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OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

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

Executive Summary

The Health Effects Division Deltamethrin Risk Assessment team has evaluated the database and the most recent human health risk assessments for the insecticide, deltamethrin, (1R,3R)-R-cyano(3-phenoxyphenyl)methyl 3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropanecarboxylate. HED performed this evaluation in order to determine the scope of work necessary to support the established tolerances and existing registrations. The primary sources of information for this evaluation were: 1) the most recent human health risk assessment performed to evaluate several proposed agricultural uses and existing residential uses, 2) a response to a recent tolerance petition for a new agricultural use, and 3) updates to the toxicity, exposure, and usage databases that were made in association with the recent tolerance petition.

Deltamethrin is a broad-spectrum pyrethroid insecticide that is registered in the U.S. for direct application to a wide variety of food/feed crops, for use on stored grains, and for use in food/feed handling establishments. Two emulsifiable concentrate (EC) formulations of deltamethrin are currently registered to Bayer CropScience for use on a variety of food/feed crops. In addition, numerous formulations are registered for use in residential outdoor, indoor, pet, and paint additive products.

One of the other pyrethroids, tralomethrin, is very similar to deltamethrin structurally. Tralomethrin breaks down into deltamethrin through debromination (loss of a Br_2 molecule and formation of a double bond) and, therefore, they are considered to be the same with respect to mammalian toxicity and endpoint selection for risk assessment. Tralomethrin is registered for use in a wide variety of residential settings and on a small number of crops. While this scoping document does not directly address tralomethrin data requirements, the most recent aggregate risk assessment for deltamethrin is protective for tralomethrin with respect to dietary as well as residential exposure pathways. The assessment is protective for tralomethrin because the dietary assessment included both tralomethrin and deltamethrin crop uses, and because the use rates and potential residential exposures for deltamethrin are greater than those for tralomethrin. HED is currently preparing a separate scoping document for tralomethrin.

Toxicology

The hazard characterization of deltamethrin was recently revised (E. Scollon, D367616, 8/13/2009). No additional studies have been submitted to the Agency since the revision. The toxicology database for deltamethrin is adequate for risk assessment. Acceptable studies include subchronic and chronic studies in rats, mice, and dogs; developmental studies in rats and rabbits; a reproduction study in rats; and acute, subchronic, and developmental neurotoxicity studies in rats. Sufficient studies are also available to assess dermal exposure, metabolism, and mutagenicity. As part of the new EPA Part 158 data requirements, an immunotoxicity study in rats and/or mice is required.

The target organ system for deltamethrin is the nervous system. In rats, mice, and dogs, effects included salivation, unsteadiness, convulsions, altered posture, hypersensitivity to sound, and decreased motor activity. Increased duration of dosing did not either significantly lower the NOAEL for the neurotoxic effects or increase the severity of these effects, most likely because of

rapid metabolism and elimination. Decreases in body weight and body weight gain were also noted in subchronic, chronic, and reproductive studies. There was no evidence of systemic or local effects in rats when deltamethrin was applied dermally.

In the prenatal developmental studies in rats and rabbits and in the developmental neurotoxicity (DNT) study, deltamethrin had no adverse effects on offspring in the absence of maternal effects. Evidence of qualitative susceptibility was found in the reproduction study as increased deaths and signs of neurotoxicity in the F1 generation. The qualitative increase in toxicity was likely due to an increase in deltamethrin intake as the pups were weaned and their immature deltamethrin clearance mechanisms. Furthermore, the increase in qualitative susceptibility was only noted at a dose 20-fold greater than the NOAEL selected for the acute and chronic dietary reference dose. Therefore, despite evidence of increased qualitative susceptibility, a 10x safety factor for susceptibility is not warranted based on the results of the 2-generation rat study because the endpoint and dose selected for risk assessment would be protective. However, several literature studies provided evidence of susceptibility in that there were age-dependent toxicokinetic differences between young and adult animals. As a result, HED concluded there was residual uncertainty for post-natal toxicity, and the FQPA 10x Safety Factor was retained for all exposure scenarios involving postnatal exposure of infants and children. No additional safety factor was necessary for adult or potentially pregnant populations.

There was no evidence of carcinogenicity in the combined chronic/carcinogenicity study in rats or in the carcinogenicity study in mice. Deltamethrin is classified as "not likely to be carcinogenic to humans." In a battery of mutagenicity studies, there was no evidence of a mutagenic effect.

Decreased motor activity with a calculated NOAEL of 1 mg/kg/day from an acute oral study (Wolansky, et al, 2006) was selected for deltamethrin risk assessment. The dose and endpoint are considered to be applicable for all exposure scenarios and durations because the rapid elimination of deltamethrin from the body precludes bioaccumulation, and no additional toxicity would be expected with increased dosing duration. A traditional uncertainty factor of 100x (10x for interspecies extrapolation and 10x for intraspecies variation) was applied. As the 10x FQPA Safety Factor was retained for population subgroups comprised of infants and children, the uncertainty factor is 1000x for all exposure scenarios involving these subgroups, and 100x for all other populations.

The pyrethroids, as a group, including deltamethrin, have been determined to share a common mechanism of toxicity. A cumulative risk assessment has not yet been performed because the Agency is currently examining approaches for completing this type of assessment. However, future actions involving deltamethrin should consider the impact of the evolving cumulative risk assessment.

Dietary Exposure

The dietary exposure database is adequate to support the registration review of deltamethrin. No additional data are required. The most recent dietary exposure analysis performed for deltamethrin includes deltamethrin residues that might be present in commodities for which

tralomethrin is registered (i.e., broccoli, cottonseed, head lettuce, leaf lettuce, soybeans, and sunflowers). If a new drinking water assessment is performed during registration review, the updated estimated drinking water concentrations will be used in the dietary exposure assessment. The chronic dietary (food and drinking water) risks are not of concern for the existing uses of deltamethrin. The acute dietary (food and drinking water) risks are of concern for the existing uses of deltamethrin for the population subgroups comprised of infants and children. These population subgroups and their corresponding %aPAD values are: all infants (110% aPAD), children 1-2 (130% aPAD), children 3-5 (140% aPAD), and children 6-12 (110% aPAD). During registration review, monitoring data and new percent crop treated estimates should be used to refine the acute dietary exposure analysis. It is likely that these refinements will result in dietary risk estimates that are below HED's level of concern for all population subgroups.

Residential Exposure

Deltamethrin has numerous registered residential uses. The end-use products consist of various indoor and outdoor insecticides (broadcast and crack and crevice), a pet collar, and an insecticidal paint additive. These products are formulated as ready-to-use sprays, dusts, liquids, and granules. All residential handler scenarios resulted in dermal and inhalation MOEs $\geq$ 100 and were not of concern. Postapplication exposures resulting from use of deltamethrin on lawns are not of concern for either adults or children. For adults, there are no risks of concern resulting from postapplication indoor exposure scenarios. However, there were dermal and oral postapplication scenarios for children that had risks of concern.

