conclusion that the PD contribution to the FQPA safety factor is 1X remains the same. With regard to PK, recent data including human PBPK models, as well as *in vivo* and *in vitro* data on protein binding, enzyme ontogeny and metabolic clearance, support the conclusion that the PK contribution to the FQPA safety factor is 1X for all populations. Therefore, the Agency concludes that the default 10X FQPA safety factor can be reduced to 1X for all populations for the pyrethroid pesticides.

References

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Appendix A. Study Summaries

MRIDs 49821801, 49920501, and 50556801: Analytical method for the determination of deltamethrin in plasma

Analytical methods to determine DLM in plasma were developed by University of Georgia (MRID 49821801) as well as Frontage Laboratories (MRIDs 49920501 and 50556801) The limit of quantification (LOQ) was set at 1 - 500 ng/mL for plasma. It was possible to detect 0.3 - 1000 ng/mL for plasma. The limit of detection (LOD) has been set at 0.3 ng/mL for plasma with a lower limit of quantification (LLOQ) of 1.0 ng/mL. It was possible to detect 0.1 ng/mL.

MRID 49821802: Analytical method for the determination of deltamethrin in brain homogenate

Two methods to accurately quantify deltamethrin (DLM) in brain homogenate were developed by University of Georgia. One method (A) involves a protein precipitation extraction while the second method (B) uses sample cleanup with dispersive solid phase extraction (d-SPE). *Cis*-permethrin (CIS) was used as the internal standard. DLM and CIS have been shown to be efficiently extracted using the procedures described. Both methods passed validation according to the acceptance criteria. The limit of quantification (LOQ) has been set at 0.3 - 500 ng/mL and 0.5 - 500 ng/L for brain homogenate for Method A and Method B, respectively. The limit of detection (LOD) has been set at 0.1 ng/mL and 0.3 ng/L using Method A and Method B, respectively.

MRID 50556802: Method of qualification: analysis of deltamethrin in rat brain tissue by LC/MS/MS

A method to quantify deltamethrin (DLM) in brain homogenate was developed by Frontage Laboratories, Inc. The calibration range was 2.00-1000 ng/g. The lower limit of quantification (LLOQ) was 2.00 ng/g. The QC low was 6.00 ng/g.

MRID 49821803: Analytical method for the determination of deltamethrin in liver homogenate

Two methods to accurately quantify deltamethrin (DLM) in liver homogenate were developed. One method (A) involves a protein precipitation extraction while the second method (B) uses sample cleanup with dispersive solid phase extraction (d-SPE). *Cis*-permethrin (CIS) was used as the internal standard. DLM and CIS have been shown to be efficiently extracted using the procedures described. Both methods passed validation according to the acceptance criteria. The limit of quantification (LOQ) has been set at 0.3 - 1000 ng/mL and 1.0 - 500 ng/L for liver homogenate for Method A and Method B, respectively. The limit of detection (LOD) has been set at 0.1 ng/mL and 0.3 ng/L using Method A and Method B, respectively.

MRID 49821804: Analytical method for the determination of deltamethrin in muscle homogenate

Two methods to accurately quantify deltamethrin (DLM) in muscle homogenate were developed. One method (A) involves a protein precipitation extraction while the second method (B) uses sample cleanup with dispersive solid phase extraction (d-SPE). *Cis*-

permethrin (CIS) was used as the internal standard. DLM and CIS have been shown to be efficiently extracted using the procedures described. Both methods passed validation according to the acceptance criteria. The limit of quantification (LOQ) has been set at 0.3 ng/mL to 1000 ng/mL and 1 to 500 ng/L for muscle homogenate for Method A and Method B, respectively. The limit of detection (LOD) has been set at 0.1 ng/mL and 0.3 ng/L using Method A and Method B, respectively.

MRID 49821805: Analytical method for the determination of deltamethrin in fat homogenate

An analytical method to determine DLM in plasma was developed. *Cis*-permethrin (CIS) was used as the internal standard. DLM and CIS have been shown to be efficiently extracted using the procedure described. The limit of quantification (LOQ) has been set at 1 - 1000 ng/mL for fat. The limit of detection (LOD) has been set at 0.3 ng/mL for fat.

MRID 49821806: Analytical method for the determination of *cis*-permethrin

An analytical method to determine *cis*-permethrin (CIS) in plasma, brain, liver, muscle, and fat using piperonyl butoxide (PBO) as internal standard for the analysis was developed. CIS and PBO have been shown to be efficiently extracted using the procedure described. The lower limit of quantification (LLOQ) has been set at 0.1 - 20 µg/mL for plasma and tissue homogenates. Tissue homogenates were prepared with a dilution made by water, while the liver and brain homogenates were prepared with twice the amount of tissue weight. Muscle and fat homogenates were prepared with three times the amount of tissue weight. The standard curve range per gram of tissues are: liver and brain 0.3 - 60 µg/g; muscle and fat 0.4-80 µg/g. The limit of detection (LOD) has been set at 0.033 µg/mL for plasma, 0.1 µg/g for brain and liver, and 0.133 µg/g for muscle and fat.

MRID 49821807: Analytical method for the determination of *trans*-permethrin

An analytical method to determine *trans*-permethrin (TRANS) in plasma, brain, liver, muscle, and fat using piperonyl butoxide (PBO) as internal standard for the analysis was developed. TRANS and PBO have been shown to be efficiently extracted using the procedure described. The limit of quantification (LOQ) has been set at 0.15 – 20 µg/mL for plasma and tissues. Tissue homogenates were prepared with a dilution made by water, while the liver and brain homogenates were prepared with twice the amount of tissue weight. Muscle and fat homogenates were prepared with three times the amount of tissue weight. The standard curve range per gram of tissues are: liver and brain 0.45 - 60 µg/g; muscle and fat 0.6 - 80 µg/g. The limit of detection (LOD) has been set at 0.05 µg/mL for plasma, 0.15 µg/g for brain, and 0.2 µg/g for muscle and fat.

MRID 50556805: Method of Qualification: Analysis of cis-permethrin and trans-permethrin in rat plasma and brain tissue samples by LC/MS/MS
MRID 50556802: Method of Qualification: Analysis of cis-permethrin and trans-permethrin in lithium heparin rat plasma containing 10% NaF (0.64 M in water) by LC/MS/MS

An analytical method to determine *cis*-permethrin (CIS) and trans-permethrin (TRANS) in rat brain was developed by Frontage Laboratories. This method was also verified to quantify CIS and TRANS in lithium heparin rat plasma containing 10% NaF. For both CIS and

TRANS, the calibration range was 0.1 - 20 µg/g, the lower limit of quantification (LLOQ) was 0.100 µg/g., and the QC Low was 0.300 µg/g.

