DELTAMETHRIN

RISK CHARACTERIZATION DOCUMENT

Volume 1

HEALTH ASSESSMENT SECTION

MEDICAL TOXICOLOGY BRANCH, DEPARTMENT PESTICIDE REGULATION

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

June 13, 2000

CONTRIBUTORS AND ACKNOWLEDGMENTS

Authors:	Joseph P. Frank, D.Sc., Staff Toxicologist (Specialist) Health Assessment Section, Medical Toxicology Branch
	Thomas P. Kellner, Ph.D., D.A.B.T. Staff Toxicologist (Specialist) Product Data Review Section, Medical Toxicology Branch
Toxicology Reviews:	Joyce Gee, Ph.D., Senior Toxicologist SB-950 Data Review Section, Medical Toxicology Branch
	Peter Leung, Ph.D., D.A.B.T., Senior Toxicologist Product Data Review Section, Medical Toxicology Branch
Dietary Exposure:	Wesley Carr, M.S., Associate Pesticide Review Scientist Health Assessment Section, Medical Toxicology Branch
Peer Review:	Keith Pfeifer, Ph.D., D.A.B.T., Senior Toxicologist Health Assessment Section, Medical Toxicology Branch
	Jay Schreider, Ph.D., Primary State Toxicologist Medical Toxicology Branch, Medical Toxicology Branch

DPR acknowledges the review of this document by
the Office of Environmental Health Hazard Assessment and
the U.S. Environmental Protection Agency

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I. SUMMARY

A. INTRODUCTION

This document characterizes the potential risk, to individuals in the State of California, associated with the use of deltamethrin. The assessment was performed under the provisions of Senate Bill 950 (California Birth Defect Prevention Act), and Assembly Bill 2161 (referred to as the Food Safety Act). Senate Bill 950 requires a scientific determination that use of a registered pesticide will not cause significant adverse health effects. AB-2161 requires risk assessments on the dietary exposure to pesticides in both raw agricultural commodities and processed foods. This risk assessment was conducted as part of the registration (Section 3) process for new active ingredients.

Deltamethrin is the common name for (1R,3S)[α-cyano(3-phenoxyphenyl)methyl]-3-(2,2-dibromo-ethenyl)-2,2-dimethylcyclopropanecarboxylate (IUPAC). This compound is a pyrethroid that kills insects on contact and through ingestion. The exact mode of action for deltamethrin is currently not known. It is generally assumed, however, that pyrethroids affect neuroactivity by delaying the closing of sodium channels (Corbett et. al, 1984). This affects action potentials and often results in repetitive activity (type I) or blockage of nerve conduction (type II). Deltamethrin, a pyrethroid containing a cyano group, predominantly produces type II effects. Deltamethrin is the primary metabolite of another pyrethroid, tralomethrin. Environmental fate studies indicate that tralomethrin undergoes rapid and essentially complete debromination to form deltamethrin. In this risk assessment, therefore, tralomethrin data have been used in support of the registration petition for deltamethrin.

While the initial California registration application was for the technical material (to be used in formulating products), this risk assessment was performed on the basis of estimated California end-product uses. These include: treatment of cotton, residential and institutional establishments, non-food/feed areas of food/feed processing plants, granaries, and ornamental plants. Other potential uses involve residential, industrial, and institutional control of pests by professional pest control applicators. The primary use of deltamethrin (approximately 85% of the total production) is for crop protection (WHO: Environmental Health Criteria 97: Deltamethrin p.86 (1990).

B. TOXICOLOGY

A DPR review of the toxicology database on the effects of deltamethrin has identified potential adverse responses. This compound has been associated with clinical signs characteristic of autonomic nervous system dysfunction in humans and in laboratory animals. The human data were from reports from accidental poisonings and attempted suicides. The laboratory animal data were primarily from studies submitted in support of product registration under Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines.

Acute toxicity: Laboratory animal studies have demonstrated toxicity in response to acute exposure to technical grade deltamethrin, as well as, to acute exposure to product formulations containing deltamethrin as the active ingredient. The primary toxic signs were characteristic of agents that disrupt the autonomic nervous system and many of these signs were consistent with the neurotoxicity associated with pyrethroids. These signs included

excessive salivation, decreased activity, labored breathing, gasping, impaired limb function, ataxia, loss of righting reflex, tremors, convulsions, and lethality. Furthermore, signs of autonomic nervous system dysfunction (e.g., liquid feces, vomiting, and tremors) have been reported in studies designed to examine the effects of multiple exposures to deltamethrin. On the basis of autonomic nervous system dysfunction reported during the first week of a 13-week dog study (Chesterman, 1977) the lowest observed effect level (LOEL) for acute toxicity appeared to be 0.1 mg/kg/day (the lowest dose tested). This resulted in an estimated NOEL (i.e., ENOEL) of 0.01 mg/kg/day. The ENOEL was calculated by using the default approach of dividing the LOEL by an uncertainty factor of 10. In the process of DPR internal peer review, however, a consensus on the biological relevance of the effects reported at 0.1 mg/kg/day could not be established. Consequently, margins of exposure were calculated using both a NOEL of 0.1 mg/kg/day and a LOEL, with resultant estimated NOEL (i.e., ENOEL) of 0.01 mg/kg/day. Since oral absorption has been estimated to be 58%, (or approximately 60%) the acute NOEL of 0.1 mg/kg/day, was adjusted to 0.06 mg/kg/day, and the acute ENOEL of 0.01 mg/kg/day was adjusted to 0.006 mg/kg/day. Both values were used in this document for calculating margins of exposure (MOE's) for potential acute exposure to deltamethrin.

No evidence of delayed neurotoxicity was reported in domestic hens, however, the study was rejected by DPR as a FIFRA guideline study because no repeat dosing was conducted.

Sub-chronic toxicity: In addition to providing information that is useful in dose selection for chronic toxicity, reproductive, and oncogenicity studies, sub-chronic toxicology studies are designed to examine the adverse effects resulting from repeated exposure of a portion of the average life span of an experimental animal (Mosberg and Hays, 1989). When extrapolated to human exposure scenarios, sub-chronic toxicity studies can aid in the assessment of potential risk to agricultural workers involved with seasonal exposure to a pesticide. Furthermore, sub-chronic studies may aid in the assessment of potential risk to humans when home use is expected to be seasonal.

For NOEL determination, the same study that was demonstrated signs of autonomic nervous system dysfunction during the first week of exposure, also demonstrated these signs after 13 weeks (Chesterman, 1977). These signs included body tremors, jerking movements, vomiting, excessive salivation, liquid feces, reduced weight gain and decreased food consumption. The resulting LOELs/NOELs and adjustments were the same for sub-chronic toxicity as discussed under acute toxicity. Therefore, the sub-chronic NOEL used for risk assessment was 0.06 mg/kg/day, and the sub-chronic ENOEL was 0.006 mg/kg/day. Both values are used in this document for calculating margins of exposure (MOE's) for potential acute exposure to deltamethrin.

Chronic toxicity: In a two year oral toxicity and carcinogenicity study conducted in rats, Goldenthal (1980) reported a dose related increase in degeneration of sciatic, tibial, and plantar nerves. On the basis of nerve degeneration, the estimated critical NOEL for chronic toxicity was 0.06 mg/kg/day.

Oncogenicity: On the basis of the data reviewed, no evidence of oncogenicity potential was associated with deltamethrin exposure.

Genotoxicity: Deltamethrin was tested for genotoxic potential *in vitro* using *Schizosaccharomyces Pombe* to test for gene mutation, Chinese Hamster Ovary (CHO) cells to test for chromosome aberrations and rat primary hepatocytes to test for unscheduled DNA synthesis (UDS). In these test systems, no genotoxic potential was reported. In other recently published studies appearing in the open literature, positive genotoxicity was reported for deltamethrin technical (or formulations with deltamethrin as the active ingredient) in both *in vivo* (e.g., chromosome aberrations and micronucleus test) and *in vitro* (sister-chromatid exchange in human lymphocytes) test systems.

Reproductive Toxicity: A rat reproduction study submitted by the registrant indicated minor effects (reduced pup weight) but was considered unacceptable to DPR based on FIFRA guidelines (Wrenn, 1980). Microscopic examinations were limited to F_{3b} weanlings and no parental microscopic data were collected. After a review of the open literature, a study was found that indicated a number of reproductive effects in rats treated with deltamethrin. Deltamethrin significantly decreased the weight of testes, seminal vesicle, and prostate glands. Significant decreases were also noted in sperm cell concentrations, percentage of live cells and sperm motility. Furthermore, plasma testosterone concentration was significantly decreased and the pregnancy rate was depressed (Abd El-Aziz, 1994).

Developmental Toxicity: In the studies submitted in support of registration, no significant developmental toxicity was reported in rats (Schardein, 1990a) or in rabbits (Schardein, 1990b). Effects in rats have been reported, however, in the open literature (Abd El-Khalik, et. al, 1993). These researchers reported that a 5% deltamethrin formulation results in dose-dependent early embryonic death, retardation of fetal growth, hypoplasia of the lungs, and dilation of the renal pelvis.

C. EXPOSURE

Occupational and residential exposures to deltamethrin has been estimated, using surrogate data, by the Worker Health and Safety branch of DPR (Thongsinthusak, 1996). Anticipated deltamethrin uses include agricultural (treatment of cotton), residential, industrial, institutional, on flowers and ornamentals. Deltamethrin formulations considered representative of potential products for sale in California included Decis 0.2 EC (2.5% active ingredient), Decis 1.5 EC (16.6%ai)(agricultural use), K-Othrin SC (4.75 % ai; residential, industrial, and institutional), and K-Othrin Dust (0.05% ai; flowers and ornamentals). Daily, seasonal, annual, and lifetime dosages were calculated for specific exposure scenarios. In addition, deltamethrin exposure resulting from the consumption of commodities treated with deltamethrin was considered. The commodities evaluated for dietary exposure potential included cotton products, tomatoes and tomato products. Finally, combined occupational and dietary exposures were evaluated.

D. RISK CHARACTERIZATION

In order to characterize the potential risks associated with exposure to deltamethrin, margins of exposure (MOE's) were calculated for each of the exposure scenarios previously described. An MOE is defined as the ratio of the No-Observed-Effect-Level (NOEL) to the absorbed dosage. When the NOEL for an adverse effect is derived from a laboratory animal study, a calculated MOE of 100 is generally considered adequate for protection against potential toxicity of a chemical. This benchmark of 100 includes an

uncertainty factor of 10 for intraspecies variability, as well as an uncertainty factor of 10 for inter-species variability. This latter uncertainty factor assumes that the least sensitive human is 10 times more sensitive to the effects of a toxin than the most sensitive laboratory animals (Davidson et al., 1986; Dourson and Stara, 1983,1985; USEPA, 1986b). If the critical NOEL is from a human study, a benchmark of 10 is used, incorporating a single uncertainty factor which assumes there is only a 10-fold difference between the least sensitive and most susceptible human. Margins of exposure for deltamethrin exposure were all based on NOEL's from laboratory animal data.

The following is a summary of the MOEs for the various exposure scenarios:

Acute Occupational Exposure Excluding Dietary Contribution: For Decis, 0.2 EC, using an ENOEL of 0.006 mg/kg/day, the estimated acute (daily) margin of exposure for flaggers was 100 (Table 30a). For all other worker activities, MOE's were less than 100. For mixer/loaders and applicators, involved with the aerial application of the product, estimated MOE's are 5 and 8, respectively. With ground boom application, the MOE's for mixer/loaders, applicators, and mixer/loader/applicators were 8, 67, and 7, respectively. MOE's for cotton scouts were 35 and 21 for gloved and not gloved workers, respectively. When the MOE's were based on the average acute exposure rather than the upper-bound estimate, the values ranged from 13 to 200. The MOE's were greater than 100 for flaggers and applicators involved with ground boom application. The MOE's were less than 100 for all other activities. When the MOE's were based on a NOEL of 0.06 mg/kg/day, the respective values were elevated 10-fold.