Hand-to-mouth exposure estimates were refined in the 2004 risk assessment (Memo, D262496, D. Dotson, et al., 11/15/2004) with the submission of a chemical-specific hand press study. HED is aware that the registrant is planning on submitting a probabilistic CARES assessment which is being performed for the purpose of refining the residential exposure and risk estimates. Furthermore, as a result of the revisions to HED's Residential Standard Operating Procedures (SOPs), the parameters and algorithms for dermal, inhalation, and hand-to-mouth exposure calculations will likely change. These changes could result in significantly different exposure estimates for indoor surface and treated pet collar postapplication exposure estimates. Therefore, during registration review, HED will conduct a new residential exposure assessment that incorporates any potential changes in endpoint selection, uncertainty factors, and new methods or policies for estimating exposure associated with residential use patterns.

Occupational Exposure

Occupational handler and postapplication inhalation exposures were assessed in the 2004 risk assessment for use of deltamethrin on a variety of agricultural and residential settings. A cursory review of the occupational handler and postapplication dermal exposure scenarios (with the exception of the plastic foam insulation panels) using the dermal NOAEL has also been performed. All other occupational scenarios resulted in dermal and inhalation MOEs $\geq$ 100, and are not of concern.

During registration review, revised occupational handler and postapplication assessments should be conducted based on updated doses and endpoints for dermal and inhalation risk assessment.

These assessments may include additional and more detailed review of the submitted risk assessment for the foam insulation product.

Introduction

HED evaluated the most recent human health risk assessments for deltamethrin to determine if sufficient data are available and if updates are needed to support registration review. To perform this evaluation, HED considered the following documents and assessments: 1) the most recent human health risk assessment performed to evaluate several proposed agricultural uses and existing residential uses (Memo, D262496, D. Dotson, et al., 11/15/2004), 2) a response to a tolerance petition for a new agricultural use (Memo, D335134, D. Dotson, et al., 8/11/2009, 3) updates to the toxicity, exposure, and usage databases that were made in association with the proposed new use, and 4) the latest Agency science policies and risk assessment methodologies. The structure of deltamethrin, as well as its chemical names and other identifiers can be found in the chemical identity table attached to this document (Attachment 1).

Deltamethrin is a broad-spectrum pyrethroid insecticide that is registered in the U.S. for direct application to a wide variety of food/feed crops, for use on stored grains, for use in food/feed handling establishments, and for a variety of residential uses. Two emulsifiable concentrate (EC) formulations of deltamethrin are currently registered to Bayer CropScience for use on food and feed crops. One is a 1.5 pound active ingredient per gallon (lb ai/gal) EC (Decis 1.5EC Insecticide, EPA Registration #264-1011), and the other is a 0.2 lb ai/gal EC (Decis 0.2EC Insecticide, EPA Registration #264-1007).

Tolerances are established under 40 CFR §180.435 for residues of deltamethrin that result from agricultural uses as well as food and feed handling establishment uses. For all commodities, tolerances are established in terms of parent deltamethrin and its major metabolites, *trans* deltamethrin and *alpha*-R deltamethrin. The CAS names of these compounds are as follows: deltamethrin [(1*R*,3*R*)-3-(2,2-di-bromovinyl)-2,2-dimethylcyclopropanecarboxylic acid (*S*)-a*lpha*-cyano-3-phenoxybenzyl ester, *trans* deltamethrin [(*S*)- *alpha* -cyano-*m*-phenoxybenzyl(1R,3S)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate], and *alpha*-*R*-deltamethrin [(*R*)-*alpha*-cyano-*m*-phenoxybenzyl-(1*R* ,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate]. During registration review, the residues of concern for tolerance enforcement will be re-assessed.

During registration review, the tolerance expression should be revised so that it addresses both coverage and measurement. The tolerance expression should be revised as follows: Tolerances are established for residues of deltamethrin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only deltamethrin and the residues of concern established during registration review.

One of the other pyrethroids, tralomethrin, is very similar to deltamethrin structurally. Tralomethrin breaks down into deltamethrin through debromination (loss of a Br_2 molecule and

formation of a double bond). Tralomethrin is registered for use in a wide variety of residential settings and on a small number of crops (40 CFR §180.422).

Hazard Identification/Toxicology

Deltamethrin is a pyrethroid pesticide that causes neurotoxicity in insects and mammals by a similar mechanism of action, the modulation of nerve axon sodium channels. Pyrethroids interfere with the ability of the nervous system to relay nerve transmissions resulting in tremors, whole body convulsions, or excessive salivation, among other effects.

The hazard characterization for deltamethrin has recently been updated (Memo, D367616, E. Scollon, 8/13/2009). Major revisions included the selection of new endpoints for risk assessment and the incorporation of a dermal assessment. No new studies have been submitted since the last update. For a complete review of the toxicology and historical decisions, see Memo, D367616, E. Scollon, 8/13/2009. Briefly, the toxicology database for deltamethrin is robust but not complete. In accordance with the new 40CFR Part 158 data requirements for conventional pesticide registration, an immunotoxicity study in rats and/or mice is now required. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies might offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity. The Deltamethrin Registration Review Team recommends that, once all data have been received and reviewed, the points of departure and uncertainty and safety factors used for risk assessment purposes be reexamined and a new risk assessment performed, if necessary.

Deltamethrin has moderate acute toxicity via the oral (category II) and inhalation (II/III) routes of exposure and minimal toxicity via the dermal (category III) route of exposure. It is minimally irritating to the eye (category III) and non-irritating to the skin (category IV). It is not a skin sensitizer.

Deltamethrin targets the nervous system. In guideline animal studies, effects in the rat, dog, and rabbit included salivation, unsteadiness, convulsions, altered posture, hypersensitivity to sound, and decreased motor activity. Increased duration of dosing did not significantly lower the NOAEL for the neurotoxic effects and it did not increase the severity of these effects. In fact, neurotoxicity effects were identified in the chronic and subchronic rat studies within hours to days of initial dosing, but decreased over several weeks. Decreases in body weight and body weight gain were also noted in subchronic, chronic, and reproductive studies. Additionally, there was no evidence of systemic or local effects in rats when deltamethrin was applied dermally. Low toxicity via the dermal route is most likely due to the low potential for dermal absorption through the skin.

In the prenatal developmental studies in rats and rabbits and in the DNT study, deltamethrin had no adverse effects on fetuses or offspring in the absence of maternal effects. There was evidence of qualitative susceptibility in the reproduction study as increased deaths and signs of neurotoxicity in the F1 generation. The qualitative increase in toxicity was correlated with:

1) an increase in deltamethrin intake as the pups were weaned and began consuming greater quantities of dosed chow and, 2) immature clearance mechanisms for deltamethrin in the pups. Furthermore, the increase in qualitative susceptibility was only noted at 21.6 mg/kg/day, 20-fold greater than the NOAEL selected for the acute and chronic dietary reference dose (1 mg/kg/day). Therefore, despite evidence of increased qualitative susceptibility, a 10x safety factor for susceptibility is not warranted based on the results of the 2-generation rat study because the endpoint and dose selected for risk assessment would be protective. Despite the lack of quantitative and qualitative susceptibility found in the guideline studies, the 10x FQPA Safety Factor was retained for all exposure scenarios involving infants and children. The decision to retain the factor was based on residual uncertainty for post-natal toxicity because of age-dependent toxicokinetic data that were found in literature studies.

