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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: **5/10/2012**

SUBJECT: **Prallethrin.** Human Health Assessment Scoping Document in Support of Registration Review

PC Code: 128722
Decision No.: 458525
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
MRID No.: NA

DP Barcode: D396742
Registration No.: NA
Regulatory Action: Registration Review
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CAS No.: 23031-36-9
40 CFR: 180.545

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Attached is the Health Effects Division's (HED) human health risk assessment scoping document for prallethrin to support registration review.

Executive Summary

The Health Effects Division Prallethrin Registration Review Team has evaluated the database and the most recent human health risk assessment for the insecticide prallethrin. HED performed this evaluation in order to determine the scope of work necessary to support the established tolerances and existing registrations during registration review. The primary source of information for this evaluation was the most recent human health risk assessment (D289335, M. Collantes and G. Bangs, 11/21/2003).

Prallethrin, (RS)-2-methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl(IR)-cis,trans-chrysanthemate, is a pyrethroid insecticide that is currently registered for the control of a variety of indoor and outdoor pests found in homes and commercial settings, including food handling establishments. It is also registered for the control of a number of veterinary and public health pests.

The toxicology database is sufficient for the characterization of a wide variety of toxic effects, including potential carcinogenic, mutagenic, developmental, and reproductive effects. As with the other members of the pyrethroid class, prallethrin causes neurotoxic effects that do not increase in severity with increasing duration. However, repeated exposure does lead to hepatotoxicity. Prallethrin is classified as "not likely" to be carcinogenic to humans. The prallethrin database lacks acceptable immunotoxicity and developmental neurotoxicity (DNT) studies. EPA has determined that DNTs for pyrethroid insecticides do not adequately characterize potential susceptibility of the young. In 2009, EPA stated that registrants who have not fulfilled requirements for the DNT may instead cite 6 previously submitted pyrethroid DNT studies, rather than conducting a full new study. The Agency recently issued a screening-level cumulative risk assessment for pyrethroid insecticides, and is in the process of developing a response to public comments. This may affect the data needed for prallethrin during registration review.

No new residue chemistry data are needed for the purpose of registration review. A tolerance of 1.0 ppm is established in 40CFR §180.545 for residues of prallethrin in or on all food items in food handling establishments where food and food products are held, processed, prepared, and/or served. During registration review, the tolerance expression should be revised to reflect the residues of concern for both coverage and compliance purposes.

Introduction

HED evaluated the most recent human health risk assessment for prallethrin in association with updates to its toxicity, exposure, and usage databases to determine if sufficient data are available, and if further updates are needed, to support registration review. The most recent human health risk assessment was performed in 2003 when the registrant proposed the use of prallethrin as a mosquito adulticide (D289335, M. Collantes and G. Bangs, 11/21/2003). In performing the 2003 risk assessment, HED used the latest Agency science policies and risk assessment methodologies.

Prallethrin is a pyrethroid insecticide that is currently registered for the control of a variety of indoor and outdoor pests found in homes and commercial settings, including food handling

establishments. It is also registered for the control of a number of veterinary and public health pests. In 40 CFR §180.545, a tolerance of 1.0 ppm is established for residues of prallethrin resulting from use in food handling establishments. The tolerance is established in terms of (RS)-2-methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl(IR)-cis,trans-chrysanthemate.

Registered formulations include pressurized sprays (aerosols) and liquids. They are packaged for application as space and surface sprays and as total release foggers. There are also spray, wipe, and shampoo formulations for use on dogs and horses. Because of the broad-spectrum insecticidal properties of prallethrin, many end-use products are labeled for use in multiple sites. To broaden the efficacy of prallethrin, the registrants have formulated it with a number of other insect control agents such as insecticide synergists (piperonyl butoxide and MGK 264) and other pyrethroids (sumithrin, esfenvalerate, etc.).

The structure, the chemical names, and other identifiers can be found in the chemical identity table in Attachment 1.

Hazard Identification/Toxicology

As with the other pyrethroids, prallethrin causes neurotoxicity in insects and mammals by the modulation of nerve axon sodium channels. Pyrethroids interfere with the ability of the nervous system to relay nerve transmissions, and in mammals, they can cause tremors, convulsions, salivation, and other clinical effects.