For Decis 1.5 EC, using an ENOEL of 0.006 mg/kg/day, all estimated MOE's for acute exposure to deltamethrin were less than 100. The MOE's range from 4 (mixer/loaders involved with aerial application) to 67 (flaggers). When the MOE's were based on the average acute exposure rather than the upper-bound estimate, the values ranged from 8 to 120. When the MOE's are based a NOEL of 0.06 mg/kg/day, the respective values were elevated 10-fold.

For the residential use of deltamethrin products, using an ENOEL of 0.006 mg/kg/day, calculated MOE's were less than 100 for PCO's, infants, and adult males (<1, <1, and 1, respectively). When the MOE's were based on the average acute exposure rather than the upper-bound estimate, the values remained the same. When the MOE's were based a NOEL of 0.06 mg/kg/day, respective values were elevated 10-fold.

For acute exposure associated with the use of K-Othrine Dust on flowers and ornamentals, using an ENOEL of 0.006 mg/kg/day, the calculated MOE was 8 for loader/applicators. When the MOE's were based a NOEL of 0.06 mg/kg/day, The MOE was increased to 80.

Acute Dietary Exposure: Using an ENOEL of 0.006 mg/kg/day, margins of exposure were less than 100 for all population sub-groups examined. Using a NOEL of 0.06 mg/kg/day the MOE's increased by 10-fold, however, all estimated MOE's were still less than 100.

Combined Acute Occupational and Dietary Exposure: When potential acute occupational exposure to deltamethrin was combined with potential dietary exposure, all margins of exposure based on an acute ENOEL of 0.006 mg/kg/day or an acute NOEL of 0.06 mg/kg/day were less than 100.

Seasonal Occupational Exposure Excluding Dietary Contribution: For seasonal exposure to deltamethrin from the use of Decis 0.2 EC and Decis 1.5 EC, and using an ENOEL of 0.006 mg/kg/day, the calculated MOE's were greater than 100 for flaggers and applicators involved with ground boom application. The MOE's for all other worker activities are less than 100. When the MOE's were based a NOEL of 0.06 mg/kg/day, values were elevated 10-fold.

Seasonal exposure does not apply to residential PCO or home applications; therefore, margins of exposure were not calculated for these activities.

For seasonal exposure associated with the use of K-Othrine Dust, the calculated margins of exposure were greater than 100 for both NOEL's.

Combined Seasonal Occupational and Dietary Exposure: When potential seasonal occupational exposure to deltamethrin was combined with potential dietary exposure, all margins of exposure based on a sub-chronic ENOEL of 0.006 mg/kg/day were less than 100 for Decis 0.02 EC and Decis 1.5, and for flower and ornamental use. When margins of exposure were based on a sub-chronic NOEL of 0.06 mg/kg/day, the MOEs were less than 100 for mixer/loaders involved with aerial application of Decis 0.02 EC and Decis 1.5 EC and applicators involved with the aerial application of Decis 1.5 EC.

Annual Occupational Exposure Excluding Dietary Contribution: On the basis of annual exposure estimates, calculated margins of exposure for all agricultural and residential activities were greater than 100, except for residential PCO's. Their MOE was 2.

Annual Dietary Exposure: The lowest annual dietary MOE's were 64 and 80 for children 1-6 and children 7-12, respectively. All other population sub-groups had MOE's greater than 100.

Combined Annual Occupational and Dietary Exposure: When potential annual occupational exposure to deltamethrin was combined with potential annual dietary exposure, all margins of exposure based on a chronic NOEL of 0.06 mg/kg/day were greater than 100 except for those involved in home uses. The MOE for pest control operators was 2. For adult males the MOE was 97 and for infants the calculated MOE was 100.

Life-time exposure; On the basis of the toxicology data base evaluated, the NOEL for life-time exposure to deltamethrin was the same as that used for annual exposure, i.e., 0.06 mg/kg/day. The average daily dosage for life-time exposure was estimated by taking the average daily dosage for annual exposure and amortizing over a lifetime. This assumes 40 years of exposure over a lifetime of 70 years. Since the amortization reduces the potential exposure by approximately 57% (40/70), MOE estimations were not considered necessary for life-time deltamethrin exposures (i.e., risk estimates considered acceptable for annual exposure would by default be acceptable for life-time exposures).

E. TOLERANCE ASSESSMENT

An acute exposure assessment using the residue level equal to the tolerance was conducted for each individual label-approved commodity. The TAS Exposure-4™ software

program and the USDA consumption database were used in the assessment. On the basis of acute exposure to deltamethrin from tomatoes, all population sub-groups had calculated margins of exposure of less than 100 when residue levels were based on tolerance. When tolerance levels of deltamethrin were assumed for exposure from use on cottonseed, margins of exposure were less than 100 for non-Hispanic blacks (88), nursing infants (91), non-nursing infants (93), all infants (89), children ages 1-6 (58), and children ages 7-12 (68). All other population sub-groups had MOE's greater than 100.

An annual exposure assessment using residues equal to the established tolerances for individual or combinations of commodities has not been conducted because it is highly improbable that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from FDA and DPR (formerly California Department of Food and Agriculture) pesticide monitoring programs which indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (CDFA, 1990).

II. INTRODUCTION

Deltamethrin is a broad-spectrum insecticide that has been associated with nervous system toxicity in laboratory animals and in humans. The human effects have primarily been the result of accidental poisonings and attempted suicides. This document characterizes the potential risk associated with dietary, occupational and residential exposures to this pesticide. This assessment was performed under the provisions of Senate Bill 950 (California Birth Defect Prevention Act), and Assembly Bill 2161 (referred to as the Food Safety Act). Senate Bill 950 requires a scientific determination that use of a registered pesticide will not cause significant adverse health effects. AB-2161 requires risk assessments on the dietary exposure to pesticides in both raw agricultural commodities and processed foods.

A. CHEMICAL IDENTIFICATION

Deltamethrin is the common name for (1R,3S)[α-cyano(3-phenoxyphenyl)methyl]-3-(2,2-dibromo-ethenyl)-2,2-dimethylcyclopropanecarboxylate (IUPAC). Deltamethrin is a pyrethroid that kills insects on contact and through ingestion. The exact mode of action for deltamethrin is currently not known. It is generally assumed that pyrethroids affect neuroactivity by delaying the closing of sodium channels (Corbett et. al, 1984). This affects action potentials and often results in repetitive activity (type I) or blockage of nerve conduction (type II). Deltamethrin, a pyrethroid containing a cyano group, predominantly produces type II effects.

It is important to note that deltamethrin is the initial and primary metabolite of the pyrethroid tralomethrin. This risk assessment assumes that, in general, all properties and characteristics of tralomethrin would be the same for deltamethrin. Tralomethrin data (e.g., environmental fate) will, therefore, be utilized to supplement experimental data from deltamethrin studies (Frank, 1996).

B. REGULATORY HISTORY

As of January 9, 1997, there were 4 active California registrations for pesticide products containing deltamethrin. These include Deltadust, a 0.05% active ingredient product, a 2.6% active ingredient emulsifiable concentrate, K-Othrine SC Insecticide with 4.75% active ingredient and Delta Tech, with 98% active ingredient. As of August 1996, 16 products containing deltamethrin were registered by the U.S. EPA. The U.S. Environmental Protection Agency has established tolerances for residues of deltamethrin in cottonseed and tomatoes (EPA, 1996).

C. TECHNICAL AND PRODUCT FORMULATIONS

Deltamethrin is the active ingredient used in a number of commercial insecticide products. The producer and/or registrant for these products include: AgrEvo Environmental Health (DeltaDust and DeltaGard); AgrEvo, S.A. (Decis K-Obiol, and K-Othrine); AgrEvo USA Co. (Decis, Medmac, and Deltamac); Sanex Inc. (Deltex).

D. USAGE

The primary use of deltamethrin (approximately 85% of the total production) is for crop protection (WHO: Environmental Health Criteria 97: Deltamethrin, p.86 (1990)). Deltamethrin is also used to protect stored commodities such as cereals, grains, and coffee beans. Other uses include insect control for public health concerns, pest control in forestry, pest control in animal facilities, parasite control on animals, and as a wood preservative. (WHO: Environmental Health Criteria 97: Deltamethrin, p.85 (1990); Hartley, Agrochem HDBK 2nd edition 1987 A122/Aug 87).

While the initial California registration application was for the technical material (to be used in formulating products), anticipated California end-product uses include: treatment of cotton, residential and institutional establishments, non-food/feed areas of food/feed processing plants, granaries, and ornamental plants. Other potential uses involve residential, industrial, and institutional control of pests by professional pest control applicators.

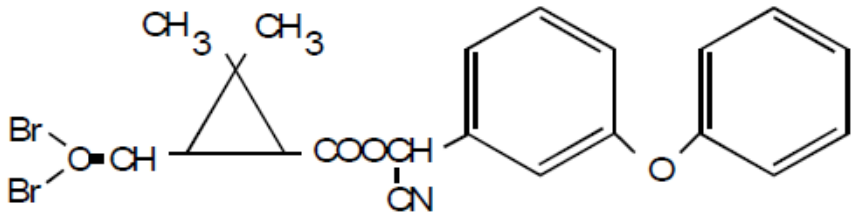
E. ILLNESS REPORTS

Since deltamethrin has only recently been registered in California, illness records do not exist in the state. The toxicity of deltamethrin to humans has, however, been documented elsewhere. He et al., (1989) have reported 325 cases of deltamethrin poisonings due to agricultural use and accidental or suicidal poisoning. Oral ingestion has been associated with epigastric pain, nausea, vomiting, coarse muscular fasciculation, and coma. Workers exposed to deltamethrin during its manufacture experienced cutaneous and mucous membrane irritation.

F. PHYSICAL AND CHEMICAL PROPERTIES[1,2]

1.	Chemical Name:	(1R,3R) [α-cyano(3-phenoxyphenyl)methyl]-3-(2,2-dibromo-ethenyl)-2,2-dimethylcyclopropanecarboxylate (IUPAC)
2.	Common Name:	Deltamethrin
3.	Trade Names:	Butoflin™; Butox™; Decis™; K-Othrin™; K-Othrine ™ Dust; Striker™ IEC insecticide

4. Structural Formula:



5.	Empirical Formula:	$C_{22}H_{19}Br_2NO_3$
6.	CAS Registry Number:	52918-63-5
7.	Molecular Weight:	505.2 g/mole
8.	Specific Gravity:	1.053g per ml at 20°C (Decis) 0.5g per ml at 20°C (Technical Grade of AI)
9.	Physical State:	White to beige crystalline powder
9.	Boiling Point	Not applicable
10.	Solubility:	Soluble in acetone, dimethylformamide, dioxane, ethyl acetate, and toluene (all 23 - 39%), relatively insoluble in water (i.e., 0.2 ppb in 24 hours)
11.	Vapor Pressure:	1.5×10^{-8} mmHg at 25°C (> 90% AI)
12.	Octanol/Water Partition Coefficient:	2.7×10^{5} at 25°C
13.	Henry's Law Constant:	2.7×10^{-6} atm/m^3 per mole
14.	pH:	5.9 (in a 1% aqueous dispersion)

[1,2](Grelet, 1990 and Lambert, 1991)