Several literature studies indicate that infants and children might be more susceptible to deltamethrin toxicity as a result of post-natal exposure. Young rats are quantitatively susceptible to deltamethrin toxicity at doses greater than 4 mg/kg. The enzymes accounting for the metabolism of deltamethrin either are not present in the same levels in children as they are in adults, or they are not as active in children. Similarly, enzyme profiles in infants and children are less developed than they are in adults and can be highly variable in quantity and activity, especially in infants. Until sufficient evidence is available demonstrating that infants and children have the capacity to metabolize deltamethrin in a manner comparable to the way in which adults metabolize it, quantitative susceptibility is being assumed.

Decreased motor activity observed in an acute oral study in rats (Wolansky et al., 2006) was selected as the endpoint for deltamethrin risk assessment. The NOAEL for this study was 1 mg/kg/day. The endpoint and dose are considered to be applicable for all exposure scenarios and durations because the rapid elimination of deltamethrin from the body precludes bioaccumulation, and no additional toxicity would be expected with increased dosing duration. In the past, deltamethrin risk assessments did not include a dermal assessment because a dermal toxicity study indicated there were no toxic effects up to the limit dose; however, the dermal toxicity study was conducted in adult rats and does not consider potential pup susceptibility. Therefore, a dermal endpoint and dose were selected for infants/children in the revised hazard characterization. In addition, as the dermal study did not assess neurotoxic parameters, a dermal assessment was also conducted for adults based on the endpoint selected from the Wolansky study, and a dermal absorption factor of 1%. The default uncertainty factor of 100x (10x for interspecies extrapolation and 10x for intraspecies variation) was applied to all exposure scenarios. Therefore, as the 10x FQPA Safety Factor was retained for population subgroups comprised of infants and children, the uncertainty factor is 1000x for all exposure scenarios involving these subgroups, and 100x for all other populations.

There was no evidence of carcinogenicity in the combined chronic/carcinogenicity study in rats or the carcinogenicity study in mice. Deltamethrin is classified as “not likely to be carcinogenic to humans.” In a battery of mutagenicity studies, there was no evidence of a mutagenic effect.

Tralomethrin is structurally similar to deltamethrin. It is metabolized into deltamethrin and shares the same major metabolites *in vivo*. Additionally, tralomethrin endpoints for dietary,

occupational, and residential exposure scenarios are similar, or equivalent, to those for deltamethrin and are based upon a combined tralomethrin/deltamethrin toxicity database.

The summary tables of toxicity endpoints from the most recent update of the hazard characterization (Memo, D367616, E. Scollon, 8/13/2009) are provided in Attachment 2.

During registration review, the toxicity database should be reconsidered based on the registered uses. Endpoints, doses, and safety factors should be determined in order to assess risks associated with all potential exposure scenarios. This re-evaluation should consider all additional studies received since the RED and those now required as part of the new Part 158 data requirements.

Conclusions for Hazard Identification/Toxicology

An immunotoxicity study is required and should be submitted in conjunction with registration review. During registration review, the toxicity database should be re-evaluated based on the results of the immunotoxicity study and any other data received in conjunction with the registered uses. Endpoints, doses, and safety factors should be determined in order to assess risks associated with all potential exposure scenarios.

Dietary Exposure

Deltamethrin kills insects on contact and through ingestion. It is used to control numerous insect pests on field crops. It is also used to control apple and pear suckers, aphids (on apples, plums, and hops), caterpillars (on *Brassica* crops), pea moths, plum fruit moths, winter moths (on apples and plums), and codling and tortrix moths (on apples). In addition, it is used in glasshouses to control aphids, mealy bugs, scale insects and whitefly on cucumbers, tomatoes, peppers, potted plants, and ornamentals. Formulations include emulsifiable concentrates (EC), wettable powders (WP), flowable formulations (F), and granules (G). There are no known incompatibilities with other common insecticides and fungicides.

Deltamethrin is a broad-spectrum pyrethroid insecticide that is registered in the U.S. for direct application to a wide variety of food/feed crops, for use on stored grains, and for use in food/feed handling establishments. Two emulsifiable concentrate (EC) formulations of deltamethrin are currently registered to Bayer CropScience for these uses. One is a 1.5 pound active ingredient per gallon (lb ai/gal) EC (Decis 1.5EC Insecticide, EPA Registration #264-1011), and the other is a 0.2 lb ai/gal EC (Decis 0.2EC Insecticide, EPA Registration #264-1007). Technical deltamethrin is made up predominantly of the *cis* isomer, which comprises on the order of 99% of the technical material.

Tolerances are established under 40CFR §180.435 for residues of deltamethrin that result from agricultural uses as well as use in food and feed handling establishments. For all commodities, tolerances are established in terms of parent deltamethrin and its major metabolites, *trans* deltamethrin and *alpha*-R deltamethrin. Although the 40CFR refers to *trans* and *alpha*-R deltamethrin as metabolites, they are, in fact, isomers of *cis*-deltamethrin as well as metabolites of it. During registration review, the tolerance expression will be revised so that it addresses

both coverage and measurement. The tolerance expression should be revised as follows: Tolerances are established for residues of deltamethrin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only deltamethrin and the residues of concern established during registration review.

HED used the Dietary Exposure Evaluation Model (DEEM-FCID™ Version 2.03) to conduct the most recent acute and chronic aggregate dietary (food and drinking water) risk assessments for deltamethrin. This 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. Anticipated residues based on field trial data and estimates of percent crop treated were used in both the acute and chronic dietary risk assessments. Empirical and DEEM default processing factors were used for the various processed commodities. Deltamethrin was classified as "not likely to be carcinogenic to humans." As a result, a cancer dietary risk assessment was not conducted.

The estimated acute dietary exposure to deltamethrin resulted in an estimated risk equivalent to 8.7% of the aPAD (acute population adjusted dose) for the general U.S. population at the 99.9th percentile of exposure. The acute dietary risks are of concern for the existing uses of deltamethrin for the population subgroups comprised of infants and children. These population subgroups and their corresponding %aPAD values are: all infants (110% aPAD), children 1-2 (130% aPAD), children 3-5 (140% aPAD), and children 6-12 (110% aPAD). During registration review, monitoring data and new percent crop treated estimates should be used to refine the acute dietary exposure analysis.

The estimated chronic dietary exposure to deltamethrin resulted in an estimated risk equivalent to <1% of the cPAD (chronic population adjusted dose) for the general U.S. population. The most highly exposed population subgroup was Children 1-2 years old, which utilized 11% of the cPAD

EFED recommended that modeled estimates of residues in drinking water be used in the most recent dietary risk assessment. If a new drinking water assessment is performed during registration review, the updated estimated drinking water concentrations will be used in the dietary exposure assessment.

Conclusions to Dietary Exposure

The dietary exposure database is adequate to support the existing registrations and tolerances. No new residue chemistry data are required. A new drinking water assessment will be conducted during registration review. In addition, a revised dietary risk assessment will need to be conducted. It will include the revised estimated drinking water concentrations, any changes in toxicological endpoints, and refinements to the residue levels and percent crop treated estimates used in the assessment. These refinements will likely result in dietary risk estimates that are below HED's level of concern for all population subgroups.