MRID 49840705: Deltamethrin: assessment of partition coefficients

The objective of this study was to determine tissue:plasma partition coefficients for deltamethrin (DLM) for brain, liver, skeletal muscle and fat in PND15 and PND21 pups and PND90 adult male Sprague-Dawley rats. An oral loading dose coupled with constant infusion of DLM provided systemic steady-state or equilibrium of the chemical in PND21 pups and adult rats. Only constant infusion of DLM was used for PND15 pups due to toxicity observed with the combination of the oral dose and then constant infusion. An Alzet® infusion pump containing DLM was surgically implanted subcutaneously (SC) on the dorsum of members of these age-groups, with constant infusions of 0.36 mg DLM/hr in the adult rats or 0.021 mg DLM/hr and 0.028 mg DLM/hr in the PND21 rat pups and PND15 rat pups, respectively. Three to four hours post-start, PND21 pups and adult rats were gavaged with 0.25 mg DLM/kg and 30 mg DLM/kg, respectively. Adult rats were euthanized at 72 hr and PND15 and PND21 pups were euthanized at 48 and 72 hr. DLM concentrations were measured by high performance liquid chromatography (HPLC) or gas chromatography-negative chemical ionization-mass spectrometry (GC-NCI-MS).

DLM distributed evenly between erythrocytes and plasma for adult rats and equilibrium was achieved after 48 hours and maintained for the duration of the study (72 hr). DLM was distributed throughout the tissues based on triglyceride content. Adipose tissue was not visible for PND15 and PND21 pups, which should be taken into account during PBPK modeling. Partition coefficients are listed in the table below.

Table A.1. Partition Coefficients (PCs) for deltamethrin

Age	Fat	Skeletal Muscle (thigh area; 48-hr)	Skeletal Muscle (thigh area; 72-hr)	Brain (48-hr)	Brain (72-hr)	Liver (48-hr)	Liver (72-hr)
PND15	--	2	1.91	0.23	0.25	1.24	1.24
PND21	--	0.78	1.02	0.10	0.10	0.10	0.07
Adult	68.7	--	3.9	--	0.22	--	0.50

-- : No measurement taken

MRID 49840706: *Cis*-permethrin: assessment of partition coefficients

The objective of this study was to determine tissue:plasma partition coefficients for *cis*-permethrin (CIS) for brain, liver, skeletal muscle and fat in PND15 and PND21 pups and PND90 adult male Sprague-Dawley rats. An oral loading dose coupled with constant infusion of CIS provided systemic steady-state or equilibrium of the chemical in PND21 pups and adult rats. Only constant infusion of CIS was used for PND15 pups due to toxicity observed with the combination of the oral dose and then constant infusion. An Alzet® infusion pump containing CIS was surgically implanted subcutaneously (SC) on the dorsum of members of these age-groups, with constant infusions of 0.36 mg CIS/hr in the adult rats or 0.021 mg CIS/hr and 0.031 mg CIS/hr in the PND21 rat pups and PND15 rat pups, respectively. Three to four hours post-start, PND21 pups and adult rats were gavaged with 0.25 mg CIS/kg and 150 mg CIS/kg, respectively. Adult rats were euthanized at 72 hr and PND15 and PND21 pups were euthanized at 48 and 72 hr. CIS concentrations were

measured by high performance liquid chromatography (HPLC) or gas chromatography-negative chemical ionization-mass spectrometry (GC-NCI-MS).

CIS distributed evenly between red blood cells (RBC) and plasma for adult rats and equilibrium was achieved after 48 hours and maintained for the duration of the study (72 hr). CIS was distributed throughout the tissues based on triglyceride content. Adipose tissue was not visible for PND15 and PND21 pups, which should be taken into account during PBPK modeling. Partition coefficients are listed in the table below.

Table A.2. Partition Coefficients (PCs) for *cis*-permethrin

Age	Fat	Skeletal Muscle (thigh area; 48-hr)	Skeletal Muscle (thigh area; 72-hr)	Brain (48-hr)	Brain (72-hr)	Liver (48-hr)	Liver (72-hr)
PND15	--	2.39	4.02	0.94	1.14	1.07	1.39
PND21	--	3.98	7.09	0.63	1.0	0.50	0.76
Adult	88.0	--	3.43	--	0.65	--	0.30

-- : No measurement taken

MRID 49916407: *Trans*-permethrin: assessment of partition coefficients

The objective of this study was to determine tissue:plasma partition coefficients for *trans*-permethrin (TRANS) for brain, liver, skeletal muscle and fat in PND15 and PND21 rat pups and PND90 adult male Sprague-Dawley rats. An oral loading dose coupled with constant infusion of TRANS provided systemic steady-state or equilibrium of the chemical in PND21 pups and adult rats. Only constant infusion of TRANS was used for PND15 pups due to toxicity observed with the combination of the oral dose and then constant infusion. An Alzet® infusion pump containing CIS was surgically implanted subcutaneously (SC) on the dorsum of members of these age-groups, with constant infusions of 0.36 mg TRANS/hr in the adult rats or 0.05 mg TRANS/hr in the PND21 rat pups and PND15 rat pups. Three to four hours post-start, PND21 pups and adult rats were gavaged with 1.15 mg TRANS/kg and 150 mg TRANS/kg, respectively. Adult rats were euthanized at 72 hr and PND15 and PND21 pups were euthanized at 48 and 72 hr. TRANS concentrations were measured by high performance liquid chromatography (HPLC) or gas chromatography-negative chemical ionization-mass spectrometry (GC-NCI-MS).

TRANS distributed evenly between red blood cells (RBC) and plasma for adult rats and equilibrium was achieved within 1 hour and maintained for the duration of the study (72 hr). TRANS was distributed throughout the tissues based on lipid content. Adipose tissue was not visible for PND15 and PND21 pups, which should be taken into account during PBPK modeling. Partition coefficients are listed in the table below.