G. ENVIRONMENTAL FATE

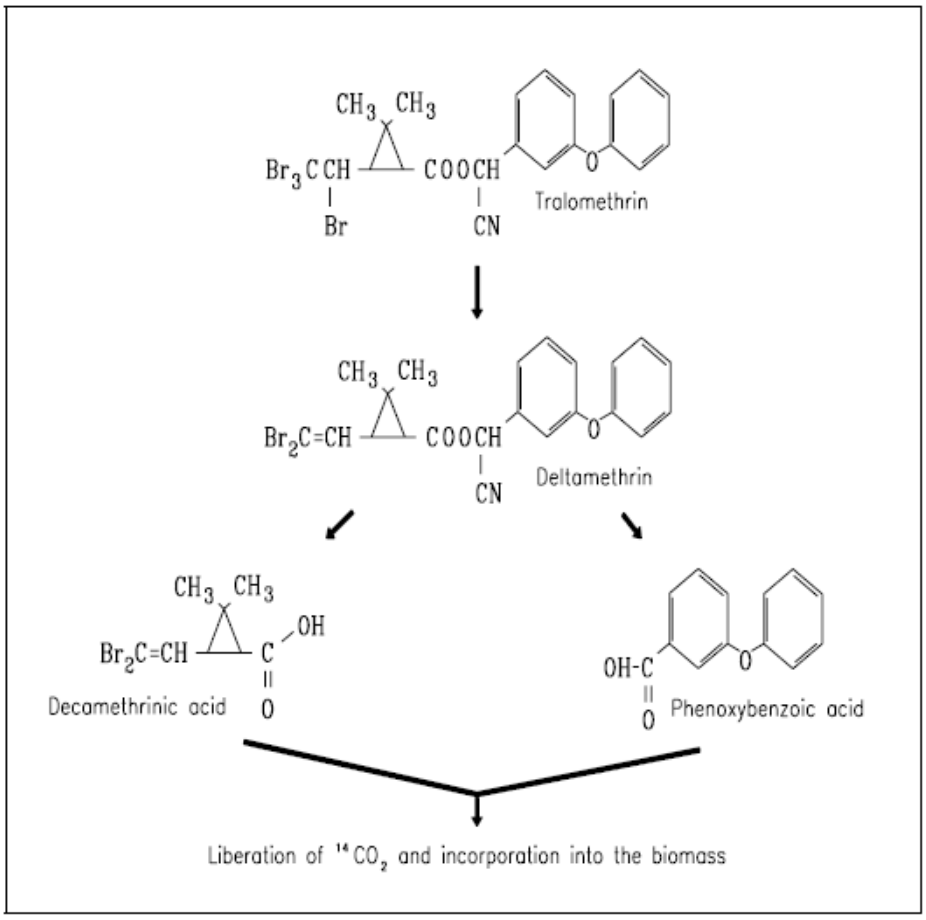
1. Summary

In addition to being sold as a pesticide, deltamethrin is the primary metabolite of another pyrethroid, tralomethrin. Environmental fate studies have indicated that tralomethrin is unstable under both aerobic and anaerobic conditions and rapidly undergoes debromination to form deltamethrin. The half-life of tralomethrin is approximately 3 days (aerobic conditions). For this risk assessment, the environmental fate of deltamethrin is assumed to be the same as that previously reported for tralomethrin (Frank, 1995). The calculated half-life of deltamethrin is approximately 33 days (aerobic conditions). Molecular cleavage of deltamethrin gives rise to decamethrin and phenoxybenzoic acid. The major degradation products are the same after hydrolysis, aqueous photolysis, soil photolysis, and plant metabolism. Studies indicate that due to soil adsorption properties, tralomethrin has a low potential for ground water contamination. A study with bluegill sunfish indicated that tralomethrin can bio-accumulate. Furthermore, the physical and chemical properties (e.g., low water solubility, high octanol/water partition coefficient, and low vapor pressure) are characteristic of a chemical that would be relatively immobile in soil, have a low potential to leach, and a high potential to bio-accumulate (Ney, 1990).

2. Aerobic Metabolism

The aerobic soil metabolism of tralomethrin was investigated by Wang (1990a). Under aerobic conditions in a sandy loam soil, with an application rate of 0.2 ppm, tralomethrin rapidly underwent debromination to form deltamethrin. Subsequent molecular cleavage gave rise to decamethrin and phenoxybenzoic acid. These two metabolites were then mineralized to carbon dioxide and incorporated into the soil biomass (see Figure 1 on next page for a graphic representation). The reported half-life for the parent compound was approximately 3 days. The formation and decline of deltamethrin appeared to reach equilibrium by 7 days post-application. The calculated average half-life for deltamethrin was 33 days.

Figure 1: Deltamethrin (and Tralomethrin): Proposed Metabolic Pathway in Sandy Loam Soil Under Aerobic Conditions



3. Anaerobic Metabolism

The metabolism of tralomethrin under anaerobic conditions was investigated by Wang (1990b). Under laboratory conditions at 25°C in the dark, tralomethrin was allowed to degrade aerobically for 3 days (approximately one half-life under aerobic conditions). This was followed by 91 days of anaerobic conditions induced by flooding with degassed deionized water. As with the aerobic study discussed above, an application rate of 0.2 ppm in sandy loam soil was used. Tralomethrin rapidly underwent debromination to form deltamethrin. Final anaerobic metabolites were essentially the same as reported for aerobic metabolism.

After 30 days of flooding, no tralomethrin was detected. Furthermore, deltamethrin accounted for 35% to 40% of the applied chemical. After 91 days deltamethrin accounted for 11% to 13%. Br_2CA increased steadily until reaching approximately 60% by day 91. Phenoxybenzoic acid increased to approximately 21% during the first 60 days of flooding, declining to approximately 3% by day 91.

4. Hydrolysis

The hydrolytic behavior of tralomethrin at pH 4, 5, 7, and 9 was examined by Wang (1990c). The test was conducted in the dark at 25°C. Initial debromination of the parent compound to form deltamethrin was detected at all pH levels. The calculated half-lives of tralomethrin were 95, 94, 33, and 37 days at pH 4, 5, 7, and 9, respectively (Note: the value at pH 5 [94] was reported as 940 but was assumed to be a typographical error and should have been 94) The major degradation products were the same as those reported in the soil metabolism studies.

5. Aqueous Photolysis

The photodegradation of tralomethrin in a pH 5 aqueous solution under simulated sunlight was examined by Wang (1991a). The irradiation was conducted at 25°C with intermittent 12 hour light and dark cycles each day for 30 days. Samples were harvested at 0, 2, 3, 7, 14, 21, and 30 days post treatment. The calculated half-life for tralomethrin under these test conditions was 3.6 days. The major degradation products were the same as those reported in the soil metabolism studies.

6. Soil Photolysis

The photodegradation of tralomethrin in sandy loam soil, under simulated sunlight, was examined by Wang (1991b). The irradiation was conducted at 26°C with intermittent 12 hour light and dark cycles each day for 30 days. The calculated half-life for tralomethrin under test conditions was 6.4 days. The major degradation products were the same as those reported in the soil metabolism studies. The calculated half-life for combined pyrethroids under test conditions was 18 days.

7. Leaching Potential

A soil adsorption/desorption study was conducted at 25°C, in the dark, with radiolabeled tralomethrin and four soil types (i.e., sand, sandy loam, loam, and clay loam). Tralomethrin was found to be immobile in all four soil types. Quantitative interpretation of the study was hindered, however, by excessive adsorption of the test material to the test containers. The study director did, however, indicate that the study results implied that tralomethrin would adsorb to soil rather than remain in solution.

8. Plant Residues/Metabolism

The metabolism of tralomethrin in plants has been investigated (Hoechst-Roussel, 1985). The isomeric mixture of tralomethrin and its individual isomers was reported to dissipate from cotton leaves with half-lives of 10 days. Tralomethrin was debrominated to deltamethrin. The half-life of deltamethrin was also reported to be 10 days. The degradation of deltamethrin produced decamethrinic acid and phenoxybenzoic acid (see animal metabolism).

9. Fish Accumulation

The uptake, depuration, and bioconcentration, by fish, of radiolabeled tralomethrin were investigated by Thompson (1983). In this study, bluegill sunfish were exposed to 0.085 µg/l ^{14}C-tralomethrin for 30 days (groups of 100 fish each were placed in duplicate and control test chambers). Water and fish were observed every 24 hours during the uptake (exposure) period. Following the 30 day exposure period, water in the test chambers was replaced with clean well water and the fish were held in this "depuration" phase for 21 days. Radio-analysis of whole fish, fillet, and viscera was conducted at various times throughout the uptake and depuration phases of the study. A gradual uptake of ^{14}C-tralomethrin was reported. Daily bioconcentration factors ranged from 180-490, 47-100, and 310-920 for whole fish, fillet and viscera, respectively. Uptake tissue concentration ranges were 13-36 ppb, 3.5-10 ppb, and 23-68 ppb for whole fish, fillet and viscera, respectively. Accumulation was reported to reach a steady-state plateau after 14 days of exposure. During this depuration period, radio-analysis indicated 89, 79, and 88 percent clearance rates for whole fish, fillet, and viscera, respectively. Utilizing linear regression analysis, an uptake rate constant of 58 ppb in whole fish, per ppb in water, per day was calculated. A steady-state bioconcentration factor of 530 was calculated.

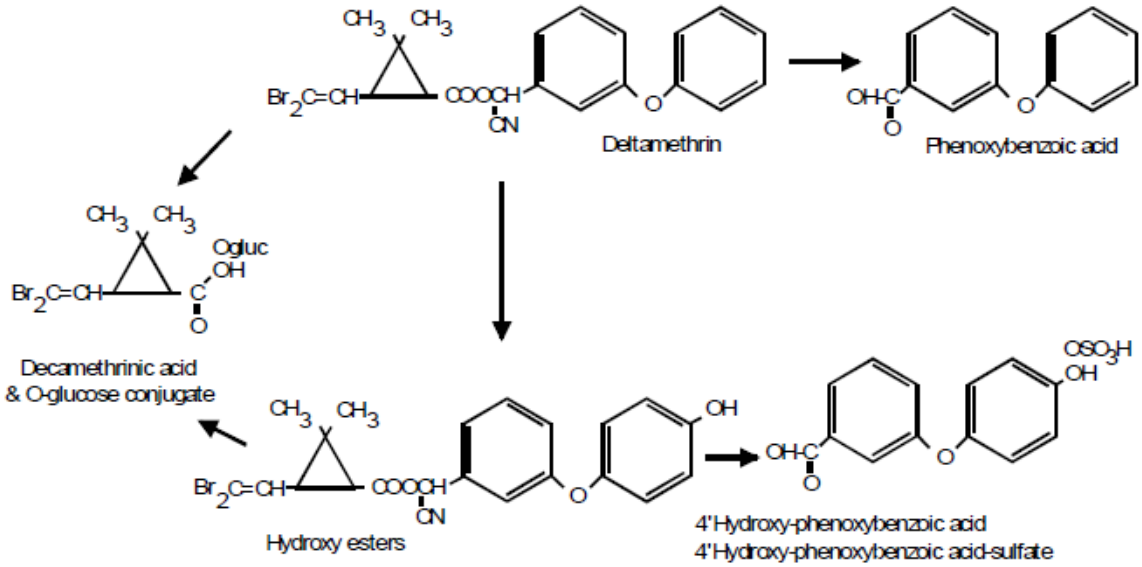
III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

1. Rat

The metabolism of deltamethrin by the rat has been extensively studied by Cole, *et al.* (1982) and Bosch (1990). Deltamethrin is hydroxylated at the 2', 4' and 5 positions of the alcohol moiety and the methyl group trans to the carboxylate linkage; extensive ester cleavage of deltamethrin yields a series of alcohols and carboxylic acids and their glucuronide, glycine, and sulfate conjugates. The proposed metabolic pathway is presented in Figure 2:

Figure 2: Deltamethrin: Proposed Metabolic Pathway in Rats.