Residential Exposure

Deltamethrin is used in numerous residential settings. It is formulated as various indoor and outdoor end-use products for both broadcast as well as crack and crevice application. Included among its uses are pet collars and insecticidal paint additives. These products are formulated as ready-to-use sprays, dusts, liquids, and granules. The products are applied by a wide range of application methods including hose-end sprayers, push-type spreaders, shaker cans, aerosol cans, low/high pressure hand wands, backpack sprayers, paint brush/rollers, and airless sprayers. Tralomethrin application rates in residential settings are all equal to, or lower than, the deltamethrin application rates for the same uses. As a result, the most recent risk assessment for deltamethrin is protective for tralomethrin exposures.

With the exception of the pet collar scenario, all residential exposure assessments for deltamethrin were conducted using the current version of the SOPs for residential exposure assessment. However, the Agency has recently undertaken a major revision of these SOPs, the proposed new exposure assessment assumptions, data and algorithms were presented to the Agency's Science Advisory Panel (SAP) in October, 2009. HED is currently evaluating the SAP's response and recommendations, and is not routinely using the proposed SOP revisions.

Handlers

In accordance with current guidance, only adults are assumed to make pesticide applications in residential settings. Residential handler inhalation exposure scenarios were assessed in the 2004 risk assessment (Memo, D262496, D. Dotson, et al, 11-15-04). A cursory review of the residential handler dermal exposure scenarios was performed for the 2009 tolerance petition evaluation using the oral NOAEL of 1 mg/kg/day and a 1% dermal absorption factor (Memo, D335134, D. Dotson and M. Collantes, 8-13-09). All residential handler scenarios resulted in dermal and inhalation MOEs ≥ 100, and were not of concern.

Postapplication

Residential postapplication exposure scenarios can occur as a result of deltamethrin's use as a broadcast and crack and crevice application to lawns and indoor surfaces, its use in treated pet collars, and its use in insecticidal paints and termiticides (Memo, D335134, D. Dotson and M. Collantes, 8-13-09). Postapplication re-entry into treated areas can result in dermal, inhalation, and incidental oral (i.e., hand-to-mouth, for children only) exposures.

Potential postapplication dermal exposure resulting from the use of deltamethrin on lawns is not of concern for either adults or children. All dermal MOEs were greater than or equal to 100 for adults and greater than or equal to 1000 for children. In addition, for adults, all indoor scenarios resulted in dermal and inhalation MOEs ≥ 100 and were not of concern.

Postapplication scenarios that resulted in risks of concern were: 1) dermal and oral (hand-to-mouth) children's exposure resulting from indoor broadcast and crack and crevice application of sprays ranging from 0.06% to 0.02% in concentration; and 2) oral (hand-to-mouth) children's exposure resulting from broadcast application to lawns.

Pet Collars

Both adults' and children's exposures from the use of a treated pet collar result in risks of concern (Current Guidance for Residential Exposure Risk Assessment for Pet Insecticide Treatments, D350531, W. Britton, 1/14/2009). The details regarding calculations of the amount of ai in the pet collar, as well as the MOEs, are presented in the appendixes of this document. While adult handler's risks for applying a pet collar are not of concern, scenarios with risk concerns include adults' and children's dermal post-application exposure resulting from use of treated pet collars and children's oral (hand-to-mouth) exposure resulting from treated pet collars.

The short-term oral MOE for incidental ingestion of granules (DeltaGard®G Insecticide) was 190, which is of concern to HED (MOE ≤ 1,000). However, as explained in the 2004 risk assessment (Memo, D262496, D. Dotson, et al., 11/15/2004), HED considers ingestion of granules to be an episodic event, not routine behavior. As granular ingestion does not occur on a regular basis, HED's concern for human health is related to acute poisoning rather than short or intermediate-term residue exposure. While HED continues to conclude that exposure from granular ingestion is likely to be very low, risk from this scenario should be re-examined in light of the new target MOE of 1000.

Combined Residential Risk Estimates

Residential scenarios consist of dermal and hand-to-mouth postapplication exposures for toddlers resulting from lawn and indoor broadcast application of deltamethrin and contact with treated pets from use of treated dog collars. As the dermal and oral postapplication exposure to toddlers resulting from broadcast application to lawns represent lower risks of concern than the worst case scenario (indoor postapplication exposures), they are not included in the combined residential exposure and risk estimates. The combined residential exposure resulted in a total MOE of 140 for indoor broadcast application and 24 for treated pet collars. Based on the current estimated chronic exposure from food and water, a combined residential MOE of 1,100 (i.e., including dermal and hand-to-mouth exposure) is needed to reach an aggregate (dietary + residential) risk estimate that is below HED's level of concern (i.e., to reach an aggregate MOE of >1000). Therefore, current combined residential risk estimates are of concern to HED. Table 1 provides a summary of the combined residential indoor broadcast and treated pet collar exposures and risks.

Table 1. Combined Residential (Toddler) Exposure and Risk Estimates

Postapplication Scenarios	Daily Dose (mg/kg/day) [1]	MOE [2]	Combined MOE [3]
Indoor Broadcast			
Toddler Dermal surface	0.0028	350	**140**
Toddler Hand-to-Mouth	0.0044	230	
Treated Pet Collar			
Toddler - Dermal	0.042	24	**15**
Toddler – Hand-to-Mouth	0.0224	45	

[1] Daily Dose for Indoor Broadcast use see Memo, D307927, M. Collantes, 10/14/2004 (Table 7)
Daily Dose for Pet Collar: see Table A.5.b in Attachment 5

[2] Toddler Dermal MOE = $\frac{\text{NOAEL (1 mg/kg/day)}}{\text{Dermal Dose}}$

Toddler Oral MOE = $\frac{\text{NOAEL (1 mg/kg/day)}}{\text{Oral Dose}}$

[3] Toddler Combined MOE = 1/(dermal dose + oral dose)

Conclusions for Residential Exposure

As a result of the revisions to HED's Residential SOPs, the parameters and algorithms for dermal, inhalation, and hand-to-mouth exposure calculations will likely change, and could result in significantly different estimates of indoor surface and treated pet collar postapplication exposures. Postapplication exposure scenarios cannot be refined without additional chemical-specific data (i.e. pet collar study) and incorporation of the revised residential SOP algorithms in the registration review process. Furthermore, the registrant plans to submit a probabilistic CARES assessment for the purpose of refining the residential exposure and risk estimates. The input parameters and results of the CARES assessment should be considered during registration review.

Aggregate Risk Assessment

HED has identified aggregate risks of concern based on acute dietary risks of concern for children, and residential risks of concern for both adults and children. During registration review, an updated aggregate risk assessment will be conducted, taking into consideration any changes that are made to 1) the toxicological doses and endpoints that are selected, 2) the estimated drinking water concentrations, 3) the % crop treated estimates for food commodities, and 4) the potential refinements for residential exposure estimates for adults and children.