The scientific quality of the submitted studies is high, and the toxicity profile is sufficient for characterization of potential carcinogenic, mutagenic, developmental, and reproductive effects. In addition to the requisite guideline studies, a special functional observational battery (FOB) study has been conducted for several pyrethroids (D385562, 7/28/2011), including prallethrin. This study was conducted for the purpose of determining relative potency factors for the pyrethroid cumulative risk assessment (D394576, K. Whitby, 10/4/2011).

An immunotoxicity study has not been submitted and is therefore considered to be a data gap. OPP is conducting an independent retrospective analysis of more than 120 immunotoxicity studies submitted to the Agency. Preliminary findings of OPP's retrospective analysis suggest that immunotoxicity studies have not yet provided lower points of departure than those that are selected from other guideline experimental toxicology studies. As a result, to this point, immunotoxicity studies would not have impacted the Agency's risk assessments. The OPP retrospective analysis is anticipated to be completed in the summer of 2012. In the interim, HED recommends that the immunotoxicity studies continue to be required for registration and registration review chemicals.

In addition, a developmental neurotoxicity study was required in the last risk assessment. The Agency now allows pyrethroid registrants to cite the 6 pyrethroid DNT studies previously submitted to the Agency in lieu of conducting a new DNT study (Memo, R. Keigwin, Director, PRD/OPP, 9/4/09).

There is a complete series of acute (lethality) toxicity studies for prallethrin. These studies indicate that prallethrin is moderately acutely toxic to rats via the oral and inhalation route (Category II) but is not very acutely toxic via the dermal route (Category IV). It is mildly irritating to the eyes (Category III), non-irritating to the skin, and is not a dermal sensitizer.

The toxicity database indicates that there appear to be two major targets for this chemical: the neuromuscular system and the liver. The neuromuscular effects were characterized by the following; 1) clinical signs included tremors, ataxia, and exaggerated effects, 2) effects occurred across species, sexes, and routes of administration, and 3) effects did not increase in severity with increasing duration of exposure. All of these traits are typical of pyrethroids. The liver effects are seen in oral studies in rats, mice, and dogs. The effects were manifested as increased liver weight, serum cholesterol, and enzyme activity. Hepatic hypertrophy and other indications of histopathology were also noted. Most of these effects are likely to be due to induction of microsomal enzymes in the liver and might be more of a physiological response as opposed to an adverse toxicological effect. Other effects observed included decreased body weight, gross heart abnormalities in the female dog (i.e., miocardial fiber degeneration), and thyroid histology in the rat. These effects were either not dose-dependent or occurred at higher dose levels compared to the neurotoxicity and hepatotoxicity previously discussed. Other than the hepatoxicity, there were no indications of long-term or chronic toxicity. Prallethrin is classified as "not likely" to be carcinogenic to humans based on a lack of evidence for carcinogenicity in mice and rats and a lack of mutagenic activity.

There was no evidence of increased quantitative or qualitative susceptibility in the prallethrin toxicity database. In the prenatal developmental toxicity studies in rats and rabbits, no evidence of developmental toxicity was seen at any dose level. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity. Further, offspring effects were not considered to be more severe than those observed in the parental animals.

The Agency previously reduced the FQPA Safety Factor to 1x for prallethrin based on the overall completeness of the database and the absence of residual uncertainties for pre- and/or post-natal toxicity. However, the Agency has since determined that there is a potential for susceptibility of offspring to all pyrethroids based on evidence of age-dependent toxicity seen in literature studies (D381210, E. Scollon, 6/27/11). The young test animals appear to be more susceptible based on decreased metabolic capacity to detoxify pyrethroids. Furthermore, the Agency has recently conducted a cumulative risk assessment for pyrethroids based on their shared ability to interact with voltage-gated sodium channels. For the purpose of the pyrethroid cumulative risk assessment, HED retained a 3x FQPA Safety Factor for children, and supported reduction of the FQPA Safety Factor to 1x for adults. For new use assessments and during registration review, this approach (i.e., retention of the 3x FQPA Safety Factor for children) will have an impact on risk assessment for prallethrin.

In the most recent human health risk assessment for prallethrin, the point of departure for oral exposure was based on both neurotoxic and systemic endpoints. Dermal and inhalation risks were based on endpoints selected from the respective route-specific studies.