Metabolism of ^{14}C-Deltamethrin was studied in male and female rats dosed orally with ^{14}C-Deltamethrin labeled in two positions (^{14}C-benzyl at 59.2 mCi/mmol or ^{14}C-dimethyl deltamethrin at 60 mCi/mmol) (Bosch, 1990). Groups of 5 Crl:CD(SD)BR rats per sex were given 0.55 mg/kg (single oral dose), 0.55 mg/kg (14 non-radiolabeled doses followed by a radiolabeled dose on day 15) or 5.50 mg/kg (single oral dose). It was shown that most of the radioactivity was excreted in the urine and feces within 24 hours of dosing and that tissue and carcass residues were less than 2% of the dose at 7 days. Most residual radioactivity was stored in the fat; for the low dose groups, radioactivity concentrations ranged from 0.047 to 0.093 ppm. For the high doses, these values ranged from 0.504 to 0.840 ppm. Rats dosed with ^{14}C-benzyl deltamethrin had 30 to 49% excreted in the urine as the sulfate conjugate 4'SO_4-mPBAcid and 2% to 4% as unconjugated mPBAcid. In the feces, 17 to 46% was excreted as deltamethrin (the higher dosage rats excreted a higher percentage in the feces as deltamethrin and a lower percentage in the urine as 4'SO_4-

mPBAcid). For rats dosed with ^{14}C-Dimethyl deltamethrin, 22 to 38% of the dose was excreted in the urine as the glucuronide conjugate Br_2CA-glucuronide and 4 to 10% as the unconjugated Br_2CA; in the feces, 21 to 35% was excreted as deltamethrin.

2. Mouse

Metabolic studies on deltamethrin have also been performed in mice (WHO, 1990). The major metabolic pathways in mice were similar, but not identical to those in rats. One of the differences seen in mice was the presence of more unchanged deltamethrin in the feces. In mouse feces, there were 4 monohydroxy ester metabolites (2'-OH-, 4'-OH-, 5-OH- and trans-OH-deltamethrin) and one dihydroxy metabolite (4'-OH-*trans*-OH-deltamethrin) that were not found in mouse urine. Major metabolites from the acid moiety in mice were Br_2CA, *trans*-OH-Br_2CA (only detected in mice), and their glucuronide and sulfate conjugates. Large amounts of *trans*-OH-Br_2CA and its conjugates were formed in mice and a major metabolite of the alcohol moiety in mice was the taurine conjugate of PBacid in the urine, which is not detected in rats. Mice also tend to produce less phenolic compounds compared to rats. Other metabolites found in mice, but not rats, included 3-phenoxy benzaldehyde (PBald), 3-phenoxy benzyl alcohol (PBalc), and its glucuronide, and the glucuronide of 3-(-4-hydroxy phenoxy)benzyl alcohol (4'-OH-PBalc) and 5-hydroxy-3-phenoxy benzoic acid (5-OH-PBacid).

3. Humans

Studies of deltamethrin metabolism have been performed in human volunteers (WHO, 1990). Each of three young males received a single oral dose of 3 mg of ^{14}C-deltamethrin mixed in 1 g of glucose and diluted in 10 ml polyethylene glycol 300 and then in 150 ml water (total radioactivity was 1.8±0.9 mBq). Samples of blood, urine, saliva and feces were collected at intervals over a 5 day period. Clinical and biological examinations, performed every 12 hours during the trial and one week after termination, revealed no abnormal findings. The peak plasma radioactivity appeared between 1 and 2 hours after administration and remained over the detection limit (0.2 Kbq/l) during the next 48 hours. Apparent elimination half-life was between 10.0 and 11.5 hours and the radio-label detected in blood cells and saliva was extremely low. Urinary excretion was about 50% of the initial radioactivity and 90% of the radio-label was excreted during the initial 24 hours following administration. The apparent half-life of urinary excretion was 10.0 to 13.5 hours (consistent with plasma levels). Fecal elimination at the end of the observation period represented 10-26% of the dose and the total of fecal plus urine elimination was approximately 64 to 77% of the initial dose after 96 hours. On the basis of this information, human oral absorption is assumed to be at least 50%.

4. Oral absorption

The extent of absorption following oral exposure to a chemical can be estimated on the basis of excretion analysis following oral and intravenous (i.v.) exposures (i.e., If the i.v. exposure is assumed to represent 100% absorption, then the extent of absorption following oral exposure is the percent urinary excretion after oral exposure divided by the percent of urinary excretion after intravenous exposure).

$$\text{Extent of absorption} = \frac{\%\ \text{urinary excretion}_{\text{(oral study)}}}{\%\ \text{urinary excretion}_{\text{(i.v. study)}}}$$

Rat: For deltamethrin, the estimated absorption was based on the metabolism and excretion of tralomethrin by SD rats (Tanoue 1988). The use of tralomethrin data as a surrogate for deltamethrin was considered appropriate since tralomethrin is rapidly and completely debrominated to form deltamethrin in the G.I. tract. Five male and 5 female SD rats were used for the oral dosing portion of the test while 7 to 8 males were used for the i.v. portion of the study. Animals were treated with ^{14}C-labeled acid, alcohol, or cyano tralomethrin at a concentration of 0.3 mg/kg. Urine and feces were collected at 24 hour intervals until the animals were killed (after 4 days for the acid and alcohol moieties, and 7 days for the CN moiety). Oral dosages of 0.3 mg/kg of tralomethrin ^{14}C-labeled at the acid, alcohol or CN moiety resulted in urinary excretion of 43.9, 46.0 and 14.6%, respectively. For i.v. administration, the corresponding urinary excretion was 69.1, 75.7 and 28.7%, respectively. The final extent of absorption values were, therefore, 63.5, 60.8 and 50.9% for the acid, alcohol and CN-labeled tralomethrin, respectively. On the basis of these excretion values, a mean oral absorption of 58.4% was calculated.

Table 1: Deltamethrin oral absorption estimates based on tralomethrin bio-transformation and urinary excretion studies in rats (Tanoue 1988).

^{14}C-labeled tralomethrin	% Urinary Excretion		% Oral Absorption[1]	Mean
	Oral Study	i.v. Study		
acid	43.9	69.1	63.5	
alcohol	46.0	75.7	60.8	58.4
cyano	14.6	28.7	50.9	

[1] $\text{Extent of absorption} = \frac{\%\ \text{urinary excretion}_{\text{(oral study)}}}{\%\ \text{urinary excretion}_{\text{(i.v. study)}}}$

For this risk assessment, the oral absorption of deltamethrin in rats was assumed to be approximately 60%. This was based on the above urinary excretion studies and supported by the fecal excretion calculations from this study (not shown). Furthermore, this value is consistent with the oral absorption estimate from human data (i.e., at least 50%).

5. Dermal absorption

The dermal absorption of deltamethrin in male rats has also been studied (Ampofo, 1995). Seven week old male Sprague-Dawley rats were given doses of 0.015, 0.551 and 1.70 mg (equivalent to 1.23, 44 and 136 ug/cm^2, respectively) of ^{14}C-deltamethrin, with the exposed area covered by non-occlusive filter paper. Rats were sacrificed at 0.5, 1, 2, 4, 10, 24 and 120 hours and daily urine and fecal samples were collected. Results indicated that the treated skin sites retained a high percentage of the applied dose (4.1 to 17%) and excretion in the urine and feces was relatively slow; less than 1% of the applied dose was excreted for the two higher doses and 1.3% for the lowest dose within 24 hours. The amounts of radioactivity eliminated in excreta and retained in the carcass were considered a result of direct dermal absorption. At 120 hours postdose, these levels were 6.22%, 4.39% and 3.00% (equivalent to 0.0009, 0.024 and 0.051 mg deltamethrin) for rats dosed at 0.015, 0.551 and 1.70 mg/animal, respectively. In order to resolve the issue of bound skin residue, cumulative percent dose in urine and feces for different time intervals extrapolated beyond 120 hours were used. The asymptote was estimated by employing an exponential saturation model with lag time (Thongsinthusak, 1996). An equation representing this model is : Recov=Max*(1-EXP(-Rate*(Time+Lag))). [Where: Recov=Y value or % dose excreted, Max=% dose at asymptote, EXP=curve fitting equation, Rate=slope factor, Time=X value, Lag=time from exposure to detection]. The data was plotted using Systat® software and the dermal absorption value was the sum of percent dose at the asymptote ("Max" term) and percent of dose recovered in carcass, blood and cage wash/cage wipe. The adjusted dermal absorption values were 6.8% and 6.5% for the low and medium dose, respectively. An average value of 6.7% was used in the estimation of an absorbed dose for dermal exposure.

B. ACUTE TOXICITY

1. Summary

The primary signs associated with acute exposure to deltamethrin were characteristic of disruption of the autonomic nervous system and were consistent with the neurotoxicity associated with synthetic pyrethroids. These signs included excessive salivation, decreased activity, labored breathing, gasping, impaired limb function, ataxia, loss of righting reflex, weight loss, lung congestion, enlarged lymph nodes, iritis, conjunctivitis, piloerection and ptosis. With technical grade deltamethrin or Decis 5 Flow (a product containing 50 g/l or 5% deltamethrin), no lethality or noteworthy clinical observations were reported when administered by the oral or dermal route. In contrast, rats receiving acute oral doses of Decis 1.0 Gel, Decis 1.5 EC or Decis 0.2 EC formulations showed severe toxic effects (e.g., salivation, tremors, convulsions, piloerection, labored breathing, urine and fecal stains, reddened glandular stomach mucosa and mottled red/congested lungs) and lethality (LD_{50} values ranging from 37.3 to 416 mg/kg).

The acute toxicity profile for deltamethrin (technical) and Decis 5 Flow is summarized in Tables 2 and 3, respectively. In the rat, both of these materials had LD_{50} values that exceeded the highest dose tested (5,000 and 15,000 mg/kg, respectively). Neither the technical material nor the 5% formulation was lethal up to 2,000 mg/kg in the rabbit dermal toxicity studies. In the rabbit eye irritation studies, the technical material was classified as Category III while Decis 5 Flow was classified as a toxicity Category IV.

Table 2: Acute toxicity of technical grade deltamethrin.

Deltamethrin (technical)

Oral LD_{50} (rat)	>5000 mg/kg[a]
Dermal LD_{50} (rabbit)	>2000 mg/kg[b]
Inhalation LC_{50} (rat)	2.2 mg/l[c]
Eye Irritation (rabbit)	Category III[d]
Derma Irritation (rabbit)	Category IV[e]

a, Myer, 1989a; b, Myer, 1989b; c, Ulrich, 1990a; d, Myer, 1989c; e, Myer, 1989d.

Table 3: Acute toxicity of Decis 5 Flow, 5% deltamethrin formulation (liquid suspension).

Decis 5 Flow (~5%Deltamethrin)

Oral LD_{50} (rat)	>15,000 mg/kg[a]
Dermal LD_{50} (rabbit)	>10,000 mg/kg[b]
Inhalation LC_{50} (rat)	1.02 mg/l[c]
Eye Irritation (rabbit)	Category IV[d]
Dermal Irritation (rabbit)	Category IV[e]

a, Catez and Audegond, 1991; b, Vandeputte and Audegond, 1991a; c, Holbert, 1990; d, Vandeputte and Audegond,1991b; e, Vandeputte and Audegond, 1991c.

In contrast to the lack of toxic symptoms seen after oral exposure to deltamethrin technical or Decis 5 Flow formulation, rats receiving acute oral doses of Decis 1.0 Gel, Decis 1.5 EC or Decis 0.2 EC formulations showed severe toxic effects, resulting in LD_{50} values ranging from 37.3 to 416 mg/kg. Clinical signs included salivation, tremors, convulsions, piloerection, labored breathing, urine and fecal stains. Findings after necropsy included reddened glandular stomach mucosa and mottled red/congested lungs.