Occupational Exposure

Occupational handler and postapplication inhalation exposures were assessed in the 2004 risk assessment (Memo, D262496, D. Dotson, et al, 11/15/04) for use of deltamethrin on a variety of agricultural crops, stored grain bins and warehouses, and commercial products including termiticides, insecticidal paint additives, and insecticidal plastic foam insulation. A cursory review of the occupational handler and postapplication dermal exposure scenarios (with the exception of the plastic foam insulation panels) using the dermal NOAEL has also been performed. All occupational scenarios resulted in dermal and inhalation MOEs $\geq$ 100 and are not of concern.

In support of the use of plastic foam insulation panels, the registrant, Dow Chemical Company, submitted a screening risk assessment document (MRID 45345802), that was reviewed to verify the potential absorbed dose based on information provided in the study report. However, as there was no dermal endpoint in 2003, dermal exposure assessment was not performed for this scenario. Furthermore, HED currently does not have unit exposures to assess this handler exposure scenario in order to determine exposure resulting from construction workers installing foam insulation containing deltamethrin.

Conclusions for Occupational Exposure Assessment

During registration review, revised occupational handler and postapplication assessments should be conducted based on updated doses and endpoints for dermal and inhalation risk assessment. These assessments may include additional and more detailed review of the submitted risk assessment for the foam insulation product.

Public Health and Pesticide Epidemiology Data

HED has prepared an incident report for deltamethrin (Memo, D369651, M. Hawkins, et al., 11/24/2009). For this evaluation, both the OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk (SENSOR) database were consulted for poisoning incident data.

For IDS, HED identified 118 case reports allegedly attributable to deltamethrin reported to the IDS between 2002 and 2008. Among the case reports, the majority of the reported symptoms involved upper respiratory and dermal effects. Upper respiratory effects include symptoms such as shortness of breath, asthma, respiratory distress, respiratory irritation, coughing/choking, difficulty breathing, sinus problems, chest congestion and pain and combination effects. Most of the incidents were not severe. However, a patient could exhibit multiple symptoms. There does not appear to be a change in reported incidents over time.

For the NIOSH SENSOR database, there are 120 cases reported. Cases that involve deltamethrin alone and where exposure was determined to be definite, probable, or possible, were reviewed in detail. These selection criteria resulted in the inclusion of 65 cases. For these cases, there were no fatalities. Fifty-eight of the cases were classified as low severity and 7 were classified as moderate severity. Eighteen of the deltamethrin cases involved minors (less than18 years old). The health effects most often reported include: gastrointestinal (46%), neurological (44%), respiratory (37%), dermal (35%), and ocular (23%). A patient could report various symptoms.

In twelve cases, people were exposed through spray drift. Ten workers and two children were exposed by spray drift from an adjacent field sprayed with deltamethrin. All reported neurological (headache) and gastrointestinal symptoms (nausea and/or vomiting). It appears that there was an increase in incidents in 2002; however, twelve of these incidents were the drift incidents mentioned above, that occurred at the same time and place. With the exception of the 2002 incidents, there does not appear to be a change in reported incidents over time.

In general, both the IDS and NIOSH SENSOR queries for deltamethrin resulted in moderately large numbers of case reports. However, most of these incidents were of low severity, and no patterns or trends were discerned among the reported cases. Subsequently, it is not clear human incident data warrant further analysis for the risk assessment and/or risk management of deltamethrin. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

Tolerance Assessment and International Harmonization

Tolerances are established for residues of deltamethrin in or on food and feed commodities under 40CFR §180.435. Tolerances have been established for numerous individual commodities and several crop groups. In addition, deltamethrin has been registered for use on stored grains and in food/feed handling establishments. For all commodities, tolerances are established in terms of parent deltamethrin and its major metabolites *trans* deltamethrin and *alpha*-R deltamethrin. A summary table of international MRLs can be found in Attachment 4.

Canada has not established any MRLs for deltamethrin; however, there are numerous uses in British Columbia and/or Eastern Canada. Mexico has established MRLs based on the U.S. tolerances. These MRLs are at the same level as the U.S. tolerances and are as follows: 1 ppm for the cereal grains group, 0.1 ppm for soybeans, 0.04 ppm for cottonseed, and 0.2 ppm for crambe, rapeseed, and tomatoes. Codex has established numerous MRLs for deltamethrin. Several of the commodities with Codex MRLs also have U.S. tolerances; however, many of them do not. In many cases, the U.S. tolerances are the same as, or higher than, the Codex MRL. There are a few commodities for which the U.S. tolerance is lower than the Codex MRL, however. Codex has a MRL of 2 ppm for cereal grains, whereas the U.S. tolerance is 1.0 ppm. Codex has a MRL of 1 ppm for pulses (dry beans, including soybeans), whereas the U.S. tolerance for soybeans is 0.1 ppm. Codex has a MRL of 0.5 ppm for the fat of cattle, goat, horse, and sheep, whereas the U.S. tolerance is 0.05 ppm. Finally, the Codex MRL for poultry fat is 0.1 ppm, whereas the U.S. tolerance is 0.05 ppm.

In effect, harmonization of tolerances with Canada and Mexico is not an issue because Canada has not established any MRLs for deltamethrin, and the Mexican MRLs are already harmonized with the U.S. tolerances. There are harmonization issues with Codex. These differences will be addressed during registration review.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in the most recent 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.eh.doe.gov/nepa/tools/guidance/Volume1/2-6-EO_12898 envjustice.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intakes by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups, and exposure assessments are performed when conditions or circumstances warrant.

The Office of Pesticide Programs (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 under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (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.

Between October 2009 and February 2010, EPA is issuing test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Deltamethrin is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines, and the Tier 1 screening battery, please visit the Agency's website: http://www.epa.gov/endo/.

Cumulative Risk Assessments

Deltamethrin is a member of the pyrethroid class of insecticides. This class also includes permethrin, cypermethrin, cyfluthrin, fluvalinate, bifenthrin, fenpropathrin, and lambda-cyhalothrin, among others. EPA developed a draft science policy document on the proposed common mechanism of toxicity for naturally-occurring pyrethrins and synthetic pyrethroids (Proposed common mechanism grouping for the pyrethrins and pyrethroids, draft, May 19, 2009; http://www.regulations.gov/search/Regs/home.html#documentDetail?R=09000064809a62df). This document was supported by the FIFRA Scientific Advisory Panel (SAP) and EPA will

finalize the policy document on the pyrethroid common mechanism of toxicity taking into account the SAP comments. Pesticides with a common mechanism of toxicity are subject to cumulative risk assessment under the FQPA. Research is ongoing by EPA's Office of Research and Development (ORD) to make improvements to the SHEDS Probabilistic Exposure Model which are important for the cumulative risk assessment. EPA ORD is also developing physiologically-based pharmacokinetic models for several pyrethroids. The status of both of these research modeling efforts will be reviewed by the FIFRA SAP in July, 2010. For information regarding EPA's efforts to evaluate the risk to pyrethroids, refer to http://www.epa.gov/pesticides/cumulative/.