Hazard Conclusions

Based on the submitted toxicology data, there is only a data gap for an immunotoxicity study. With respect to the DNT study, the registrant is encouraged to cite the DNT studies completed for 6 other pyrethroid chemicals, in order to satisfy the requirement for a guideline study. During registration review, HED will consider the impact of the pyrethroid cumulative risk assessment on endpoint and dose selected for the single chemical assessment of prallethrin, and might select new endpoints and doses for risk assessment.

Dietary Exposure

The only registered food use for prallethrin is in food handling establishments where food and food products are held, processed, prepared, and/or served. The tolerance is set at 1.0 ppm. It is possible for residues to be found in drinking water as a result of the mosquito adulticide use. For the last risk assessment, EFED provided a drinking water assessment based on this use scenario. Acute and chronic estimated drinking water concentrations (EDWCs) were generated.

HED used the Dietary Exposure Evaluation Model (DEEM-FCID™ Version 2.03) to conduct the most recent acute and chronic dietary risk assessment for prallethrin. The DEEM-FCID™ Model incorporates consumption data from the USDA's Continuing Survey of Food Intakes by Individuals taken between 1994 and 1996 along with a supplemental children's survey taken in 1998. The dietary risk assessment was a partially refined assessment that was based on anticipated residues and an estimate of the percentage of food handling establishments that are treated. Drinking water concentrations were not directly incorporated into the assessment. At the time, HED was calculating drinking water levels of comparison (DWLOCs) and comparing them to the estimated drinking water concentrations (EDWCs) provided by EFED to determine whether or not the risk estimates were of concern.

Under current policy, HED does not include food handling establishment residues in acute dietary risk assessments. When the last risk assessment was performed in 2003, however, HED did include food handling residues in acute assessments. Acute dietary risk estimates were below HED's level of concern for the general U.S. population and all population subgroups. During registration review, HED might perform an acute dietary exposure assessment that includes residues in drinking water that result from the outdoor uses registered at that time.

Chronic dietary exposure resulted in an estimated risk of 3.5% of the cPAD (chronic population adjusted dose) for the general U.S. population. The most highly exposed population subgroup was All Infants < 1 year old, which used 6.7% of the cPAD. The chronic DWLOCs were all greater than the EDWCs. As a result, the chronic dietary risk estimates were not of concern.

For the 2003 dietary risk assessment, EFED provided conservative EDWCs in both surface water and groundwater (D274758, J. Melendez, 6/30/2003). EDWCs that were used in that risk assessment reflect exposure to parent prallethrin only. The tier 1 EDWCs for prallethrin were calculated using FIRST (Version1.0) for surface water and SCIGROW (Version 2.2) for groundwater. As the label does not stipulate the maximum number of applications per season or a minimum application interval for outdoor residential or public health uses, various runs were

performed with different numbers of applications (i.e., 150 and 365 daily applications). It was found that the peak and annual average value did not increase substantially. As a result, it was assumed that prallethrin would be applied daily for 365 days. The surface water acute and chronic EDWCs (0.591 ppb and 0.0375 ppb, respectively) were greater than the groundwater estimate of 0.00104 ppb, and were used for comparison to the DWLOCs. These values represent upper bound estimates of the concentrations that might be found in surface water and groundwater resulting from the use of prallethrin on outdoor residential sites at the maximum application rate. Prallethrin has a very high octanol/water partition coefficient. For this reason, HED does not anticipate that the EDWCs will increase significantly at any point in the future. HED also does not anticipate that residues in drinking water will contribute significantly to dietary exposure or risk estimates.

No residue chemistry data deficiencies were cited in the previous risk assessment for prallethrin.

Conclusions for Dietary Exposure

No new data are needed to assess potential dietary exposure and risk for prallethrin. However, during registration review, a new drinking water assessment might be needed to incorporate the use of the most current drinking water models. At the time of registration review, HED will compare the updated EDWCs and the endpoints selected for dietary risk assessment with those that were used in the last risk assessment. HED will then decide whether or not any differences in those values warrant a new dietary exposure assessment.

Residential Exposure

The residential products containing prallethrin include (1) indoor and outdoor sprays for crawling insect control (also used for crack and crevice treatments) on hard surfaces and carpets, (2) indoor and outdoor space sprays, (3) indoor total release foggers, (4) outdoor patio and yard foggers, (5) wasp and hornet sprays, and (6) sprays for controlling pests of pets and horses.