Table A.3. Partition Coefficients (PCs) for *cis*-permethrin							
Age	**Fat**	**Skeletal Muscle (thigh area; 48-hr)**	**Skeletal Muscle (thigh area; 72-hr)**	**Brain (48-hr)**	**Brain (72-hr)**	**Liver (48-hr)**	**Liver (72-hr)**
PND15	--	2.84	5.41	0.49	0.53	1.15	1.59
PND21	--	1.35	1.15	0.39	0.49	0.02	0.12
Adult	44.7	--	1.53	--	2.18	--	0.06

-- : No measurement taken

MRID 49817601: Deltamethrin: assessment of age differences in rat plasma protein binding

The ability of deltamethrin (DLM) to bind to proteins and lipoproteins in rat plasma (Sprague-Dawley) was examined. Four age groups were assessed: post-natal day (PND) 10, 15, 21, and 90. Concentrations of ^{14}C-DLM (250 nM to 100 µM) were incubated with rat plasma for 3 hours at 37°C and then extracted to isolate unbound, lipoprotein-bound, and protein bound fractions. Radioactivity was measured with a liquid scintillation counter, and specific activity was used to determine the DLM concentration in each fraction. Albumin and total plasma proteins were measured for each age group.

Binding capacity (B_{max}) of DLM to the plasma as well as to plasma proteins is lower in PND10 and PND15 pups compared to PND21 pups and adult (PND90) rats. However, binding of DLM to lipoproteins was significantly increased in the PND10 pups compare to adult rats. In PND21 pups and adult rats, 20% remained unbound, ~50% bound to plasma protein, and ~30% bound to lipoprotein. In PND 10 and PND15 pups, 30-50% remained unbound; this greater unbound fraction can lead to increased diffusion of deltamethrin from the blood to many sites including fat, liver, and brain. Albumin levels were significantly lower in PND10 and PND15 pups compared to PND21 pups and adult rats. Additionally, total protein was significantly lowered in all juvenile age groups (PND10-21) and may contribute to altered systemic disposition of the chemical in young pups.

The percent binding decreased with an increase of DLM concentration. Adult plasma had the greatest extent of binding over a wide range of DLM concentrations, while PND10 pup plasma had the lowest binding. Binding to plasma proteins decreased more than binding to lipoproteins with an increase in DLM concentration, suggesting that lipoproteins can take up and retain DLM when protein binding becomes saturated.

<u>Conclusion:</u> Age-related differences in binding of DLM to plasma proteins and lipoproteins should only have a significant impact on the disposition of DLM in rats younger than 21 - days.

MRID 49817605: Deltamethrin: assessment of age differences in human plasma protein binding

The ability of deltamethrin (DLM) to bind to proteins and lipoproteins in human plasma was examined. Seven age groups were assessed: birth to 1 week; >1 week to 4 weeks; >4 weeks to 1 year; >1 year to 3 years; >3 years to 6 years; >6 years to 18 years; and >18 years (adults). Concentrations of ^{14}C-DLM (250 nM to 100 µM) were incubated with human

plasma for 3 hours at 37°C and then extracted to isolate unbound, lipoprotein-bound and protein bound fractions. Radioactivity was measured with a liquid scintillation counter, and specific activity was used to determine the DLM concentration in each fraction. Albumin and total plasma proteins were measured for each age group. Total binding (%) was constant from 250-750 nM DLM in plasma of all age-groups. Once DLM binding occurs at >4 weeks of age adults, 10% of DLM remained unbound, ~55% bound to plasma proteins, and ~35% bound to lipoprotein. Percent binding reached and remained at adult levels in infants >4 weeks of age. Lipoprotein binding remained constant with age, so plasma proteins must contribute to the early increase in binding. Albumin comprised 62-78% of total plasma proteins throughout human maturation.

The percent binding decreased with an increase of DLM concentration. Adult plasma had the greatest extent of binding over a wide range of DLM concentrations, while neonatal plasma had the lowest binding. Binding to plasma proteins decreased more than binding to lipoproteins with an increase in DLM concentration, suggesting that lipoproteins can take up and retain DLM when protein binding becomes saturated.

Conclusion: Age-related differences in binding of DLM to plasma proteins and lipoproteins should not have a significant impact on the disposition of DLM in children and infants older than 4 weeks of age.

MRID 49840701: *Cis*-permethrin: assessment of age differences in rat plasma protein binding

The ability of *cis*-permethrin (CIS) to bind to proteins and lipoproteins in rat plasma (Sprague-Dawley) was examined. Four age groups were assessed: post-natal day (PND) 10, 15, 21, and 90. Concentrations of ^{14}C-CIS (250 nM to 100 µM) were incubated with rat plasma for 3 hours at 37°C and then extracted to isolate unbound, lipoprotein-bound and protein bound fractions. Radioactivity was measured with a liquid scintillation counter, and specific activity was used to determine the CIS concentration in each fraction. Albumin and total plasma proteins were measured for each age group.

Binding capacity (B_{max}) of CIS to the plasma as well as to plasma proteins is lower in PND10 and PND15 pups compared to PND21 pups and adult (PND90) rats, with saturation in plasma proteins occurring at 10 and 50 µM for PND10 and PND15 pups, respectively. However, binding of CIS to lipoproteins was significantly increased in the PND10 pups compared to adult rats. In PND21 pups and adult rats, 20% remained unbound, ~50% bound to plasma protein, and ~30% bound to lipoprotein. In PND 10 and PND15 pups, ~30% remained unbound; this greater unbound fraction can lead to increased diffusion of deltamethrin from the blood to many sites including fat, liver, and brain. Albumin levels were significantly lower in PND10 and PND15 pups compared to PND21 pups and adult rats. Additionally, total protein was significantly lowered in all juvenile age groups (PND10-21) and may contribute to altered systemic disposition of the chemical in young pups.
The percent binding decreased with an increase of CIS concentration. Adult plasma had the greatest extent of binding over a wide range of CIS concentrations, while PND10 pup plasma had the lowest binding. Binding to plasma proteins decreased more than binding to

lipoproteins with an increase in CIS concentration, suggesting that lipoproteins can take up and retain CIS when protein binding becomes saturated.

Conclusion: Age-related differences in binding of CIS to plasma proteins and lipoproteins should not have a significant impact on the systemic disposition of CIS in rats older than PND 21.