In addition, levels of eye and dermal irritation after exposure to these formulations were also greater in severity. For Decis 0.2 EC, corneal opacity in some of the rabbits persisted to day 28. Severe erythema and edema (e.g., scores of 3 and 4) were noted in the dermal irritation studies, with residual irritation persisting up to day 21 in the case of Decis 1.0 Gel. The resulting acute toxicity categories for eye and dermal irritation were I and II, respectively, for all of the formulations listed below (Tables 4 through 6).

Table 4: Acute toxicity of Decis 1.0 Gel, 11.7% deltamethrin.

Decis 1.0 Gel (11.7% Deltamethrin)

Oral LD_{50} (rat)	196.3 mg/kg[a]
Dermal LD_{50} (rabbit)	>2,000 mg/kg[b]
Inhalation LC_{50} (rat)	no study
Eye Irritation (rabbit)	Category I[c]
Dermal Irritation (rabbit)	Category II[d]

a, Douds, 1995a; b, Douds, 1995b; c Douds, 1995c, d Douds, 1995d

Table 5: Acute toxicity of Decis 1.5 EC, 16.6% deltamethrin.

Decis 1.5 EC (16.6%Deltamethrin)

Oral LD_{50} (rat)	37.3 mg/kg[a]
Dermal LD_{50} (rabbit)	>2,000 mg/kg[b]
Inhalation LC_{50} (rat)	0.57 mg/l[c]
Eye Irritation (rabbit)	Category I[d]
Dermal Irritation (rabbit)	Category II[e]

a, Myers and Christopher, 1993; b, Myers and Christopher, 1993; c, Nachreiner, 1993; d, Myers and Christopher, 1993; e, Myers and Christopher, 1993.

Table 6: Acute toxicity of Decis 0.2 EC, 2.5% deltamethrin.

Decis 0.2 EC (2.5%Deltamethrin)

Oral LD_{50} (rat)	416 mg/kg[a]
Dermal LD_{50} (rabbit)	>2,000 mg/kg[b]
Inhalation LC_{50} (rat)	2.69 mg/l[c]
Eye Irritation (rabbit)	Category I[d]
Dermal Irritation (rabbit)	Category II[e]

a, Myer, 1990a; b, Myer, 1990b; c, Ulrich, 1990b; d, Myer, 1990c; e, Myer, 1990d.

Three additional insecticide formulations containing various percentages of deltamethrin (Deltadust, Decis 5% WP and K -Othrine WP 5) showed little toxicity in acute studies. A fourth insecticide, K-Othrine SC (4.75% active ingredient) was assumed, for registration

purposes, to have the same toxicity as Decis 5 Flow (~5% active ingredient). A summary of the acute toxicity profiles of the three mentioned formulations are shown in Tables 7 and 8.

Table 7: Acute toxicity of Deltadust, 0.05% deltamethrin.

Deltadust (0.05% Deltamethrin)

Oral LD_{50} (rat)	>5050 mg/kg[a]
Dermal LD_{50} (rabbit)	>5050 mg/kg[b]
Inhalation LC_{50} (rat)	>26.1 mg/l[c]
Eye Irritation (rabbit)	Category IV[d]
Dermal Irritation (rabbit)	Category IV[e]

a, Kuhn, 1992; b, Kuhn, 1993; c, Holbert, 1992; d, Kuhn, 1992; e, Kuhn, 1993.

Table 8: Acute toxicity of Decis 5% WP and K-Othrine WP 5 , 5% deltamethrin.

Decis 5% WP and K-Othrine WP 5 (5.0%Deltamethrin)

Oral LD_{50} (rat)	>5,000 mg/kg[a]
Dermal LD_{50} (rabbit)	>5,000 mg/kg[b]
Inhalation LC_{50} (rat)	>7.75 mg/l[c]
Eye Irritation (rabbit)	Category III[d]
Dermal Irritation (rabbit)	Category IV[e]

a, Audegond, 1991a; b, Audegond, 1991b; c, Holbert, 1990; d, Audegond, 1991c; e, Audegond, 1991e

C. SUB-CHRONIC TOXICITY

1. Summary

The sub-chronic toxicity of deltamethrin was investigated in rats and dogs. As with the previously mentioned acute studies, the primary toxic effects were characteristic of autonomic nervous system dysfunction. The dog appeared to be more sensitive than the rat to deltamethrin toxicity. The spectrum of effects reported were unsteadiness, body tremors, jerking movements, vomiting, excessive salivation, liquid feces, reduced weight gain and decreased food consumption (see Table 12).

2. Oral Study (Rat)

Deltamethrin was administered with a polyethylene glycol (PEG) 200 vehicle by gavage to Sprague-Dawley rats for 13 weeks (Hunter, 1977). Treatment dosages included 0, 0.1, 1.0, 2.5 or 10.0 mg/kg/day, with twenty male and female animals being treated at each dose level. Hypersensitivity in high-dose males was reported by week 6; a statistically significant ($p<0.05$) reduction in weight gain was noted in the 2.5 and 10 mg/kg/day rats, when compared to controls, over the 13 week study. The NOEL for this study was considered to be 10.0 mg/kg/day as the reported effects were not considered to be adverse. The Department of Pesticide Regulation (DPR) of the California Environmental Protection Agency considered this study acceptable as a Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guideline study.

3. Oral Study (Dog)

A 13-week oral toxicity study was conducted in Beagle dogs (Chesterman, 1977). In this study, deltamethrin was dissolved in PEG 200 and inserted into gelatin capsules prior to administration. Treatment dosages were 0, 0.1, 1.0, 2.5 or 10.0 mg/kg/day. Three animals per sex per group were used for controls and 0.1 mg/kg/day. All other dose groups had 5 animals per sex. Effects reported in this study were consistent with autonomic nervous system dysfunction from pyrethroid toxicity and included unsteadiness, body tremors, jerking movements, vomiting, excessive salivation, liquid feces, nervous behavior, and abnormal reflex responses. Table 9 presents the doses and associated signs. Since the study was designed with the control and low dose groups having fewer animals than the subsequent dose groups, signs were presented as percent incidence, i.e., actual incidence divided by (the number of dogs x number of days in the study).

Table 9: Clinical signs reported in dogs exposed to deltamethrin for 13 weeks (Chesterman, 1977).

Signs	**Dosage (mg/kg/day)**				
	Control (6 dogs)	**0.1** (6 dogs)	**1.0** (10 dogs)	**2.5** (10 dogs)	**10** (10 dogs)
Liquid Feces incidence (actual/potential)[a]	6.4%	7.8%	9.0%	22.0%	31.9%**
percent of animals involved	100%	100%	100%	100%	100%
Vomiting incidence (actual/potential)[a]	.37%	.55%	.88%*	1.2%**	5.1%**
percent of animals involved	33%	50%	50%	60%	90%
Tremors/Uncoordination incidence (actual/potential)[a]	0	0	.22	.44	14.3**
percent of animals involved	0%	0%	20%	40%	100%

[a] The incidence ratio was calculated by dividing the actual incidence by the potential occurrences. The potential occurrences was equal to the number of dogs (6 or 10) times the number of days in the study (91). **=($p\leq 0.01$); *=($p\leq 0.05$) Fisher exact comparison.

There was a general increase in liquid feces and vomiting with an increase in dose. A positive trend in the incidence of liquid feces was demonstrated, with increasing doses,

with statistical significance ($p \leq 0.01$) demonstrated at 10 mg/kg/day. The incidences occurred between 1 and 7 hours after dosing. A positive trend was also demonstrated for increases in vomiting, with statistical significance ($p \leq 0.05$) at 1 mg/kg/day and ($p \leq 0.01$) at 2.5 and 10 mg/kg/day. In additional to the increases in the incidences of vomiting, a dose-related increase in the percent of animals involved was also reported. No gender-related patterns were noted. For tremors and uncoordinated body movements, dose-related increases were noted at 1, 2.5, and 10 mg/kg/day, with statistical significance ($p \leq 0.01$) indicated at 10 mg/kg/day.

In addition to daily observations, neurological exams were performed at weeks 5 and 12 of deltamethrin exposure. In addition to the tremors and uncoordinated body movements, abnormal reflex responses were reported (Table 10). An increase in abnormal patellar reflex was reported at dose levels of 1 mg/kg/day and greater at both the 5 and 12-week examinations. A dose-related increase in abnormal flexor reflex was reported at all dose levels at 5 weeks and at the high dose at 12 weeks. Exceptions to the dose-relationship is noted, e.g., the abnormal patellar reflex at 12 weeks in the high dose is higher than control but less than 2.5 mg/kg/day, and the abnormal flexor reflex at 12 weeks in the control animals is greater than all but the high dose group. Without additional clinical observations, an explanation for these exceptions cannot be determined. The overall pattern of the reported observations, however, is consistent with a treatment relationship. Furthermore, the dose-related abnormal reflex responses were consistent with abnormal patellar reflex reported in dogs following treatment with tralomethrin (Chesterman, et al., 1978) . This is of interest since, as previously stated, tralomethrin undergoes rapid and essentially complete debromination to form deltamethrin.

Table 10: Clinical signs reported in dogs during weeks 5 and 12 of a 13-week study (Chesterman, 1977).

Signs	**Dosage (mg/kg/day)**				
	Control (6 dogs)	**0.1** (6 dogs)	**1.0** (10 dogs)	**2.5** (10 dogs)	**10** (10 dogs)
Abnormal Patellar Reflex					
Week 5	17%	0%	30%	60%	60%
Week 12	17%	17%	60%	80%*	20%
Abnormal Flexor Reflex					
Week 5	0%	50%	40%	40%	60%*
Week 12	33%	10%	20%	20%	50%

* $p<0.05$
[a] Values represent the percent of demonstrating the effect

On the basis of the spectrum of effects consistent with autonomic nervous system dysfunction, the LOEL appeared to be 0.1 mg/kg/day (the lowest dose tested) for sub-chronic toxicity. In the process of DPR internal peer review, however, a consensus on the biological relevance of the effects reported at 0.1 mg/kg/day could not be established. Consequently, margins of exposure were calculated using 0.1 mg/kg/day as both a NOEL and a LOEL, with resultant estimated NOEL (i.e., ENOEL) of 0.01 mg/kg/day. The ENOEL

was calculated by using the default approach of dividing the LOEL by an uncertainty factor of 10.

Acute toxicity. In addition to the reported sub-chronic effects, this study was also used to evaluate the acute toxic potential of deltamethrin. Since the autonomic nervous system effects were observed within the first 24 hours after dosing, effects reported during the first week of treatment were assumed to be in response to acute exposure. They are tabulated in Table 11. As indicated, the cases of liquid feces were apparent at dose levels of 0.1 mg/kg/day and greater with all increases being statistically significant ($p \leq 0.05$). The occurrences of liquid feces were all observed within 7 hours of dosing. The number of animals involved was also dose-related. With vomiting, the reported cases per animal and the number of animals involved increased in a dose-related fashion at 2.5 and 10 mg/kg/day. Statistical significance was seen at 10 mg/kg/day. Furthermore, during this time period, vomiting episodes occurred between 1 and 7 hours after dosing. Increases in tremors and/or uncoordinated body movements were apparent only at the high dose (10 mg/kg/day). Statistical significance ($p \leq 0.01$) at the high dose was seen. During the first week of the study, these affects were reported to have occurred within 5 hours of dosing.

On the basis of the spectrum of effects consistent with autonomic nervous system dysfunction, the empirical LOEL appeared to be 0.1 mg/kg/day (the lowest dose tested) for acute toxicity. In the process of DPR internal peer review, however, a consensus on the biological relevance of the effects reported at 0.1 mg/kg/day could not be established. Consequently, margins of exposure were calculated using 0.1 mg/kg/day as both a NOEL and a LOEL, with resultant estimated NOEL (i.e., ENOEL) of 0.01 mg/kg/day. The ENOEL was calculated by using the default approach of dividing the LOEL by an uncertainty factor of 10.