Residential Handler Exposures

A few prallethrin-containing products were assessed for residential handler exposure (D263377, M. Collantes, 2/17/2000). The products assessed include surface and crack and crevice treatments, space and pet sprays, and total release foggers. Based on the use pattern of these household products, handlers are expected to be exposed for short-term durations. The estimated risks for homeowners were all below HED's level of concern of a margin of exposure (MOE) of 100. Since the last risk assessment was performed, several products having higher percent active ingredient levels were registered and might require reassessment during registration review. In addition, updated policies and procedures for conducting residential exposure assessments might require an updated assessment for residential handlers.

Residential Postapplication Exposures

Postapplication exposure of adults and children resulting from the use of household sprays and pet products was assessed specifically for the following: (1) dermal exposure was assessed for

adults and children resulting from contact with treated indoor surfaces and pets, (2) oral exposure was assessed for children resulting from hand to mouth activity with indoor treated surfaces and pets, and (3) inhalation exposure was assessed for adults and children resulting from use of indoor surface sprays and total release foggers. All of the estimated MOEs were much higher than HED's level of concern of 100 and were not of concern.

The use of professional structural and public health products in residential and recreational settings results in short-term postapplication dermal exposure to adults and children, and short-term oral (i.e., hand-to-mouth) exposure to children. In an assessment of potential exposure and risk associated with the public health use of prallethrin as a mosquitocide, postapplication exposure resulted in MOEs >1000 for adults and children were not of concern. Residential postapplication exposures from use of structural pest control products by professional applicators have not been assessed, and might need to be evaluated during registration review. Finally, there was no assessment of the potential for bystander exposure associated with the mosquitocide uses; however, such exposures might need to be assessed during registration review.

Conclusions for Residential Exposure

Residential exposure and risk estimates were calculated using methodologies and data that were considered appropriate at the time the products were registered. Several of the residential uses of prallethrin might require reassessment because of the registration of product formulations having higher active ingredient levels. HED might conduct a new residential exposure assessment that incorporates any potential changes in new methods or policies for estimating exposure associated with residential use patterns as a result of the revisions to HED's Residential Standard Operating Procedures (SOPs) during registration review. Furthermore, residential bystander exposures might occur as a result of prallethrin aerial applications of mosquitocides, volatilization, and/or transport from treated areas. HED will evaluate the need for a bystander assessment during registration review.

Aggregate Risk Assessment

For aggregate risk assessment, risk estimates resulting from food, drinking water, and residential uses are combined. In the last risk assessment performed for prallethrin, the acute aggregate risk assessment consisted of dietary exposures from food and drinking water only. The acute aggregate risk estimates were not of concern for the U.S. population or any of the subgroups.

For short- and intermediate-term exposure scenarios, aggregate risk assessment consisted of dietary exposures and postapplication dermal, inhalation, and total oral exposure (hand-to-mouth, object-to-mouth, and soil ingestion). Registered residential uses (indoor fogger, pet mousse, carpet spray, pet spray) result in significantly higher exposures than the mosquito control use and were therefore used for the short- and intermediate-term aggregate assessment. The short/intermediate-term aggregate risk estimates were not of concern for the general U.S. population or any of the population subgroups.

The chronic aggregate risk assessment consisted of dietary exposures from food and drinking water only. The chronic aggregate risk estimates were not of concern for the general U.S. population or any of the population subgroups.

Conclusions for Aggregate Exposure and Risk

Based on the current uses of prallethrin and HED's policies and procedures for performing aggregate risk assessment, there are no aggregate risk concerns. During registration review, updated aggregate assessments might be conducted as needed to include any changes that might be made in toxicological endpoints and doses for risk assessment, dietary exposure estimates, and the methods or data HED uses to calculate residential exposure estimates.

Occupational Exposure

Occupational Handler Exposures

Liquid formulations of prallethrin are registered for the control of a variety of structural insect pests in indoor and outdoor settings. There are also liquid products registered for controlling public health pests in residential and recreational areas and veterinary pests of small animals and horses (Attachment 4).