Human Studies

Past deltamethrin risk assessments relied in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure. Many such studies, involving exposure to many different pesticides, comprise generic pesticide exposure databases such as the Pesticide Handlers Exposure Database (PHED), the Agricultural Reentry Task Force (ARTF) Database, and the Outdoor Residential Exposure Task Force (ORETF) Database. EPA has reviewed all the studies in these multi-pesticide generic exposure databases, and on the basis of available evidence has found them to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied.

Data Requirements

To support registration review, an immunotoxicity study should be submitted for deltamethrin. This study is a new requirement under the 40CFR Part 158 data requirements for registration of a pesticide (food and non-food uses). For purposes of refining postapplication dermal and oral exposures resulting from use of pet collars, a pet collar residue transfer study is required. This study should measure the amount of active ingredient that can transfer from the treated animal to the hands of individuals contacting the animal.

References

Author(s)	Barcode/ TXR No.	Date	Title
D. Dotson, N. McCarroll, A. Levy, & M. Collantes	D262496	11/15/2004	PP#s 0F6080 and 1E6232: Human Health Risk Assessment for the Proposed Section 3 Uses of Deltamethrin on Various Crops and Residential Scenarios
Douglas Dotson	D284297	11/12/2004	Acute Probabilistic and Chronic Dietary Exposure Assessments for the Section 3 Registration Action
William Drew	D338791	3/4/2008	Deltamethrin. Tolerance Petition Requesting the Establishment of Permanent Tolerances (Associated with Section 3 Registration) for Food Use of the Insecticide on Flax. Request for a Label Amendment Increasing the Use Rate on Soybeans. Summary of Analytical Chemistry and Residue Data
E. Scollon & M. Collantes	D367616	8/13/2009	Deltamethrin. Updated Hazard Characterization
D. Dotson & M. Collantes	D335134	8/13/2009	Deltamethrin. Response to Tolerance Petition for Use on Flax
Margarita Collantes	D274950	7/18/2003	Occupational and Residential Exposure and Risk Assessment for Proposed Uses of Deltamethrin on *Brassica* Vegetables; Bulb, Root and Tuber Vegetables; Cucurbit Vegetables, Fruiting Vegetables, Leafy Vegetables; Tall Field Row Crops (Corn, Sorghum, and Sunflower); Low Field Row Crops (Soybean); Deciduous Fruit Trees (Pome, Starfruit, and Stone); Stored Grain, Tree Nuts, Termiticides and Insecticidal Paint
M. Hawkins, J. Cordova, & S. Recore	D369651	11/24/2009	Updated Review of Deltamethrin Incident Reports
Versar	MRID 45345802	07/28/02	Review of Screening Risk Assessment: Potential Dermal Exposure from Handling Plastic Foam Insulation Containing Deltamethrin
M. Wolansky, C. Jennings, & M. Crofton	MRID 47885701	2006	Relative Potencies for Acute Effects of Pyrethroids on Motor Function in Rats, Toxicol. Sci., 89(1): 271-277

Attachments

Attachment 1. Chemical Identity Table
Attachment 2. Deltamethrin Endpoint Selection Tables
Attachment 3. DCI Justification for Immunotoxicity Study
Attachment 4. International Residue Limit Status
Attachment 5. Residential Postapplication Exposure and Risk Estimates

Attachment 1. Chemical Identity Table

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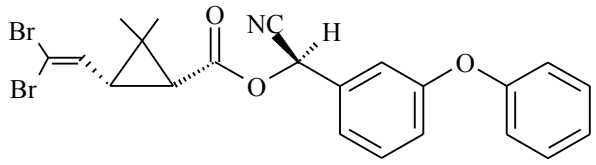
Chemical Identity	
Compound	Chemical Structure 
Common Name	*cis*-deltamethrin
Molecular Formula	$C_{22}H_{19}Br_2NO_3$
Molecular Weight	505.24
Company Experimental Name	AEF108569
IUPAC Name	(S)-α-cyano-3-phenoxybenzyl (1R,3R)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate
CAS Name	(1R,3R)-R-cyano(3-phenoxyphenyl)methyl 3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropanecarboxylate
CAS Number	52918-63-5
End-use Products (EPs)	Decis 1.5EC (EPA Registration #264-1011), Decis 0.2EC (EPA Registration #264-1007)

Attachment 2. Deltamethrin Endpoint Selection Tables

Summary of Toxicological Doses and Endpoints for Deltamethrin for Use in Human Risk Assessments

Table A.2.a. Summary of Toxicological Doses and Endpoints for Deltamethrin for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population, excluding Infants and Children)	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=1x	Acute RfD = 0.01 mg/kg/day aPAD = 0.01 mg/kg/day	The endpoint, decreased motor activity in male rats, is taken from an acute oral study (Wolansky et al., 2006). Using a nonlinear exponential threshold additivity model, a NOAEL (aka threshold dose) was obtained by fitting motor activity data across 7 dose groups; 0, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg. The NOAEL is an estimate of the highest no-effect dose level at which treated rats would not display any decrease in motor activity. Supported by subchronic rat, subchronic dog and chronic dog studies with NOAELs of 1mg/kg/day and LOAELs of 2.5 or 10 mg/kg/day based on signs of neurotoxicity including unsteadiness, tremors and jerking movements, salivation, and chewing on extremities (chronic dog only).
Acute Dietary (Infants and Children)	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=10x	Acute RfD = 0.01 mg/kg/day aPAD = 0.001 mg/kg/day	Decreased motor activity in adult male rats (Wolansky et al., 2006). See Acute Dietary-General population for supporting information.
Acute Dietary (Females 13-49 years of age)	N/A	N/A	N/A	No appropriate endpoint available
Chronic Dietary (All populations, excluding infants and children)	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=1x	Chronic RfD = 0.01 mg/kg/day aPAD = 0.01 mg/kg/day	Decreased motor activity in adult male rats (Wolansky et al., 2006). See Acute Dietary-General population for supporting information.
Chronic Dietary (Infants and children)	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=10x	Chronic RfD = 0.01 mg/kg/day aPAD = 0.001 mg/kg/day	Decreased motor activity in adult male rats (Wolansky et al., 2006). See Acute Dietary-General population for supporting information.

Table A.2.a. Summary of Toxicological Doses and Endpoints for Deltamethrin for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral; Short- (1-30 days) and Intermediate-Term (1-6 months)	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=10x	Residential LOC for MOE = 1000	Decreased motor activity in adult male rats (Wolansky et al., 2006). See Acute Dietary-General population for supporting information.
Dermal (General population excluding infants and children) All Durations	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=1x DAF: 1%	Residential LOC for MOE = 100	Decreased motor activity in adult male rats (Wolansky et al., 2006). See Acute Dietary-General population for supporting information.
Dermal (Infants and children) All Durations	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=10x DAF: 1%*	Residential LOC for MOE = 1000	Decreased motor activity in adult male rats (Wolansky et al., 2006). See Acute Dietary-General population for supporting information.
Inhalation (General population excluding infants and children) All Durations	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=1x IAF: 100%	Residential LOC for MOE = 100	Decreased motor activity in adult male rats (Wolansky et al., 2006). See Acute Dietary-General population for supporting information.
Inhalation (Infants and children) All Durations	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF=10x IAF: 100%	Residential LOC for MOE = 1000	Decreased motor activity in adult male rats (Wolansky et al., 2006). See Acute Dietary-General population for supporting information.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.