Table 11: Clinical signs reported in dogs during the first week of a 13-week deltamethrin exposure study (Chesterman, 1977).

Signs	**Dosage (mg/kg/day)**				
	Control (6 dogs)	**0.1** (6 dogs)	**1.0** (10 dogs)	**2.5** (10 dogs)	**10** (10 dogs)
Liquid Feces incidence (actual/potential)[a]	4.7%	24%*	20%*	37%**	30%**
percent of animals involved	33%	50%	90%	100%	100%
Vomiting incidence (actual/potential)[a]	2.3%	0%	1.4%	4.3%	21%**
percent of animals involved	17%	0%	10%	30%	90%
Tremors/Uncoordination incidence (actual/potential)[a]	0%	0%	0%	0%	20%
percent of animals involved	0%	0%	0%	0%	70%**

[a] The incidence ratio was calculated by dividing the actual incidence by the potential occurrences. The potential occurrences was equal to the number of dogs (6 or 10) times the number of days in the study (7). **=($p \leq 0.01$); *=($p \leq 0.05$) Fisher exact comparison.

Another oral 13-week study using gelatin capsules, but without a solvent (or vehicle), was performed with Beagle Dogs (Ryle *et. al.*, 1991). Treatment dosages were 0, 2, 10 or 50

mg/kg/day with each group consisting of 3 males and 3 females. The major clinical signs reported included body tremors, unsteady gait and vomiting soon after dosing at the 50 mg/kg/day level. Unsteady gait (principally in hind legs) was seen in most animals at 50 mg/kg/day approximately 1.5 to 7 hours after dosing and sometimes persisting to dosing on the following day. Body tremors were reported in combination with unsteadiness of gait for some of the dogs at 50 mg/kg/day. Increased vomiting was noted at this dose level, 1 to 6 hours after dosing during weeks 1 to 6. Other signs that were attributed to neurological effects of treatment at the high-dose level included a more severe unsteadiness of gait (such as inability of the animals to stand), quiet/subdued behavior, hunched posture, shaking head, salivation and chewing/licking of the extremities (i.e., tail, hind paws/limbs). A statistically significant ($p<0.05$) reduction in body weight gain, and food consumption, when compared to control animals, was also noted at this dose. No treatment-related clinical signs were observed at 2 or 10 mg/kg/day. A NOEL was established at 10 mg/kg/day, based on body tremors. DPR considered this study acceptable as a FIFRA guideline study.

Table 12 summaries the effects reported in the deltamethrin sub-chronic studies. As indicated, a NOEL of 10.0 mg/kg/day was established in rats and was based on a lack of reported adverse effects. In a study conducted in dogs, in which PEG 200 was used as a vehicle, a LOEL of 0.1 mg/kg/day was established on the basis of autonomic nervous system dysfunction (vomiting, liquid feces, and abnormal reflex response). In a subsequent study in dogs (without the PEG 200 vehicle) a NOEL of 10 mg/kg/day was established. This NOEL was also based on effects indicative of autonomic nervous system dysfunction (vomiting and body tremors).

Table 12: Summary of toxicity following sub-chronic exposure to deltamethrin.

Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Effects
Oral Toxicity (Rat)[1]	10.0	>10.0	hypersensitity, reduced weight gain
Oral Toxicity (Dog)[2] (PEG solvent used)	<0.1 or 0.1	0.1 or 1	vomiting, liquid feces, and abnormal reflex response
Oral Toxicity (Dog)[3] (no solvent used)	10.0	50.0	vomiting, body tremors

1 Hunter, 1977
2 Chesterman, 1977
3 Ryle, 1991

D. CHRONIC TOXICITY AND ONCOGENICITY

1. Summary.

The toxic and/or oncogenic potential associated with chronic exposure to deltamethrin was evaluated in studies with rats, mice and dogs. As mentioned previously in the acute and sub-chronic toxicity sections, the primary toxic signs were related to autonomic nervous system dysfunction. Data from chronic studies indicate that the dog is more sensitive than the mouse or rat to long-term deltamethrin exposure. The range of reported effects included unsteadiness, body tremors, abnormal head movements, increased incidence of vomiting and liquid feces. Additionally, a reduction in body weight gain, food consumption, and cutaneous lesions (sores, scars or scabs) were reported. No oncogenic potential was indicated after chronic deltamethrin exposure in the rat or mouse.

2. Combined Toxicity/Oncogenicity Study (Rat)

Deltamethrin was administered in the feed (without PEG 200) to male and female Sprague-Dawley rats for 24 months at levels of 0, 2, 20 or 50 ppm (Goldenthal, 1980). Reported dose levels were equivalent to 0, 0.11, 1.1 or 2.8 mg/kg/day. Ninety animals per sex per dose were used, with 10 animals/sex/dose for interim sacrifice at 6, 12 and 18 months exposure. Survival was similar for control and treated rats, with survival in the high-dose group being 63% and 67% for males and females, respectively, and 53% and 57% for the control males and females, respectively. A reduction in relative body weight was noted at 50 ppm ($p < 0.05$), however, no changes in general behavior, survival, food consumption or incidence in gross lesions at this level (50 ppm). Dose-related increases in the degeneration of sciatic, tibial and plantar nerves were seen at the 18-month interim sacrifice (Figure 3) . A dose-related increase in nerve damage was not, however, reported in animals continuing to the 24 month terminal sacrifice The ratio of the animals affected to those examined for both the 18 month interim sacrifice and the terminal sacrifice are presented in Table 13.

Figure 3
Nerve Degeneration at 18 Months

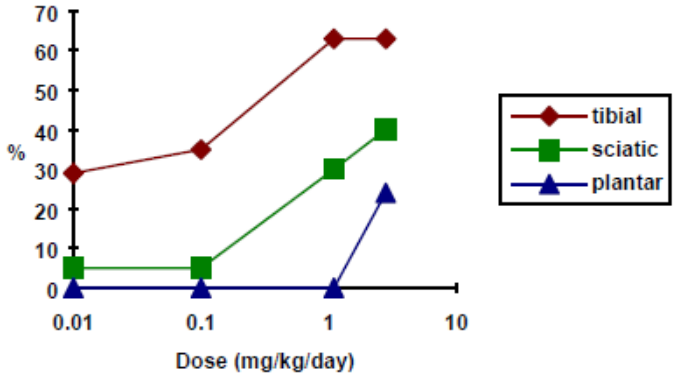


Table 13: Non-neoplastic microscopic lesions reported at the 18 month interim sacrifice of a 24-month combined toxicity/oncogenicity study conduced in rats (Goldenthal, 1980).

Nerve Type	Dosage (mg/kg/day)[1]			
	Control	**0.1**	**1.1**	**2.8**
18 months				
Sciatic	5% (1/20)	5% (1/20)	30% (6/20)	40% (8/20)
Tibial	29% (5/17)	35% (7/20)	53% (10/19)	63% (10/16)
Plantar	0% (0/20)	0% (0/20)	0% (0/17)	24% (4/17)
24 months				
Sciatic	95% (125/131)	97% (73/75)	97% (56/58)	94% (72/77)
Tibial	80% (105/131)	83% (62/75)	79% (46/58)	88% (68/77)
Plantar	86% (113/131)	87% (65/75)	75% (44/58)	74% (57/77)

[1] Values in parenthesis = (animals with lesion / animals examined).

In reviewing the study report to explain the lack of a reported effect at the termination of the study, it was noted that the background level of nerve damage increased dramatically between 18 and 24 months (Table 13). After 18 months, the control value for sciatic nerve damage was 5%. After 24-months it was approximately 95%. For tibial nerve damage, the 18-month value was 29% and the 24-month value was 80%. Plantar nerve damage showed a linear trend, with the 18-month value at 0% and the 24-month value was 86%. Increases of such a magnitude in control values would be expected to mask any response attributable to deltamethrin. DPR has concluded, therefore, that the lack of an increase over controls in animals exposed to deltamethrin for 24 months was likely due to an increases in background nerve damage between 18 and 24 months. On the basis of nerve damage reported after 18 months of exposure to deltamethrin, a chronic NOEL of 0.1 mg/kg/day was established. DPR considered the study unacceptable, due to lack of dose level justification, but upgradeable as a FIFRA guideline study with the submission of said justification.

Another combined toxicity/oncogenicity study was performed in CD rats at levels of 0, 25, 125, 500 or 800 ppm for 24 months (Ryle, 1995). Reported dose levels were equivalent to 1.1, 5.4, 22.2, or 35.9 mg/kg/day for males and 1.5, 7.3, 29.5, or 47.0 mg/kg/day for females. Fifty animals per sex, per dose were used, with an additional 20 per sex per dose as satellite animals. Signs of acute toxicity included uncoordinated movement of limbs with limbs splayed (in most high-dose males and two males and one female at 500 ppm) and unsteady gait (mostly at the 800 ppm level). These signs were first noted during week 1, gradually declining and virtually disappearing by week 8 of treatment. There were no clinical signs reported in the 25 or 125 ppm dose groups. Microscopic pathology findings included an increased incidence of cystic degeneration (or ballooned cells) in the livers of males at 125 and 800 ppm and eosinophilic hepatocytes in the livers of 500 and 800 ppm males. The NOEL that was established from these data was the high-dose level of 800

ppm (equivalent to 35.9 mg/kg/day in males and 47.1 mg/kg/day in females). DPR considered the study acceptable as a FIFRA guideline study.

3. Oral Oncogenicity Study (Mouse)

The potential oncogenic effects of deltamethrin were investigated in a 2-year study in Charles River CD-1 mice (Richard, 1995). Deltamethrin was administered in the feed (without PEG 200 vehicle) to male and female mice at levels of 0, 10, 100, 1000 or 2000 ppm (1.5, 15.7, 155.4, or 314.8 mg/kg/day for males and 2.0, 19.6, 189.3, or 395.1 mg/kg/day for females) for 97 weeks, with fifty animals per dose, per sex. There were few noteworthy clinical signs reported in the early portions of the study; in animals killed prematurely or in those found dead, emaciation and dyspnea were noted a few weeks before death. Clinical observations also included a slight increase in female mortality at the high dose level, although cutaneous lesions (i.e., sores, scars or scabs) were also reported. These were characterized as ulcerations with cellulitis under microscopic examination. A clear dose response was not, however, demonstrated. There were few other significant effects reported in this study. Deltamethrin did not demonstrate oncogenic potential in this study (i.e., there was no increase in the incidence of spontaneously occurring tumors or decreases in the latency of tumor appearance at any dose level). The NOEL for this study was the high-dose level of 2000 ppm (equivalent to 315 mg/kg/day in males; 395 mg/kg/day in females) based on a lack of reported adverse effects. This study was acceptable according to FIFRA guidelines.

4. Oral Toxicity Study (Dog)

A 1-year study was conducted to examine the effects of deltamethrin on dogs (Ryle, 1993). The test article was administered to beagles (4 males and 4 females per treatment group) orally (by capsule, without vehicle) at levels of 0, 1, 10 or 50 mg/kg/day for 52 weeks.

Indications of acute toxicity: During the first week of the study, clinical signs reported included liquid feces, vomiting, abnormal behavior (chewing, licking, and scratching), and signs related to unsteadiness and uncoordinated movements. In the high dose group, signs, consistent with autonomic nervous system dysfunction, included this liquid feces and vomiting, locomotion effects, unsteadiness, body tremors, and abnormal head movements. At 10 mg/kg/day, liquid feces and vomiting were also reported. The increased incidences of vomiting and liquid feces were usually seen 0.5 to 7 hours after dosing and frequently overnight. During the first week, a single case of liquid feces was also reported in the 1 mg/kg/day group but was not considered to be of toxicologic significance. Since these signs of autonomic nervous system dysfunction occurred within hours of dosing during the first week of treatment, they were assumed to be in response to acute exposure.