Food Handling Establishment Uses: Occupational handler exposure was assessed for a liquid product (ETOC®) fogging concentrate which is labeled for use in homes, apartments, food processing plants, warehouses, hotels, schools, and hospitals, and may be used as either undiluted or diluted sprays (D263377, M. Collantes, 2/12/2000). Application methods include ultra low volume (ULV), mechanical, and other sprayers, and fogging machines. The labeled uses result in the potential for short- and intermediate-term dermal and inhalation exposures. The short- and intermediate-term dermal MOEs for handlers ranged from 100-16,000 while the short- and intermediate-term inhalation MOEs ranged from 530-230,000. The estimated dermal risks do not exceed HED's level of concern of 100.

Public Health Uses: HED evaluated occupational exposure resulting from mosquito control fogging with a fogging concentrate (D293820, G. Bangs, 8/30/03). Risks for occupational handlers applying the mosquito adulticide using aerial ULV and ground based airblast equipment were MOEs of 110-8,400, which are not of concern. The mitigation measures for mixers and loaders included baseline clothing plus gloves. For aerial applicators, the mitigation measures consisted of the use of an enclosed cab (i.e., engineering controls).

Occupational Postapplication Exposures

Occupational postapplication dermal exposure was not estimated because of the lack of unit exposures for workers who might enter a warehouse after fogging. In a study submitted by the registrant, the estimated inhalation exposure resulted in an extremely conservative MOE of ≤ 3. HED believes that the registrant used an inappropriate method for collecting postapplication inhalation exposure data in a warehouse setting. In a follow-up assessment, in which prallethrin was applied in a simulated warehouse setting, the estimated postapplication worker exposure resulted in a risk estimate of concern (MOE=89) at an air concentration based on an 8-hour time weighted average after one hour of ventilation. A similar estimate was determined for residents assumed to be exposed to prallethrin residues in a home. The postapplication exposure estimate

was not of concern (MOE=135) at an air concentration based on a 16-hour time weighted average.

HED recommends that, before mitigating the high-end exposures found in the postapplication scenarios summarized above, the exposures be reassessed using the chemical-specific or surrogate data and methodology available at the time of registration review. If mitigation is required, the Agency can consider reducing the application rate and/or increasing the ventilation time between application and re-entry of treated areas.

Furthermore, in the previous assessment, data from two studies were used to estimate worker exposures during fogging applications. These studies include a University of Florida study on greenhouse applicators (Nigg et. al., 1987) and an MGK study that monitored applicator exposure to prallethrin during ULV cold fogging (Bergman, 2002). Both the Nigg study and MGK study have data quality concerns because only one worker was monitored. The MGK study also has ethics concerns because proper informed consent procedures were not followed. Based upon these concerns, the OPP Ethics Reviewer and HED Management decided that neither study should be used for risk assessment (EPA, 2007).

Therefore, HED is requesting the submission of the following exposure study: Applicator Exposure Monitoring Test Guideline 875.1400 (Inhalation Exposure - Indoor) to confirm that there are no risks of concern associated with postapplication inhalation exposure.

Conclusions for Occupational Exposure

All of the occupational exposure scenarios identified for the registered uses of prallethrin were assessed using methologies and data that were considered appropriate at the time the products were registered, and none of the scenarios were of concern. However, during registration review, revised occupational handler and postapplication assessments might be required if there are any new scenarios, if toxicological endpoints change, or if the Agency receives new data that impact exposure estimates. In addition, updated occupational handler exposure assessments might be required under registration review based upon revisions to the Agency's scenario-specific surrogate handler exposure data (http://www.epa.gov/pesticides/science/handler-exposure-table.pdf). Updated occupational postapplication exposure assessments might also be required under registration review based on revisions to the dermal transfer coefficients from the Science Advisory Council for Exposure Policy Number 3 (http://www.epa.gov/pesticides/science/ exposac_policy3.pdf).

Public Health and Pesticide Epidemiology Data

HED used OPP's Incident Data System (IDS) to determine the number and severity of incidents that resulted from prallethrin exposure (Memo, D398043, S. Recore, 2/14/2012). Prallethrin is always co-formulated with other active ingredients. For this reason, it is necessary to review the incidents involving multiple chemicals in this case. In general, a relatively high frequency of incidents involving prallethrin-containing products has been reported. Although most of these incidents were of low severity, prallethrin might have the potential to result in high severity outcomes. For the Main IDS, from January 1, 2006 to December 14, 2011, there was 1 incident reported for the single chemical only and an additional 169 incidents reported that involved more

than one chemical, including six that were of major severity. Of the six major-severity incidents reported, two were accompanied by potential neurotoxic symptoms including headache, vomiting, slurred speech, and memory loss. However, these symptoms are not typically associated with pyrethroid toxicity. Based on the frequency of exposures and the potential for exposures to result in high severity outcomes, the incident data might warrant further analysis in the preliminary risk assessment phase of registration review.