MRID 49817602: *Cis*-permethrin: assessment of age differences in human plasma protein binding

The ability of *cis*-permethrin (CIS) to bind to proteins and lipoproteins in human plasma was examined. Seven age groups were assessed: birth to 1 week; >1 week to 4 weeks; >4 weeks to 1 year; >1 year to 3 years; >3 years to 6 years; >6 years to 18 years; and >18 years (adults). Concentrations of ^{14}C-CIS (250 nM to 100 µM) were incubated with human plasma for 3 hours at 37°C and then extracted to isolate unbound, lipoprotein-bound and protein bound fractions. Radioactivity was measured with a liquid scintillation counter, and specific activity was used to determine the CIS concentration in each fraction. Albumin and total plasma proteins were measured for each age group. Total binding (%) was constant from 250-750 nM CIS in plasma of adults and from 250-500 nM CIS for all younger age-groups. Once maturity of CIS binding occurs at >4 weeks of age adults, 10% of CIS remained unbound, ~55% bound to plasma proteins, and ~35% bound to lipoprotein. Percent binding reached and remained at adult levels in infants >4 weeks of age. Lipoprotein binding remained constant with age, so plasma proteins must contribute to the early increase in binding. Albumin comprised 62-78% of total plasma proteins throughout human maturation. The percent binding decreased with an increase of CIS concentration. Adult plasma had the greatest extent of binding over a wide range of CIS concentrations, while neonatal plasma had the lowest binding. Binding to plasma proteins decreased more than binding to lipoproteins with an increase in CIS concentration, suggesting that lipoproteins can take up and retain CIS when protein binding becomes saturated.

Conclusion: Age-related differences in binding of CIS to plasma proteins and lipoproteins should not have a significant impact on the disposition of CIS in children and infants older than 4 weeks of age.

MRID 49840707: *Trans*-permethrin: assessment of age difference in rat plasma protein binding

The ability of *trans*-permethrin (TRANS) to bind to proteins and lipoproteins in rat plasma (Sprague-Dawley) was examined. Four age groups were assessed: post-natal day (PND) 10, 15, 21, and 90. Concentrations of ^{14}C-TRANS (250 nM to 100 µM) were incubated with rat plasma for 3 hours at 37°C and then extracted to isolate unbound, lipoprotein-bound and protein bound fractions. Radioactivity was measured with a liquid scintillation counter, and specific activity was used to determine the TRANS concentration in each fraction. Albumin and total plasma proteins were measured for each age group.

Binding capacity (B_{max}) of TRANS to the plasma as well as to plasma proteins is lower in PND10 and PND15 pups compared to PND21 pups and adult (PND90) rats, with saturation in plasma proteins occurring at 10 and 50 µM for PND10 and PND15 pups, respectively.

However, binding of TRANS to lipoproteins was significantly increased in the PND10 pups compared to adult rats. In PND21 pups and adult rats, 20% remained unbound, ~50% bound to plasma protein, and ~30% bound to lipoprotein. In PND 10 and PND15 pups, ~30% remained unbound; this greater unbound fraction can lead to increased diffusion of deltamethrin from the blood to many sites including fat, liver, and brain. Albumin levels were significantly lower in PND10 and PND15 pups compared to PND21 pups and adult rats. Additionally, total protein was significantly lowered in all juvenile age groups (PND10-21) and may contribute to altered systemic disposition of the chemical in young pups.
The percent binding decreased with an increase of TRANS concentration. Adult plasma had the greatest extent of binding over a wide range of TRANS concentrations, while PND10 pup plasma had the lowest binding. Binding to plasma proteins decreased more than binding to lipoproteins with an increase in TRANS concentration, suggesting that lipoproteins can take up and retain CIS when protein binding becomes saturated.

Conclusion: Age-related differences in binding of TRANS to plasma proteins and lipoproteins should not have a significant impact on the systemic disposition of TRANS in rats older than PND 21.

MRID 49840702: *Trans*-permethrin: assessment of age differences in human plasma protein binding

The ability of *trans*-permethrin (TRANS) to bind to proteins and lipoproteins in human plasma was examined. Seven age groups were assessed: birth to 1 week; >1 week to 4 weeks; >4 weeks to 1 year; >1 year to 3 years; >3 years to 6 years; >6 years to 18 years; and >18 years (adults). Concentrations of ^{14}C-TRANS (250 nM to 100 µM) were incubated with human plasma for 3 hours at 37°C and then extracted to isolate unbound, lipoprotein-bound and protein bound fractions. Radioactivity was measured with a liquid scintillation counter, and specific activity was used to determine the TRANS concentration in each fraction. Albumin and total plasma proteins were measured for each age group. Total binding (%) was constant from 250-750 nM TRANS in plasma of adults and from 250-500 nM TRANS for all younger age-groups. Once maturity of TRANS binding occurs at >4 weeks of age adults, 12-15% of TRANS remained unbound, 55-60% bound to plasma proteins, and 26-33% bound to lipoprotein. Percent binding reached and remained at adult levels in infants >4 weeks of age. Lipoprotein binding remained constant with age, so plasma proteins must contribute to the early increase in binding. Albumin comprised 62-78% of total plasma proteins throughout human maturation.

The percent binding decreased with an increase of TRANS concentration. Adult plasma had the greatest extent of binding over a wide range of TRANS concentrations, while neonatal plasma had the lowest binding. Binding to plasma proteins decreased more than binding to lipoproteins with an increase in TRANS concentration, suggesting that lipoproteins can take up and retain TRANS when protein binding becomes saturated.

Conclusion: Age-related differences in binding of TRANS to plasma proteins and lipoproteins should not have a significant impact on the disposition of TRANS in children and infants older than 4 weeks of age.

MRID 49817604: Investigation of the potential role of gastrointestinal membrane transporters in deltamethrin absorption

Caco-2 cells were used to establish the intestinal permeability and transport properties of DLM. Caco-2 cell monolayers were grown for 21 days to confluency on plates to assess cellular uptake of DLM and R6G [a p-glycoprotein (P-gp) substrate] in the presence and absence of P-gp inhibitors. Caco-2 cell monolayers were also grown on inserts in a Transwell® system, which allowed R6G and DLM influx and efflux to be characterized qualitatively and quantitatively. To further assess the potential P-gp transport properties of DLM, MDCK-MDR1 and wild type MDCK cells, which overexpress P-gp, were grown.