* DAF: 1%: 1% dermal absorption is based on preliminary review of the following two sources: (1) MRID 41917502, Dermal Absorption of (Carbon 14)-Capture 2 EC (FMC 54800) in the Rat: Lab Project Number: P01896: A90-3165: A490- 0723, Unpublished study prepared by Biological Test Center, Braun, R. (1990), and (2) In Vitro Dermal Absorption of Pyrethroid Pesticides in Rat and Human Skin. *The Toxicologist*, 90(1), Hughes, M. and B. Edwards, 2006

Table A.2.b. Summary of Toxicological Doses and Endpoints for Deltamethrin for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal All Durations	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x DAF: 1%	MOE = 100	The endpoint, decreased motor activity in male rats, is taken from an acute oral study (Wolansky et al., 2006). Using a nonlinear exponential threshold additivity model, a NOAEL (aka threshold dose) was obtained by fitting motor activity data across 7 dose groups; 0, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg. The NOAEL is an estimate of the highest no-effect dose level at which treated rats would not display any decrease in motor activity. Supported by subchronic rat, subchronic dog and chronic dog studies with NOAELs of 1mg/kg/day and LOAELs of 2.5 or 10 mg/kg/day based on signs of neurotoxicity including unsteadiness, tremors and jerking movements, salivation, and chewing on extremities (chronic dog only).
Inhalation All Durations	NOAEL= 1 mg/kg/day	UF_A= 10x UF_H=10x IAF: 100%	MOE = 100	Decreased motor activity in adult male rats (Wolansky et al., 2006). See Dermal for supporting information.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern.

Attachment 3. DCI Justification for Immunotoxicity Study

Guideline Number: 870.7800 **Study Title**: **Immunotoxicity**
Rationale for Requiring the Data
This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies assessing functional immunotoxic endpoints are helpful in fully characterizing a pesticide's potential immunotoxicity. These data will be used in combination with data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies to characterize potential immunotoxic effects.
Practical Utility of the Data
How will the data be used? These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have the data, a 10X database uncertainty factor might be applied for conducting a risk assessment from the available studies.

Attachment 4. International Residue Limit Status

Summary of US and International Tolerances and Maximum Residue Limits for Deltamethrin				
US		**Canada[2]**	**Mexico[3]**	**Codex**
Residue Definition:				
40CFR§180.435 deltamethrin [(1 *R* ,3 *R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid (*S*)- *alpha* -cyano-3-phenoxybenzyl ester and its major metabolites, *trans* deltamethrin [(*S*)- *alpha* -cyano- *m* -phenoxybenzyl(1R,3S)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate] and *alpha-R* -deltamethrin [(*R*)- *alpha* -cyano- *m* -phenoxybenzyl-(1 *R* ,3 *R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate]		None	deltamethrin	Sum of deltamethrin, alpha-R- and trans-deltamethrin (1R-[1alpha(R*),3alpha]]-3-(2,2-dibromoethenyl)-2,2-dimethyl-cyclopropanecarboxylic acid, cyano(3-phenoxyphenyl)methyl ester and [1R-[1alpha(S*),3beta]]-3-(2,2-dibromoethenyl)-2,2-dimethyl-cyclopropanecarboxylic acid, cyano(3-phenoxyphenyl)methyl ester)(fat-soluble).
Commodity Tolerance (ppm) /Maximum Residue Limit (mg/kg)				
Commodity	**US**	**Canada**	**Mexico**	**Codex**
Almond, hulls	2.5	None		
Apple, wet pomace	1.0			
Artichoke, globe	0.5			
Barley, bran	5.0			
Cattle, fat	0.05			
Cattle, meat	0.02			0.5 (fat)
Cattle, meat byproducts	0.05			0.03 (*) kidney, liver
Corn, field, forage	0.7			
Corn, field, refined oil	2.5			
Corn, field, stover	5.0			
Corn, pop, stover	5.0			
Corn, sweet, forage	10			
Corn, sweet, kernel plus cob with husks removed	0.03			0.02 (*)
Corn, sweet, stover	15			
Cotton, refined oil	0.2			
Cotton, undelinted seed	0.04		0.04	
Egg	0.02			0.02 (*)
Fruit, pome, Group 11	0.2			0.2 apple
Goat, fat	0.05			
Goat, meat	0.02			0.5 (fat)
Goat, meat byproducts	0.05			0.03 (*) kidney, liver
Grain, aspirated fractions	65			
Grain, cereal, Group 15, except sweet corn	1.0		1 barley 1 corn 1 millet 1 oat 1 rice 1 sorghum 1 wheat	2 Po
Hog, fat	0.05			

Summary of US and International Tolerances and Maximum Residue Limits for Deltamethrin				
US		**Canada[2]**	**Mexico[3]**	**Codex**
Horse, fat	0.05			
Horse, meat	0.02			0.5 (fat)
Horse, meat byproducts	0.05			0.03 (*) kidney, liver
Lychee[1]	0.2			
Milk, fat (reflecting 0.02 ppm in whole milk)	0.1			0.05 F
Nut, tree, Group 14	0.1			0.02 (*) hazelnuts 0.02 (*) walnuts
Onion, bulb	0.1			0.05
Onion, green	1.5			
Poultry, fat	0.05			
Poultry, meat	0.02			0.1 (fat)
Poultry, meat byproducts	0.02			0.02 (*)
Radish, tops	4.0			
Rapeseed	0.2		0.2	
Rice, hulls	2.5			
Rye, bran	5.0			
Sheep, fat	0.05			
Sheep, meat	0.02			0.5 (fat)
Sheep, meat byproducts	0.05			0.03 (*) kidney, liver
Sorghum, grain, forage	0.5			
Sorghum, grain, stover	1.0			
Soybean, seed	0.1		0.1	
Soybean, hulls	0.2			
Starfruit[1]	0.2			
Sunflower, seed	0.1			0.05 (*)
Tomato	0.2			
Tomato, paste	1.0			
Tomato, puree	1.0			
Vegetable, cucurbit, Group 9	0.2			0.2
Vegetable, fruiting, Group 8	0.3		0.2 tomato	0.3 tomato
Vegetable, root, except sugar beet, Subgroup IB	0.2			0.02 carrot 0.01 (*) radish
Vegetable, tuberous and corm, Subgroup IC	0.04			
Wheat, bran	5.0			5 PoP
Citrus fruits				0.02
Field pea dry				1 Po
Flowerhead brassica				0.1
Grapes				0.2
Leafy vegetables				2
Leek				0.2
Legume vegetables				0.2
Lentil dry				1 Po

Summary of US and International Tolerances and Maximum Residue Limits for Deltamethrin				
US		**Canada[2]**	**Mexico[3]**	**Codex**
Mushrooms				0.05
Olives				1
Potato			0.04	0.01 (*)
Pulses [dry beans]			1	1 Po
Stone fruits				0.05
Strawberry				0.2
Tea, green and black				5
Wheat flour				0.3 PoP
Wheat wholemeal				2 PoP