Tolerance Assessment and International Harmonization

A tolerance of 1.0 ppm is established in 40CFR §180.545 for residues of prallethrin in or on all food items in food handling establishments where food and food products are held, processed, prepared, and/or served. During registration review, the tolerance expression should be revised as follows:

> (1) A tolerance of 1.0 ppm is established for residues of the insecticide prallethrin, including its metabolites and degradates, as follows: (2) In or on all food items in food handling establishments where food and food products are held, processed, prepared, and/or served. Compliance with the tolerance level specified is to be determined by measuring only prallethrin, (RS)-2-methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl(1*RS*)-cis,trans-chrysanthemate.
>
> Section (3) of 40CFR §180.545, which discusses use directions and restrictions, should be deleted. Section (4) should remain, but should be re-numbered as Section (3).

The Codex Alimentarius Commission (Codex) and Canada have not established maximum residue limits (MRLs) for prallethrin. Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes. As there are no Codex MRLs for prallethrin, Mexico's MRLs are equivalent to the U.S. tolerances. The international residue limit status sheet can be found in Attachment 5.

During registration review, if the U.S. and Codex have established tolerances for agricultural uses, HED will reconsider any unharmonized tolerances and will harmonize them with Codex MRLs when the data warrant harmonization.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in the 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," (http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf). The OPP typically considers the highest potential exposures from the legal use of a pesticide when conducting human-health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who might be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of prallethrin's most recent registration decision, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), prallethrin is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. Prallethrin is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Accordingly, as part of registration review, EPA will issue future EDSP orders/data call-ins, requiring the submission of EDSP screening assays for prallethrin. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

Cumulative Risk Assessments

The Food Quality Protection Act (FQPA) requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. Prallethrin is included in the pyrethroid/pyrethrin common mechanism group (http://www.regulations.gov; EPA-HQ-OPP-2008-0489-0006). The members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. The cumulative risk assessment for the pyrethroids/pyrethrins was published on Nov. 9, 2011 and is available at http://www.regulations.gov; EPA-HQ-OPP-2011-0746. No cumulative risks of concern were

identified, allowing the Agency to consider new uses for pyrethroid actives. For information regarding EPA's efforts to evaluate the risk of exposure to pyrethroids, refer to http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.

Human Studies

Past prallethrin risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1) and the Agricultural Reentry Task Force (ARTF) Database, are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. For certain studies, that 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.

Additional Information from Literature Sources

A prallethrin literature search did not reveal information that would impact the current risk assessment.

Data Requirements

Toxicology

An immunotoxicity study (870.7800) is required to support registration review. The immunotoxicity study is a new requirement for both food and non-food uses under 40 CFR Part 158 Data Requirements for Pesticides.

A developmental neurotoxicity (870.6300) is required to support registration review. However, rather than conduct a new study, the registrant may choose to cite the six pyrethroid DNT studies previously submitted to the Agency.

Chemistry

There are no outstanding residue chemistry data requirements.

Occupational and Residential

Occupational Exposure Data Requirement: An indoor applicator inhalation exposure study (875.1400) is required to support registration review.

Residential Exposure Data Requirement: There are no outstanding residential exposure data requirements.