DLM accumulation in caco-2, MDCK-MDR1, and MDCK cells was significantly reduced by CSA and RTV, well-established P-gp inhibitors, suggesting involvement of an influx transport system. Transepithelial flux of deltamethrin was significantly higher apical (AP) to basolateral (BL) direction compared to the BL to AP direction. Papp value ratio was 0.4 (>1: efflux transportation; <1: influx transportation; ~1: passive transportation), thus DLM is transported by influx processes and has limited GI absorption *in vivo.*

MRID 49821808: Investigation of the potential role of gastrointestinal membrane transporters in *cis*-permethrin absorption

Caco-2 cells were used to establish the intestinal permeability and transport properties of CIS. Caco-2 cell monolayers were grown for 21 days to confluency on plates to assess cellular uptake of CIS and R6G [a p-glycoprotein (P-gp) substrate] in the presence and absence of P-gp inhibitors. Caco-2 cell monolayers were also grown on inserts in a Transwell® system, which allowed R6G and CIS influx and efflux to be characterized qualitatively and quantitatively.

CIS did not change R6G accumulation, suggesting CIS is not a P-gp inhibitor. Additionally, CSA (P-gp inhibitor cyclosporine) and RTV (P-gp inhibitor ritonavir) reduced CIS accumulation, suggesting inhibition of an influx transport process. Transepithelial flux of CIS was significantly higher apical (AP) to basolateral (BL) direction compared to the BL to AP direction. Papp value ratio was 0.51 (>1: efflux transportation; <1: influx transportation; ~1: passive transportation), thus CIS is transported by influx processes and has limited GI absorption *in vivo.*

MRID 49821809: Investigation of the potential role of gastrointestinal membrane transporters in *trans*-permethrin absorption

Caco-2 cells were used to establish the intestinal permeability and transport properties of TRANS. Caco-2 cell monolayers were grown for 21 days to confluency on plates to assess cellular uptake of TRANS and R6G [a p-glycoprotein (P-gp) substrate] in the presence and absence of P-gp inhibitors. Caco-2 cell monolayers were also grown on inserts in a Transwell® system, which allowed R6G and TRANS influx and efflux to be characterized qualitatively and quantitatively.

TRANS did not change R6G accumulation, suggesting TRANS is not a P-gp inhibitor. Additionally, CSA (P-gp inhibitor cyclosporine) and RTV (P-gp inhibitor ritonavir) reduced TRANS accumulation, suggesting inhibition of an influx transport process. Transepithelial

flux of TRANS was significantly higher apical (AP) to basolateral (BL) direction compared to the BL to AP direction. Papp value ratio was 0.64 (>1: efflux transportation; <1: influx transportation; ~1: passive transportation), thus TRANS is transported by influx processes and has limited GI absorption *in vivo*.

MRID 49916405: Deltamethrin: Determination of rates of metabolism of deltamethrin by tissue preparations from 15, 21, and 90-day old rats

The objective of this study was to determine rates of metabolism of deltamethrin (DLM) by liver microsome and cytosol preparations and by plasma preparations from male Sprague-Dawley rats aged 15, 21 and 90 days. The metabolism of DLM in liver microsome and cytosol preparations was determined with target DLM substrate concentrations of 0.1, 0.3,1, 3 and 10 µM. Incubations with liver microsomes were performed in both the presence (to determine metabolism by both CYP and CES enzymes) and absence (CES enzymes only) of NADPH. Rates of metabolism of DLM by hepatic microsomal CYP enzymes were greater than rates of DLM metabolism by microsomal CES enzymes. Liver microsome, liver cytosol and plasma preparations CL_{int} values for DLM metabolism were lowest in 15-day old rats and greatest in 90-day old rats, demonstrating that the metabolism of DLM is impaired in young rats compared to adults.

Table A.4. Average (±SD) kinetic data for total DLM metabolism (CYP and CES enzymes) by liver microsomes from 15, 21 and 90-day old rats

Age	Kinetic parameter		
	Cl_{int} (µl/min/mg protein)	K_m (µM)	V_{max} (pmol/min/mg protein)
PND15	67.29±15.73	1.062±0.249	69.59±14.34
PND21	225.55±77.68	1.089±0.628	214.27±70.07
PND90	503.26±109.75	0.631±0.340	292.70±99.35

Table A5. Average (±SD) kinetic data for DLM metabolism by CYP and CES enzymes in liver microsomes from 15, 21 and 90-day old rats

Enzyme Activity	Age	Kinetic parameter		
		Cl_{int} (µl/min/mg protein)	K_m (µM)	V_{max} (pmol/min/mg protein)
CYP Enzymes	PND15	59.96±12.94	0.932±.0130	54.51±7.14
	PND21	185.30±66.19	1.334±0.836	211.15±89.79
	PND90	438.92±90.58	0.579±0.363	232.39±101.12
CES Enzymes	PND15	11.10±1.89	1.4381±1.486	15.83±17.03
	PND21	43.10±11.86	0.411±0.055	17.65±5.46
	PND90	68.75±22.72	0.937±0.093	64.14±21.45

MRID 49916404: Deltamethrin: comparison of rates of metabolism of deltamethrin by rat hepatocytes and liver subcellular fraction

The objective of this study was to compare rates of metabolism of deltamethrin (DLM) in male Sprague-Dawley rat (PND90) hepatocytes with rates of metabolism in liver microsomes and cytosol. The metabolism of 0.05, 0.1, 0.3, and 1 µM DLM in rat hepatocytes and in liver microsomes and cytosol was determined by loss of substrate with time of incubation. Incubations with liver microsomes were performed in the presence of NADPH to determine DLM metabolism by both cytochrome P450 (CYP) and carboxylesterase (CES) enzymes, whereas incubations with liver cytosol were performed in the absence of NADPH (CES enzymes only). Bifenthrin was used as the internal standard for analysis of DLM in rat hepatocyte and liver microsome and cytosol incubate extracts. The mean (±SD) of unbound CL_{int} was 0.2045±0.0399 ml/min/1x10^6 viable cells, and the mean (±SD) affinity constant was 3.8597±1.0544 Ka. Metabolism rates of DLM with the CRL liver microsome and cytosol preparation varied from 1.14-1.68 fold, while metabolism rates of DLM with the LFR liver microsome and cytosol preparation varied from 1.19-1.29 fold. With both liver preparations, the rate of metabolism in the hepatocytes was similar to the rate of the microsomes, suggesting that uptake into hepatocytes may not be a major factor in determining the overall rate of *in vivo* metabolism of DLM in the rat.