[1]There are no U.S. registrations for use of deltamethrin on starfruit and lychee.
[2]While there are no tolerances in Canada, there are numerous uses in British Columbia and /or Eastern Canada: alfalfa, *Brassica* vegetables, corn, potatoes, canola, mustard, pasture, sunflower, tomato, wheat, barley, oats, flax, lentils, sugarbeets, strawberry, blueberry, asparagus, apple, kale, peach, onion, pear, pepper..
[3]Mexico defers to US tolerances and/or Codex MRLs for its export purposes.
[3]Po = postharvest; (*) = absent at the limit of quantitation.; F = measured in milk fat; PoP = postharvest processed commodity

US:

(2) A tolerance of 0.05 ppm is established for residues of the insecticide deltamethrin (1 *R* ,3 *R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid (*S*)-alpha-cyano-3-phenoxybenzyl ester and its major metabolites, trans deltamethrin (*S*)-alpha-cyano- *m* -phenoxybenzyl-(1 *R* ,3 *R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate and alpha- *R* -deltamethrin[(*R*)-alpha-cyano- *m* -phenoxybenzyl-(1 *R* ,3 *R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate] as follows:

(i) In or on all food/feed items (other than those covered by a higher tolerance as a result of use on growing crops) in food/feed handling establishments.

(ii) The insecticide may be present as a residue from application of deltamethrin in food handling establishments, including food service, manufacturing and processing establishments, such as restaurants, cafeterias, supermarkets, bakeries, breweries, dairies, meat slaughtering and packing plants, and canneries, feed handling establishments including feed manufacturing and processing establishments, in accordance with the following prescribed conditions:

(A) Application shall be limited to general surface and spot and/or crack and crevice treatment in food/feed handling establishments where food/feed and food/feed products are held, processed, prepared and served. General surface application may be used only when the facility is not in operation provided exposed food/feed has been covered or removed from the area being treated. Spot and/or crack and crevice application may be used while the facility is in operation provided exposed food/feed is covered or removed from the area being treated prior to application. Spray concentration shall be limited to a maximum of 0.06 percent active ingredient. Contamination of food/feed or food/feed contact surfaces shall be avoided.

Attachment 5. Residential Postapplication Exposure and Risk Estimates

In order to provide a summary of the residential risks, focusing on those for which there is a risk concern, HED has used the previously calculated exposures, along with the revised LOC for adult and children's residential exposure. The updated exposure and residential risk estimates for the individual exposure pathways are provided in Tables A.5.a through A.5.d, below.

Table A.5.a. Deltamethrin Residential Postapplication Exposure of Children		
Scenario	**Exposure (mg/kg/day)**	**Projected Risk Estimates LOC = MOE = 1000**
Lawn		
Dermal		
Broadcast	0.0005	2,000
Hand-To-Mouth		
Broadcast	0.00194	**515**
Ingestion of Pesticide Treated Turf		
Delta WSB (Reg No. 432-832)		2,000
Ingestion of Treated Soil		
Delta WSB (Reg No. 432-832)		150,000
Incidental Ingestion of Granules		
DeltaGard® GC Insecticide (Reg No. 432-837)		190
Indoor Broadcast		
Dermal		
0.06 – 0.03% Sprays	0.0028 – 0.0014	**350 -690**
0.02% Sprays	0.00096	**1,000**
0.01% Spray	0.00048	2,100
Hand-To-Mouth		
0.06 – 0.02% Sprays	0.0044 – 0.0015	**230 - 670**
0.01% Sprays	0.00074	1,400
Indoor Crack & Crevice		
Dermal		
0.06 – 0.03% Sprays	0.0023 – 0.0011	**430 - 870**
0.02% Sprays	0.000768	1300
Hand-to-Mouth		
0.06 – 0.02% Sprays	0.0036 – 0.0012	**280 - 830**
0.01% Sprays	0.0006	1,700
Ingestion of Paint Chips		
Bug Juice Paint Additive (Reg. No. 4733211)		2,000

Table A.5.b. Deltamethrin Residential Dermal Handler Exposure to Deltamethrin 4% Pet Collar

Application Rate [1] (mg ai/treatment)	Dermal Absorption Factor %	Fraction of A.I. Applied	Exposure [2] (mg/kg/day)	MOE [3]
1008	0.01	0.01	0.00144	700

1. Application Rate = based on product net weight of 0.9 ounces = 28,000 mg x 0.9 ozs x 0.04 % ai. = 1008 mg ai
2. Exposure (mg/kg/day) = (AR * DA * F)/ BW
3. MOE = NOAEL (1 mg/kg/day)/Exposure (mg/kg/day)

Table A.5.c. Deltamethrin Residential Dermal Postapplication Exposure to Deltamethrin 4% Pet Collar

AR [1] (mg ai/ trtmnt)	SA_{pet} [2]	F_{AR} [3]	SA_{hug} [4]	DAF %	Dose [5] (mg/kg/day)	MOE [6]
Adult						
1008	5986	0.2	5625	0.01	0.027	**37**
Toddler						
1008	5986	0.2	1875	0.01	0.042	**24**

1. Application Rate = based on product net weight of 0.9 ounces = 28,000 mg x 0.9 oz x 0.04 % a.i. = 1008 mg ai
2. SA_{pet} = surface area of a treated dog (5986 cm^2/ animal)
3. F_{AR} = fraction of the application rate available as transferable residue (0.20), or fraction determined from a chemical-specific petting study
4. SA_{hug} = surface area of a child hug (5625 cm^2 (adult), 1875 cm^2 (toddlers))

5. Dose (mg/kg/day) = $\frac{[((AR * F_{AR}) / (SA_{pet})) * (SA_{hug}) * (DA)]}{BW\ (kg)}$

6. MOE = NOAEL (1 mg/kg/day)/Exposure (mg/kg/day)

Table A.5.d. Deltamethrin Residential Oral Postapplication Exposure to Deltamethrin 4% Pet Collar

AR [1] (mg ai/ trtmnt)	SA_{pet} [2]	F_{AR} [3]	SAL [4]	SA_{hands} [5]	Frequency 6	Dose[7] (mg/kg/day)	MOE [8]
Toddler							
1008	5986	0.2	0.5	20	1	0.0224	**45**

1. Application Rate = based on product net weight of 0.9 ounces = 28,000 mg x 0.9 oz x 0.04 % a.i. = 1008 mg ai
2. SA_{pet} = surface area of a treated dog (5986 cm^2/ animal)
3. F_{AR} = fraction of the application rate available as transferable residue (0.20), or fraction determined from a chemical-specific petting study
4. SAL = saliva extraction factor (50%)
5. SA_{hands} = surface area of a child's hands (20 cm^2)
6. Freq = frequency of hand-to-mouth events (1 event/day)

7. Dose (mg/kg/day) = $\frac{[((AR * F_{AR}) / SA_{pet})) * (SAL) * SA_{hands} * Freq)]}{BW\ (kg)}$

8. MOE = NOAEL (1 mg/kg/day)/Exposure (mg/kg/day)