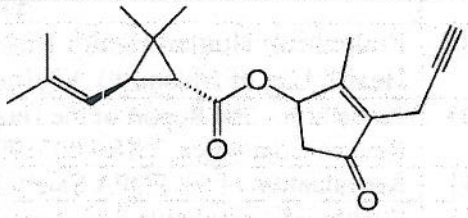
References

Memoranda Relevant to Registration Review			
Author	**Barcode**	**Date**	**Title**
M. Collantes G. Bangs	D289335	11/21/2003	Prallethrin: Human Health Risk Assessment for the Public Health Use of Mosquito Adulticides Containing Prallethrin
P. Hurley	NA	6/27/2003	Prallethrin - 2nd Report of the Hazard identification Assessment Review Committee, TXR# 0051993
E. Scollon	D381210	6/27/2011	Reevaluation of the FQPA Safety Factor for Pyrethroid Pesticides
K. Whitby	D394576	10/4/2011	Pyrethroid Cumulative Risk Assessment
W. Cutchin	D262478	1/24/2000	Chronic Dietary Exposure Analysis for the Use of Prallethrin in Food Handling Establishments
G. Bangs	D293820	9/30/2003	Prallethrin: Occupational and Bystander Exposure and Risk Assessment for the Public Health Use of Mosquito Adulticides Containing Prallethrin. (Chemical Number: 128722)
M. Collantes	D263377	2/17/2000	Revised Residential Exposure and Risk Assessment for Prallethrin
J. Melendez	D274758	6/30/2003	Tier I Estimated Environmental Concentrations of Prallethrin in Drinking Waters, Proposed New Uses in Outdoor Residential and Recreational Areas (PC Code 128722; DP Barcode D274758) Trade Names: MULTICIDE® Fogging Concentration 2798, RESPONDÉ® Insecticide
S. Recore	D398043	2/14/2012	Prallethrin: Review of Human Incidents

Attachments

Attachment 1. Chemical Identity Table
Attachment 2. Toxicology Data Requirements
Attachment 3. Prallethrin Endpoint Selection Table
Attachment 4. Prallethrin Use Pattern Summary
Attachment 5. International Residue Limit Status

Attachment 1. Chemical Identity Table

Prallethrin Nomenclature	
Chemical Structure	
Empirical Formula	$C_{19}H_{24}O_3$
Common Name	Prallethrin
Company Experimental Name	ETOC
IUPAC Name	(S)-2-methyl-4-oxo-3-(2-propynyl) cyclopent -2-enyl (1RS)-cis, trans-2,2 - dimethyl -3 - (2-methylprop-1-enyl) cyclopropanecarboxylate
CAS Name	(RS)-2-methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl(IR)-cis,trans-chrysanthemate
CAS Registry Number	23031-36-9
End-use Product/EP	MGK Multicide Fogging Concentrate (FHE) MGK ETOC Fogging Concentrate (FHE) Numerous other products are registered for residential and commercial use (see use pattern summary table in Attachment 4)
Chemical Class	Pyrethroid
Known Impurities of Concern	None

Attachment 2. Toxicology Data Requirements

The requirements (40 CFR 158.340) for a food use for prallethrin are presented below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test		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)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21/28-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	---
870.3465	21/28-Day Inhalation	yes	**yes**
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
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—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	no	---
870.6100b	90-Day Neurotoxicity (hen)	no	---
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90 Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	yes	no*
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	---
870.7800	**Immunotoxicity**	**yes**	**no**

*A developmental neurotoxicity study (870.6300) is required to support registration review. However, rather than conduct a new study, the registrant may choose to cite the 6 pyrethroid DNT studies previously submitted to the Agency.

Attachment 3. Prallethrin Endpoint Selection Table

Summary of Toxicological Doses and Endpoints for Prallethrin for Use in Human Risk Assessments			
Exposure/ Scenario	**Dose Used in Risk Assessment, UF**	**FQPA SF and Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (General population including infants and children)	NOAEL = 5.0 mg/kg/day UF = 100 Acute RfD = 0.05 mg/kg/day	FQPA SF = 1 aPAD = $\frac{\text{Acute RfD}}{\text{FQPA SF}}$ = 0.05 mg/kg/day	Chronic study in the dog (capsule). LOAEL = 10 mg/kg/day based on trembling, rapid eye blinking, hunched posture, panting, increased serum cholesterol, phospholipids, and alkaline phosphatase activity.
Chronic Dietary (All populations)	NOAEL = 5.0 mg/kg/day UF = 100 Chronic RfD = 0.05 mg/kg/day	FQPA SF = 1 cPAD = $\frac{\text{Chronic RfD}}{\text{FQPA SF}}$ = 0.05 mg/kg/day	Chronic study in the dog (capsule). LOAEL = 10 mg/kg/day based on trembling, rapid eye blinking, hunched posture, panting, increased serum cholesterol, phospholipids, and alkaline phosphatase activity.
Short-Term Incidental Oral Short- and Intermediate-Term	NOAEL = 0.05 mg/kg/day	Residential LOC for MOE = 100 Occupational LOC for MOE = NA	Chronic study in the dog (capsule). LOAEL = 10 mg/kg/day based on trembling, rapid eye blinking, hunched posture, panting, increased serum cholesterol, phospholipids, and alkaline phosphatase activity.
Dermal All Durations	NOAEL = 30 mg/kg/day (Dermal absorption factor = 20%)	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	21-day dermal study in the rat. LOAEL = 150 mg/kg/day based on clinical signs of toxicity, and decreases in body weight.
Inhalation All Durations	NOAEL = 1.01 mg/m^3 (0.174 mg/kg/day)	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	28-day inhalation study in the rat. LOAEL = 4.39 mg/m^3 (0.765 mg/kg/day) based on increased evidence and severity of irregular respiration, decreased spontaneous activity, and nasal discharge during exposure.
Cancer (oral, dermal, inhalation)	Classification: "not likely" to be carcinogenic to humans. No quantification required.		