MRID 49916403: Deltamethrin: development of a microassay to determine rates of metabolism of deltamethrin by liver preparations from humans of various ages

The objective of this study was to develop a microassay for the metabolism of deltamethrin (DLM) by human liver microsomal and cytosolic preparations. DLM metabolism was determined by loss of substrate in incubations with human liver microsome and cytosol preparations (150 donor pools). Incubations with human liver microsomes were performed in the presence and absence of NADPH, but incubations with liver cytosol were performed in the absence of NADPH only. This assay uses flat bottomed clear glass screw capped 1.5 ml vials with separate incubations conducted for each time point in a shaking water bath at 37˚C. For both human liver microsomes and cytosol, apparent CL_{int} values decreased with increasing protein concentration in the incubation mixtures.

MRID 49916402: Deltamethrin and cis- and trans- permethrin: studies on the kinetics of deltamethrin and cis- and trans- permethrin metabolism by rat and human liver microsomes

The objective of this study was to determine rates of metabolism of deltamethrin (DLM) and cis- and trans-permethrin by rat and human liver microsomal preparations. In both rat and human liver microsomes, rates of metabolism of DLM, CIS and TRANS decreased with increasing microsomal protein concentration from 0.1 to 1.0 mg protein/ml incubation mixture. DLM, CIS and TRANS exhibit nonspecific binding to liver microsomes, especially at higher concentrations.

MRID 49916406: Determination of human hepatic CES1 and CES2 age-dependent developmental expression patterns in postnatal ages birth to 18 years

Human CES1 and CES2 are expressed in both hepatic microsomal and cytosolic compartments; moreover, this expression is dependent on age. Expression of both enzymes is lower among infants 3 weeks of age or less compared to older infants and children.

Furthermore, microsomal CES1 and cytosolic CES2 do not exhibit any additional age-related differences. However, expression of microsomal CES2 and cytosolic CES1 is significantly decreased in infants of 3 weeks of age to 6 years of age, suggesting major changes occur during this developmental window. Microsomal and cytosolic CES1 have greater variance (30- and 70-fold, respectively) compared to microsomal and cytosolic CES2 (11- and 8-fold, respectively). Additionally, CES1 expression varies more than CES2 across age-groups. When assessed independent of age or any other factors, race/ethnicity appeared to have an association with microsomal CES1 and CES2 protein expression. Caucasians had greater microsomal CES1 expression than those from African Americans, which had a greater expression than Hispanics. Microsomal CES2 expression showed the same pattern as microsomal CES1 expression. Cytosolic CES1 was also greater in Caucasians compared to African Americans, but there was no difference in expression of cytosolic CES2.

MRID 49817603: Investigation of blood brain barrier transport of deltamethrin

The human brain microvessel endothelial cell line (hCMEC/D3) that displays many BBB marker and most properties of brain endothelium *in vivo*. Experiments were conducted with a substrate (Paclitaxel; PTX) and an inhibitor (Cyclosporine A; CSA) of the P-glycoprotein (P-gp) efflux transporter. DLM did not cause any change of PTX accumulation suggesting DLM is not a P-gp inhibitor. P-gp does not mediate the efflux of DLM from human brain endothelial cells. Uptake by hCMEC cells was dependent on the free fraction of DLM available for transport. Influx transport of DLM is only functional at high free fraction of DLM (~60%); however, at physiologically relevant human serum albumin (HAS) concentrations and levels of unbound DLM (~10%), a linear passive diffusion process occurs.

MRID 49840710: Toxicokinetic assessment of blood and tissue deltamethrin concentrations following the administration of a single oral dose to 15-day-old pups

The objective of this study was to characterize the toxicokinetics (TK) of deltamethrin (DLM) in 15-day-old Sprague-Dawley rats to obtain comprehensive plasma and tissue time-course concentration data to support PBPK modeling. DLM exhibited dose-dependent TK in PND15 pups, as plasma levels increased with an increase in dose with a maximum concentration (C_{max}) at 2-4 hours. The half-life was similar for all doses (212-252 minutes). The C_{max} for the 0.25 and 0.5 mg/kg doses were proportional to dose; however, the C_{max} for the 0.1 mg/kg dose was lower than expected partially due to either lower GI absorption and/or an increase in first pass metabolism. Oral clearance (Cl/F) ranged from 4.6-9.6 ml/min. Peak brain concentrations occurred 3-6 hours post-dosing and increased with an increase in dose. The AUC ratio for the lowest dose was 0.29 indicating greater relative brain exposure. Plasma concentrations at the mid- and high-dose groups were higher than brain concentrations, suggesting saturation of uptake processes into the brain. Liver C_{max} and AUC increased disproportionately with dose; however, the half-lives were comparable for all doses.

MRID 49840709: Toxicokinetic assessment of blood and tissue deltamethrin concentrations following the administration of a single oral dose to 21-day-old pups

The objective of this study was to characterize the toxicokinetics (TK) of deltamethrin (DLM) in 21-day-old Sprague-Dawley rats to obtain comprehensive plasma and tissue time-

course concentration data to support PBPK modeling. DLM exhibited dose-dependent TK in PND21 pups, as plasma levels increased with an increase in dose with a maximum concentration (C_{max}) at 2-4 hours. The half-life was similar for all doses (287-418 minutes). The plasma C_{max} for the 0.25 and 0.5 mg/kg doses were proportional to dose; however, the C_{max} for the 0.1 mg/kg dose was higher than that of the mid dose. Oral clearance (Cl/F) ranged from 3.5-13.6 ml/min, with the low dose having the lowest oral clearance, suggesting either clearance decreased and/or bioavailability increased. There was a dose-dependent clearance in the brain with a C_{max} of 6-8 hours for 0.1mg/kg and 0.25 mg/kg and 2 hrs for 0.5 mg/kg. Brain concentrations increased more slowly than plasma concentrations. Liver C_{max} and AUC increased disproportionately with dose; however, the half-lives were comparable for all doses.