As exposure continued beyond the first week, the spectrum of clinical signs, consistent with autonomic nervous system dysfunction, persisted. Specialized neurological exams (e.g., tests for cranial nerve function, spinal reflexes and postural reactions) were conducted at weeks 26 and 52 in the control and high-dose dogs. These tests revealed slight trembling in a single high-dose male and one female at week 26; at week 52 slight body tremors, high-stepping and/or unsteadiness of the gait and splayed digits were recorded for high-dose animals that had shown these signs at routine clinical examination. Neurological examinations were not performed on dogs in the 1 or 10 mg/kg/day dose groups. The

effects which persisted throughout the study are presented in Table 14. The values presented represent the total number of incidences over the 52 week time period.

Table 14: Total incidence of clinical signs reported during a one-year oral toxicity study conducted in beagles (Ryle, *et. al.,* 1993).

Signs	**Dosage* (mg/kg/day)**			
	Control	**1**	**10**	**50**
Chewing extremities	1 (0/1)	5 (1/1)	34 (4/3)	171 (4/4)
Liquid feces	14 (3/3)	20 (3/3)	48 (4/3)	190 (4/4)
Vomiting	16 (4/3)	11 (2/3)	25 (3/2)	40 (4/4)
Abnormal gate	0	0	7 (1/3)	1,011 (4/4)
Tremors	0	0	2 (1/1)	112 (4/3)
Inability to stand	0	0	0	58 (4/1)

* Four dogs/sex/dose. Values represent reported incidences.
() males/females with signs

As indicated, the incidences of signs increased in a dose-related fashion. Increases in the chewing of extremities and in the incidences of liquid feces were reported at 1 mg/kg/day and greater. Increased episodes of vomiting, abnormal gait, and tremors, were reported at dose levels of 10 and 50 mg/kg/day. The inability to stand was reported only in high dose animals. On the basis of the reported liquid feces and abnormal behavior (chewing of extremities), the empirical LOEL appeared to be 1 mg/kg/day (the lowest dose tested) for chronic toxicity. In the process of DPR internal peer review, however, a consensus on the biological relevance of the effects reported at 1 mg/kg/day could not be established. DPR considered the study acceptable as a FIFRA guideline study. The chronic toxicity and/or oncogenicity studies are summarized in Table 15.

Table 15: Summary of toxicity following chronic exposure

Study	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Signs
Combined Oral Tox./Onco (Rat)[1]	0.1	1.1	nerve degeneration
Combined Oral Tox./Onco (Rat)[2]	≥36	>36	Only acute or sub-chronic effects
Oral Oncogenicity/ Toxicity (Mouse)[3]	≥315	>315	mortality, skin ulceration
Oral Toxicity (Dog)[4,5]	<1	1	autonomic nervous system dysfunction

1 Goldenthal, 1980
2 Ryle, 1995
3 Richard, 1995
4 Ryle, 1993

E. GENOTOXICITY

1. Summary

Deltamethrin was tested for genotoxic potential *in vitro* using *Schizosaccharomyces Pombe* to test for gene mutation, Chinese Hamster Ovary (CHO) cells to test for chromosome aberrations and rat primary hepatocytes to test for unscheduled DNA synthesis (UDS). In these test systems, no genotoxic potential was reported. In other recently published studies appearing in the open literature, positive genotoxicity was reported for deltamethrin technical (or formulations with deltamethrin as the active ingredient) in both *in vivo* (e.g., chromosome aberrations and micronucleus test) and *in vitro* (sister-chromatid exchange in human lymphocytes) test systems.

2. Gene Mutation

The ability of deltamethrin to mutate cells was tested using *Schizosaccharomyces Pombe* conducted both in the presence and absence of a rat liver metabolic activation solution (Mondino, 1979). Deltamethrin was tested at levels of 0, 250, 500 and 1000 mg/l. There were no increases in mutations at any dose tested. DPR considered the study to be unacceptable due to individual data not being reported, a lack of dosing solution characterization, an inadequate number of replicates, and an incomplete description of exposure conditions. DPR did not consider the study upgradeable as a FIFRA guideline study.

3. Structural Chromosomal Aberrations

An *in vitro* cytogenetic assay was conducted with deltamethrin using Chinese hamster ovary cells (Putman, 1989). CHO cells were exposed to the test article at levels of 0, 19, 38, 75 and 150 μg/ml both in the presence and absence of a rat liver metabolic activation solution. No test article related increases in chromosomal aberrations were reported. DPR considered this to be acceptable as a FIFRA guideline study.

Deltamethrin technical was tested in Swiss albino mice for the induction of bone marrow chromosome aberrations and micronuclei in bone marrow and for sperm abnormalities (Bhunya and Pati, 1990). Deltamethrin (99.2% pure, dissolved in DMSO) was injected i.p. at levels of 10, 15 and 20 mg/kg. Cells were fixed after 24 and 30 hours and 35 days for the observation of chromosome aberrations, micronuclei and sperm abnormalities, respectively. Route response (i.p., oral and s.c.), time response (6, 24 and 48 hours) and acute-chronic (24 versus 120 h) studies were also conducted at the highest dose (20 mg/kg) of deltamethrin. Chromosomal aberrations increased in a dose-related fashion with all values statistically significant when compared to concurrent controls. These effects were seen without any significant variation in the time-response or route-response. Positive frequencies with an accompanying dose-response was also seen for the induction of micronuclei. The frequencies of micronucleated PCEs in bone marrow cells induced by deltamethrin were significantly higher than control values with all three doses used. The results of the sperm abnormality test were also positive, with the percent of abnormal sperm with amorphous appearance, banana-like heads, dwarf, triangular and hooked heads being 48, 40, 5, 3.8 and 3.2%, respectively. This study appeared in the open literature and, as such, only summary data and brief descriptions of experimental methodology were available for evaluation by DPR.

Another recently published article described an *in vivo* cytogenetic assay performed in Swiss albino male mice (5 mice/ group) using the bone marrow micronucleus assay (Gandhi, *et al.,* 1995). Three doses were selected on the basis of the maximum tolerated dose, with one dose close to the MTD range (300 mg/kg), and the remaining two being fractions of the MTD (162.5 and 32.5 mg/kg). Each dose was given twice (i.p. injections, 30 and 6 hours before bone marrow collection) with negative control groups consisting of the carrier (DMSO) and saline. The positive control group received ethyl methanesulphonate (EMS, 180 mg/kg). Bone marrow smears were prepared from mice sacrificed six hours after the second injection. A dose dependent increase in the number of micronucleated PCEs as compared to the negative control values was reported. Also, the proliferation rate of PCEs was enhanced at the lower doses, as indicated by the significant

increase in the PCE/NCE ratio. This study appeared in the open literature (i.e., only summary data were presented).

An *in vivo* cytogenetic assay was performed in female albino rats using the deltamethrin formulation Decis 2.8 EC (about 2.5% deltamethrin), given as a single dose via the i.p., s.c. or oral route (Agarwal, *et. al.,* 1994). Groups of six rats per dose were administered levels of 0 (peanut oil vehicle), 5.6, 8.4 or 11.2 mg/kg; the positive control was ethyl methanesulphonate (EMS, 100 mg/kg, i.p.). Rats were killed 30 hours after treatment and the bone marrow cells were processed and evaluated. The results indicated an increase in micronucleated erythrocytes in the rat bone marrow at 30 hours after the single i.p. dose of 5.6, 8.4 or 11.2 mg/kg. Also included in this study was an evaluation of chromosome aberrations. Treatment inhibited the mitotic index and increased chromosomal aberrations in the bone marrow at 24 hours post exposure. Parenteral routes of exposure (i.p. and s.c.) were more effective than the oral route for eliciting cytotoxicity and genetic toxicity potential. This study appeared in the open literature.

4. DNA Damage

The effects of deltamethrin on unscheduled DNA synthesis (UDS) in rat hepatocytes was investigated by Curren (1989). Deltamethrin was tested in rat primary hepatocytes at dose levels ranging from 4.2 to 4200 μg/ml in the parallel cytotoxicity assay and dose levels of 42, 130, 420, 1300 and 4200 μg/ml in the actual UDS assay. The study indicated that deltamethrin did not cause a statistically significant increase in the mean number of net nuclear grains when compared to control values. DPR considered this study an acceptable FIFRA guideline study.

5. Other Genotoxic Effects

The ability of deltamethrin to induce sister-chromatid exchanges (SCEs) in human peripheral lymphocytes was studied *in vitro* (Dolara, *et. al.,* 1992). Lymphocytes were obtained from non-smoking female donors, aged 25-35 years old. Whole blood cultures were established. Deltamethrin concentrations ranging from approximately 5 to 50 ug/ml were left in the incubation medium in the dark for 72 hours at 37^{o}C and 20 ul of colchicine was added 90 min before the end of incubation. Slides were prepared. Deltamethrin was considered to be weakly active on the induction of SCE with a $P = 0.053$. This study appeared in the open literature.

F. REPRODUCTIVE TOXICITY

1. Summary.

A rat reproduction study submitted by the registrant indicated minor effects (reduced pup weight) but was considered unacceptable to DPR based on FIFRA guidelines, (Wrenn, 1980). Microscopic examinations were limited to F_{3b} weanlings and no parental microscopic data were collected. After a review of the open literature, a study was found that indicated a number of reproductive effects in rats treated with deltamethrin. Deltamethrin significantly decreased the weight of testes, seminal vesicle, and prostate glands. Significant decreases were also noted in sperm cell concentrations, percentage of

live cells and sperm motility. Furthermore, plasma testosterone concentration was significantly decreased and the pregnancy rate was depressed (Abd El-Aziz, 1994).

2. Oral Study (Rat)

A three generation study was conducted to determine the effect of deltamethrin on reproductive performance of Charles River CD rats (Wrenn, 1980). The test compound was administered in the diet at dose levels of 0, 2, 20 or 50 ppm beginning at about 76 days before mating and continuing through sacrifice. Each of three generations included 10 males and 20 females receiving test compound. A statistically significant decrease ($p<0.05$) in mean parental body weight of the F_0 males in the 50 ppm dosage group was noted along with slight reductions in mean food consumption in the 50 ppm dosed F_1 males and F_2 females. Reduced mean pup weight was noted, in all dose groups, at lactation day 21 in the F_1, F_2 and F_3 litters with statistical significance ($p<0.01$) only shown by the F_2 litter at 2 ppm. The parental NOEL was established at 20 ppm, based on reduced body weight and food consumption at the high-dose level. This study was considered unacceptable in part because microscopic examinations were limited to F_{3b} weanlings and no parental microscopic data were collected.

3. Other Reproductive Effects

The effect of deltamethrin on male reproductive tissues was studied in rats (Abd El-Aziz, et al., 1994). Deltamethrin (Decis 5 Flow formulation with approximately 5% active ingredient) was administered, by oral gavage, in doses of 1 or 2 mg/kg to groups of 15 mature male albino rats (body wt.180-200 g) for 65 consecutive days (to cover a complete spermatogenic cycle of 56-60 days in rats). Blood samples were obtained from each group before administration, at 14, 28, 42 and 65 days during administration and at 21 days after dosing ceased. Serum was assayed for testosterone using a radio-immunoassay. After males were sacrificed, the testes, epididymis, seminal vesicles and prostate glands were dissected out and weighed. The epididymis was evaluated for sperm cell concentration, percentage of live cells, progressive motility and total head abnormality. At the end of administration, 5 males from each group were paired with a female with a regular estrous cycle for 48 hours to determine the conception rate. Another group of 5 males/group was left for 60 days and then mated to determine any reversibility of effects. The results of this study indicated that deltamethrin significantly ($p<0.01$ at 1 mg/kg and $p<0.001$ at 2 mg/kg) decreased the weight of testes, seminal vesicles and prostate glands at 65 days and 21 days post-administration. Significant decreases were also noted in sperm cell concentrations, percentage of live cells and sperm motility ($p<0.001$); an increase was seen in the percentage of total sperm abnormalities ($p<0.001$). Plasma testosterone concentration was significantly decreased from day 14 to 65 and 21 days after stopping administration ($p<0.001$ at 2 mg/kg). With 8 females per group, the pregnancy rate was also decreased (37.5% at 1 mg/kg versus 75% pregnant in controls). The apparent LOEL established from this study was 1 mg/kg. This study appeared in the open literature and was not performed under FIFRA guidelines.