UF = uncertainty factor, FQPA SF = Any additional safety factor retained to account for data deficiencies or residual concerns unique to the FQPA, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = not applicable.

Attachment 4. Prallethrin Use Pattern Summary

Use Patterns of End-use Product Formulations of Prallethrin Insecticide.				
Use Site and Product Categories	**% ai**	**Application Sites**	**Application Methods**	**Status of Exposure Assessments [1]**
Aerosol products for surface and space sprays (indoor)	0.01 - 0.3	Indoor, outdoor, residential, commercial	Surface, spot, crack & crevice, mattress, pet bedding, premises, and space sprays	Only up to 0.2% ai was assessed. [2] Higher ais (0.3%) require assessment
Aerosol sprays for wasp & hornet control (outdoor)	0.02 - 0.2	Outdoor, residential, commercial	High discharge sprays for hitting wasps from a distance	Wasp and hornet products might have to be assessed per new residential SOP.
Aerosol products for indoor fogging (indoor)	0.04	Indoor, residential, commercial	Total release aerosols	
Aerosol sprays for fogging (outdoors)	0.04	Outdoor	Patio and back yard foggers	Back yard fogger might have to be assessed per new residential SOP.
Aerosol and liquid products for pet and large animal treatments	0.13-0.33	Indoor, outdoor, residential, commercial	spray, wipe, and shampoo for dogs, cats, horses	[3] Only up to 0.1% ai were assessed. Higher ais (0.33%) might require assessment
Liquid products for space and surface spray/ fogging (indoor and outdoor)	0.03-2.0	Indoor, outdoor, residential, commercial, food handling establishm.	Space, surface, spot, and crack & crevice sprays, ULV and thermal fogger	[4] Only product (2.0% ai) was assessed. New sites or application methods might require re-evaluation under new residential SOP.
Liquid products for mosquito control (public health uses)	1.0	Outdoor, residential recreational	Fogging by air and ground equipment	[5] Public health uses might require re-evaluation to meet new residential SOP.
Technical and Manufacturing Use products (AI= 1.0 - 93.0)				
Pending registrations: 1021-ELTU, 1021-RATI, 71631-R				

1. End-use products (excluding cancelled) that were assessed under each category.
2. Assessed Reg. Nos. include 1021-1061 (0.03% ai), 1021-1633 (0.03% ai) and 1021-1691 (0.03% ai), and 1021-1710 (0.2% ai), (M. Collantes, D263377, 2/17/2000).
3. Assessed Reg. No. includes 4758-171 (0.1% ai), (M. Collantes, D263377, 2/17/2000).
4. Assessed Reg. Nos. include 1021-1718 (2.0 % ai) (G. Bangs, D293818, 2003) and 4758-163 (0.25% ai), (M. Collantes, D263436, 2/28/2000).
5. Assessed Reg. No. includes 1021-1795 (1.0% ai), (G. Bangs, D293820, 2003).

Attachment 5. International Residue Limit Status

Prallethrin (128722; 01/23/2012)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
40 CFR 180.545: Plant: Prallethrin, (*RS*)-2-Methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl(1 *RS*)-cis,trans-chrysanthemate		None		None
Commodity	Tolerance (ppm)/Maximum Residue Limit (mg/kg)			
	US	Canada	Mexico	Codex
Food commodities in Food Handling Establishments where food and food products are held, processed, prepared and/or served	1.0			
Completed: M. Negussie; 01/24/2012				

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.