MRID 49840708: Toxicokinetic assessment of blood and tissue deltamethrin concentrations following the administration of a single oral dose to mature rats

The objective of this study was to characterize the toxicokinetics (TK) of deltamethrin (DLM) in adult Sprague-Dawley rats to obtain comprehensive plasma and tissue time-course concentration data to support PBPK modeling. DLM exhibited dose-dependent TK in adults, as plasma levels increased with an increase in dose. Concentration of DLM increased for 4-5 hours, plateaued, and then slowly eliminated for ≥8 hours. No detectable concentrations of DLM were found in the brain at 0.1 mg/kg dose or in the liver at 0.1 mg/kg and 0.25 mg/kg. Liver area under the curve (AUC) and maximum concentration (C_{max}) increased disproportionally with dose. Fat concentrations increased with dose. Brain, muscle, and liver had longer residence times compared to plasma.

MRID 49884604: Toxicokinetic assessment of blood and tissue trans-permethrin concentrations following the administration of a single oral dose to 15 day old rats

The objective of this study was to characterize the toxicokinetics (TK) of *trans*-permethrin (TRANS) in 15-day-old Sprague-Dawley rats to obtain comprehensive plasma and tissue time-course concentration data to support PBPK modeling. Oral clearance was similar for all doses (3.01-4.39 L/h). The half-life for plasma and brain in the highest dose tested (600 mg/kg) was approximately 2-fold higher than that for the lower doses. Peak plasma concentrations occurred at 2 hours post-dose, while peak brain concentrations occurred at 4 hours post dose and ranged from 6.76-7.14 µg/g. Muscle T_{max} and C_{max} did not increase with dose but AUC increased with dose. Liver concentration-time profiles had the same pattern as plasma but had higher concentrations. The muscle AUCs were greater than brain and plasma, suggesting greater uptake in the muscle.

MRID 49884603: Toxicokinetic assessment of blood and tissue trans-permethrin concentrations following the administration of a single oral dose to 21 day old rats

The objective of this study was to characterize the toxicokinetics (TK) of *trans*-permethrin (TRANS) in 21-day-old Sprague-Dawley rats to obtain comprehensive plasma and tissue time-course concentration data to support PBPK modeling. Oral clearance was similar for the 300 and 450 mg/kg doses but doubled for the 600 mg/kg dose. Peak plasma concentrations occurred at 2 hours with a maximum concentration (C_{max}) similar for all doses, suggesting saturation in absorption. Peak brain concentrations occurred at 4 hours post dose. Brain AUC and C_{max} increases with dose with AUC increasing 3-fold with a 50% increase in dose,

suggesting an increase in residence time. Liver C_{max} occurred during the first time point, so the study may have missed C_{max}. The muscle AUCs were greater than brain and plasma, suggesting greater uptake in the muscle.

MRID 49884602: Toxicokinetic assessment of blood and tissue trans-permethrin concentrations following the administration of a single oral dose to adult rats

The objective of this study was to characterize the toxicokinetics (TK) of *trans*-permethrin (TRANS) in adult Sprague-Dawley rats to obtain comprehensive plasma and tissue time-course concentration data to support PBPK modeling. Plasma, brain, liver, and muscle concentrations paralleled one another with a peak concentration after 4-6 hours for the highest dose tested (300 mg/kg). TRANS levels in liver, brain, or muscle could not be reliably detected in the lowest two dose groups (120 and 150 mg/kg); however, levels in fat increased progressively and plateaued at 12 hours post-dose with concentrations three times that of plasma with no clearance during the test window. Oral clearance was similar at the lowest 2 doses but increased ~40% for the 300 mg/kg dose suggesting either clearance increased or bioavailability decreased.

MRID 49884601: Toxicokinetic assessment of blood and tissue cis-permethrin concentrations following the administration of a single oral dose to 15-day old rats

The objective of this study was to characterize the toxicokinetics (TK) of *cis*-permethrin (CIS) in 15-day-old Sprague-Dawley rats to obtain comprehensive plasma and tissue time-course concentration data to support PBPK modeling. Plasma AUC increased proportionately with an increase in dose. Oral clearance was similar for all doses (1.3-2.0 L/h). Plasma concentrations peaked at 2-4 hour post-dosing and had half-lives of 1.8-4 hours. Brain C_{max} and AUC increased proportionately with an increase in dose. Brain C_{max} was achieved at 6-8 hours and was equivalent to plasma C_{max} for the two higher doses, the low dose was 50% higher than plasma. Liver concentrations followed the same pattern as the plasma concentrations; however, liver C_{max} was 2-3-fold higher than plasma. Muscle C_{max} was higher than plasma and had a longer half-life, suggesting uptake and retention in muscle. Fat was not measurable in 15-day old rats.

MRID 49840703: Toxicokinetic assessment of blood and tissue cis-permethrin concentrations following the administration of a single oral dose to 21-day old rats

The objective of this study was to characterize the toxicokinetics (TK) of *cis*-permethrin (CIS) in 21-day-old Sprague-Dawley rats to obtain comprehensive plasma and tissue time-course concentration data to support PBPK modeling. The plasma TK profile was similar for all doses tested with a peak plasma concentration at 2-4 hours post-dose. Plasma AUC was similar for all doses, for oral clearance increased with an increase in dose. Peak brain concentrations occurred at 4-6 hours post-dose. Brain AUC and C_{max} were approximately equal for the two lowest doses tested but increased at the highest concentration tested. Liver AUC paralleled plasma AUC but were higher. The muscle C_{max} were greater than brain and plasma, suggesting greater uptake in the muscle. Fat was not measurable in 21-day old rats.

MRID 49840704: Toxicokinetic assessment of blood and tissue cis-permethrin concentrations following the administration of a single oral dose to mature rats

The objective of this study was to characterize the toxicokinetics (TK) of *cis*-permethrin (CIS) in adult Sprague-Dawley rats to obtain comprehensive plasma and tissue time-course concentration data to support PBPK modeling. Plasma AUC increased proportionately with increase in dose, and the oral clearance was equivalent for all 3 doses tested. Liver profile paralleled the plasma profile but at a higher concentration. Peak concentrations in the muscle and brain occurred at 6-8 hours. Fat concentrations increased throughout the 24-hour monitoring period. Liver and brain C_{max} changed disproportionately with dose. AUC values suggested that liver and brain concentrations were saturated at the 90 and 120 mg/kg doses.

MRID 49916401: Effects of pyrethroids on human sodium channels co-expressed with beta-1 and beta-2 subunits

The effects of 9 pyrethroids (cypermethrin, bifenthrin, pyrethrum, prallethrin, permethrin, esfenvalerate, deltamethrin, tefluthrin, and allethrin) on human sodium channels commonly found in the young and adult central nervous system were examined *in vitro*. The study uses HEK cells stably expressing the alpha subunit of 4 isoforms of VGSC (Nav1.1, 1.2, 1.3 and 1.6). These cells were then transfected with a plasmid containing the beta 1 and beta 2 subunits, which are the common beta subunits in adult brain. There was no successful demonstration of the presence of beta1 protein using western blots. Although this could be due to lack of a suitable antibody the electrophysiology also does not support expression of this subunit, as rather than causing a hyperpolarizing shift in Nav1.3 current of 10-13 mV, a depolarizing shift of ~3mV was observed in cells transfected with beta subunits. Deltamethrin, cypermethrin and permethrin were all generally without effects on sodium currents of any type. The conclusions of the report are not informative. However, given the overall uncertainty in the report, it is unlikely that the results can be informative regarding toxicodynamic differences in age-sensitivity.

MRID 50600302: Cispermethrin: a study to determine the kinetics of metabolism of cyphenothrin in rat and human plasma, rat and human liver microsomes and rat and human liver cytosol

The purpose of this study was to assess the kinetics of metabolism of *cis*-permethrin in human and rat liver microsomes, human and rat liver cytosol and human and rat plasma. The human tissue preparations were comprised of commercially available pools of liver microsome, liver cytosol and plasma, while the rat tissue preparations were comprised of liver microsomes, liver cytosol and plasma from male Sprague-Dawley rats (PND 15, 21, and 90). Cytochrome P450 (CYP) and carboxylesterase enzymes (CES) were investigated as well as metabolism in the presence of NADPH. CYP only metabolism was estimated by examining the difference between with NADPH and without NADPH metabolic rates.

Cis-permethrin was predominantly metabolized by CYP enzymes in all three ages of rat liver assessed but was predominantly metabolized by CES enzymes in human liver microsomes. Metabolism was highest in the 90-day rat liver microsomes, cytosol and plasma and lowest in the 15-day rat liver microsomes, cytosol and plasma. In human liver microsomes, metabolism by CES enzymes was 59% of the rate from CYP enzymes. Metabolism was not observed in human plasma.

MRID 50600304: Deltamethrin: a study to determine the kinetics of metabolism of deltamethrin in rat and human plasma, rat and human liver microsome and rat and human liver cytosol

The purpose of this study was to assess the kinetics of metabolism of deltamethrin in human and rat liver microsomes, human and rat liver cytosol and human and rat plasma. The human tissue preparations were comprised of commercially available pools of liver microsome, liver cytosol and plasma, while the rat tissue preparations were comprised of liver microsomes, liver cytosol and plasma from male Sprague-Dawley rats (PND 15, 21, and 90). Cytochrome P450 (CYP) and carboxylesterase enzymes (CES) were investigated as well as metabolism in the presence of NADPH. CYP only metabolism was estimated by examining the difference between with NADPH and without NADPH metabolic rates.

Deltamethrin was predominantly metabolized by CYP enzymes in all three ages of rat liver assessed but was predominantly metabolized by CES enzymes in human liver microsomes. Metabolism was highest in the 90-day rat liver microsomes, cytosol and plasma and lowest in the 15-day rat liver microsomes, cytosol and plasma. In human liver microsomes, metabolism was entirely due to CES enzymes, as rates could not be calculated for CYP enzymes.

Table A.6. Additional Studies received by the Agency		
Study Title	**EPA MRID**	**EPA Pin Punch Date**
Application of Density Gradient Ultracentrifugation to Evaluate the Potential of Lipophilic Compounds to Associate with Plasma Lipoproteins and Utility to Estimate Lymphatic and Utility to Estimate Lymphatic Absorption in Rat	50400601	9/27/2017
Association of 14C-Deltamethrin to Rat Lipoproteins in vitro	50400602	9/27/2017
Investigation into the in vivo association of 14C-Deltamethrin with Rat Plasma Lipoproteins	50400603	9/27/2017
Sample Analysis: Analysis of Deltamethrin in Rat Plasma and Brain Tissue Samples by LC/MS/MS Final Report	50556804	3/27/2018
Sample Analysis: Analysis of Cis-Permethrin and Trans-Permethrin in Rat Plasma and Brain Tissue Samples by LC/MS/MS Final Report	50556806	3/27/2018
Cispermethrin: A Study to Determine the Kinetics of Metabolism of Cispermethrin in Selected Expressed Human Carboxylesterase (CES) and Cytochrome P450 (CYP) Enzymes	50609101	6/15/2018
Deltamethrin: A Study to Determine the Kinetics of Metabolism of Deltamethrin in Selected Expressed Human Carboxylesterase (CES) and Cytochrome P450 (CYP) Enzymes	50509102	6/15/2018
Trans-permethrin: A Study to Determine the Kinetics of Metabolism of Transpermethrin in Selected Expressed Human Carboxylesterase (CES) and Cytochrome P450 (CYP) Enzymes	50409103	6/15/2018

Table A.6. Additional Studies received by the Agency		
Study Title	**EPA MRID**	**EPA Pin Punch Date**
Bifenthrin: A Study to Determine the Kinetics of Metabolism of Bifenthrin in Rat and Human Plasma, Rat and Human Liver Microsomes and Rat and Human Liver Cytosol	50600301	6/1/2018
Cyphenothrin: A Study to Determine the Kinetics of Metabolism of Cyphenothrin in Rat and Human Plasma, Rat and Human Liver Microsomes and Rat and Human Liver Cytosol	50600303	6/1/2018
Esfenvalerate: A Study to Determine the Kinetics of Metabolism of Esfenvalerate in Rat and Human Plasma, Rat and Human Liver Microsomes and Rat and Human Liver Cytosol	50600305	6/1/2018
Transpermethrin: A Study to Determine the Kinetics of Metabolism of Transpermethrin in Rat and Human Plasma, Rat and Human Liver Microsomes and Rat and Human Liver Cytosol	50600306	6/1/2018
β-cyfluthrin: A Study to Determine the Kinetics of Metabolism of β-cyfluthrin in Rat and Human Plasma, Rat and Human Liver Microsomes and Rat and Human Liver Cytosol	50600307	6/1/2018
λ-Cyhalothrin: A Study to Determine the Kinetics of Metabolism of λ-Cyhalothrin in Rat and Human Plasma, Rat and Human Liver Microsomes and Rat and Human Liver Cytosol	50600308	6/1/2018