G. DEVELOPMENTAL TOXICITY

1. Summary.

In the studies submitted in support of registration, no significant developmental toxicity was reported in rats (Schardein, 1990a) or in rabbits (Schardein, 1990b). Effects in rats have been reported, however, in the open literature (Abd El-Khalik, et. al, 1993). These researchers reported that a 5% deltamethrin formulation results in dose-dependent early embryonic death, retardation of fetal growth, hypoplasia of the lungs, and dilation of the renal pelvis.

2. Gavage Study (Rat)

A teratology study was conducted using Charles River CD (Sprague-Dawley derived) rats (Schardein, 1990a). Pregnant rats were administered deltamethrin by oral gavage as a single daily dose on gestation days 6 through 15 at initial dose levels of 0, 1, 3.3, or 11 mg/kg/day. Due to excessive toxicity at the high-dose level, a fourth treatment level at 7 mg/kg/day was added; due to unacceptable concentration analyses, one additional control and two additional treatment groups at 1 and 3.3 mg/kg/day were added. Clinical observations in the high-dose dams included convulsions, anogenital staining, abnormal vocalization, and sensitivity to external stimuli. Increased salivation was seen in 11 of 25 dams in the 7 mg/kg/day group and one dam at the high-dose. Piloerection showed a similar pattern. Maternal weight gain was reduced in the mid- and high-dose groups. Animals in the high dose group showed reduced body weight gain (10%) throughout gestation. From the initiation of treatment (gestation day 6) to day 9, animals in the 7 mg/kg/day dose group gained about half as much weight as the control animals. Following cesarean section examination, no dose-related malformations were noted. This study was considered acceptable as a FIFRA guideline study.

Another teratology study was conducted using the 5% water miscible formulation (Decis 5 Flow) of deltamethrin in Wistar derived albino rats (Abd El-Khalik, *et. al.,* 1993). Pregnant females were assigned to one of four groups, with 20 females per group, and were administered doses of 0, 1, 2.5 or 5 mg/kg/day by oral gavage on days 6 through 15 of gestation. Animals were sacrificed on day 19 of gestation; uteri were opened and implantation sites were counted. Fetuses and placentas were weighed and the fetal length was recorded. One third of the fetuses were fixed in Bruin solution for two weeks and subjected to visceral examination. The remaining two thirds were subjected to skeletal examination using the alizarin red S staining method. The results, shown in Table 16, indicated a dose-dependent early embryonic death (postimplantation loss) leading to complete resorption. Retardation of fetal growth was noted in all deltamethrin-dosed groups and the visceral examination indicated hypoplasia of the lungs and dilatation of the renal pelvis in all treated groups. Mean placental weight was increased in deltamethrin-treated females. No skeletal abnormalities were noted. The apparent LOEL from this study was 1 mg/kg/day. This study appeared in the open literature.

Table 16: Teratology study using the 5% water miscible formulation (Decis 5 Flow) of deltamethrin in Wistar derived albino rats (Abd El-Khalik, *et. al.,* 1993).

Reproductive Parameters	Dosage (mg/kg/day)			
	0	**1**	**2.5**	**5**
Pregnant females	20	20	20	20
Total Implantation sites	191	182	189	184
Mean Implantation sites	9.5±1.3	9.1±1.7	9.4±1.8	9.2±1.7
Total live Fetuses	178	160	147	110
Mean Fetuses per rat	8.9±0.9	8.0±1.3**	7.3±1.1**	5.5±2.1**
Mean Fetal wt. (g)	4.4±0.1	4.0±0.1**	3.8±0.1**	3.5±0.2**
Mean Fetal length	3.8± 0.05	3.4±0.07**	3.3±0.05**	3.2±0.05**
Total (and %), hypoplasia, lungs	0 (0%)	0 (0%)	5 (3.4%)	10 (9.1%)
Total (and %), dilation renal pelvis	0 (0%)	0 (0%)	15 (10.2%)	26(23.6%)
Mean weight of placenta: (g)	0.44±0.03	0.57±0.02**	0.57±0.02**	0.62±0.02**

** significantly different from control ($p<0.01$).

3. Gavage Study (Rabbit)

A teratology study was performed using New Zealand White Rabbits (Schardein, 1990b). Pregnant rabbits were administered deltamethrin on gestation days 7 through 19 at a volume of 3 ml/kg. Dose levels were 0, 10, 25 or 100 mg/kg/day. One of the 100 mg/kg does died on gestation day 27 (possibly compound-related) and another doe given 10 mg/kg died en route to the scheduled sacrifice on gestation day 29 (probably not compound-related). Although there were no dose-related fetal malformations reported, some fetal variations including wrist flexure and retardation of ossification in the hyoid body, pubic bones and tail bones were reported with higher frequency in the high-dose group. The NOEL established for this study was 100 mg/kg/day, based on a lack of adverse developmental effects. This study was acceptable as a FIFRA guideline study.

H. NEUROTOXICITY (HEN)

The acute delayed neurotoxicity of deltamethrin in the domestic hen was studied by Ross, *et al.* (1978). Before the main neurotoxicity study, the oral toxicity of deltamethrin dissolved in either corn oil (ten hens per dose at levels of 800, 1200, 1600, 2000, 3000 and 5000 mg/kg) or in sesame oil (at levels of 1000 and 2500 mg/kg) was determined. All of the birds were dosed by single oral gavage, except at the higher dose levels, which required that dose volumes be given in multiple doses administered over a 6-hour period. The neurotoxicity testing was performed using both vehicles, with 10 hens per group receiving 0, 500, 1250 or 5000 mg/kg dissolved in corn oil and another 10 hens per group receiving 0

or 1000 mg/kg in sesame oil. A positive control group consisting of ten hens receiving 500 mg/kg TOCP in corn oil was also included.

During the toxicity test, one hen died at 5000 mg/kg (in corn oil) , one died at 1000 mg/kg (sesame oil) and three died at 2500 mg/kg (sesame oil). During the neurotoxicity test, two died at the 1000 mg/kg level (in sesame oil) and eight birds dosed with TOCP died or were sacrificed during the post-treatment observation period. The surviving birds in this group showed signs of ataxia ranging from moderate to severe. There was no ataxia or other indications of delayed neurotoxicity in any of the birds receiving deltamethrin. Microscopic examination of the sciatic nerve and spinal cord also showed no treatment-related changes. DPR considered the study unacceptable as a FIFRA guideline study because no repeat dosing was conducted after 21 days.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

1. Acute Toxicity

Laboratory animal studies have demonstrated toxicity in response to acute exposure to technical grade deltamethrin, as well as, to acute exposure to product formulations containing deltamethrin as the active ingredient. The primary toxic signs were characteristic of agents that disrupt the autonomic nervous system and many of these signs were consistent with the neurotoxicity associated with pyrethroids. These signs included excessive salivation, decreased activity, labored breathing, gasping, impaired limb function, ataxia, loss of righting reflex, tremors, convulsions, and lethality. Furthermore, signs of autonomic nervous system dysfunction (e.g., liquid feces, vomiting, and tremors) have been reported in studies designed to examine the effects of multiple exposures to deltamethrin.

In a 13 week dog study, endpoints (e.g., liquid feces, vomiting, and tremors) considered characteristic of autonomic nervous system dysfunction were reported during the first week of treatment (Chesterman, 1977); therefore, it was concluded that the endpoints could be used to characterize the risk from potential acute exposure to deltamethrin. Increases were reported both in the incidence and the number of animals. The incidence of liquid feces increased in a dose-related fashion at 0.1, 1, 2.5, and 10 mg/kg/day with all increases being statistically significant ($p \leq 0.05$). Furthermore, all occurrences were observed within 7 hours of dosing. The vomiting also increased at 2.5 and 10 mg/kg/day, with the incidence statistically different ($p \leq 0.05$) from the concurrent control group at 10 mg/kg/day. While the incidence at 2.5 mg/kg/day was not statistically different from the concurrent controls, the response was indicative of a continuum for these responses at lower doses to deltamethrin. On the basis of these reported effects, the LOEL appeared to be at 0.1 mg/kg/day. An estimated NOEL (ENOEL) of 0.01 mg/kg/day was, therefore, established by using the default approach of dividing the LOEL by an uncertainty factor of 10. However, during a review of the risk assessment by DPR toxicologists, a scientific consensus on the biological relevance of the effects reported at 0.1 mg/kg/day could not be established. Therefore, for acute exposure, in addition to calculating margins of exposure assuming an ENOEL of 0.01 mg/kg/day, margins of exposure were also calculated assuming a NOEL of 0.1 mg/kg/day. Since oral absorption has been estimated to be 58%, (or approximately 60%) **the acute NOEL of 0.1 mg/kg/day, was adjusted to 0.06 mg/kg/day, and the acute ENOEL of 0.01 mg/kg/day was adjusted to 0.006 mg/kg/day.** Both values were used in this document for calculating margins of exposure (MOE's) for potential acute exposure to deltamethrin.

2. Sub-chronic Toxicity

In addition to providing information that is useful in dose selection for chronic toxicity, reproductive, and oncogenicity studies, sub-chronic toxicology studies are designed to examine the adverse effects resulting from repeated exposure of a portion of the average life span of an experimental animal (Mosberg and Hays, 1989). The sub-chronic toxicity assessment is intended to assist in determining potential risk to agricultural workers involved with seasonal exposure to deltamethrin. Potential adverse effects have been

associated with sub–chronic exposure to deltamethrin in a number of studies (see Toxicology Profile section of this document).

As described in the toxicology profile section, deltamethrin was evaluated in a 13-week oral toxicity study conducted in dogs (Chesterman, 1977). In that study, deltamethrin was dissolved in PEG and administered in gelatin capsules at doses of 0, 0.1, 1.0, 2.5, and 10 mg/kg/day. A dose-related increase in signs indicating autonomic nervous system dysfunction was reported. The effects included vomiting, liquid feces, uncoordinated body movements, tremors, and abnormal reflex responses. They occurred in a dose-related fashion at levels greater than 0.1 mg/kg/day. In the first half of a 52-week toxicity study conducted in dogs (deltamethrin without solvent) abnormal gait, trembling, vomiting, and liquid feces were reported at dosages greater than 1 mg/kg/day (Ryle et. al, 1993). In this study, specialized neurological exams (tests for cranial nerve function, spinal reflexes, and postural reactions) were conducted at weeks 26 and 52. At the 26-week examination, tremors were reported in two animals in the high dose-group. It is important to note, however, that these specialized tests were not conducted at the low and mid doses. Potential for effects at these doses, therefore, can not be ruled out. On the basis of the information available, the NOEL established for this study was 1 mg/kg/day. As previously discussed under acute toxicity, the studies conducted with technical grade deltamethrin were not considered appropriate for risk assessment.

On the basis of the spectrum of effects consistent with autonomic nervous system dysfunction reported in the 13-week dog study (Chesterman, 1977), the empirical LOEL appeared to be 0.1 mg/kg/day (the lowest dose tested) for sub-chronic toxicity. This was the same study that was demonstrated signs of autonomic nervous system dysfunction during the first week of exposure, and used for acute NOEL determination. The resulting LOELs/NOELs and adjustments were the same for sub-chronic toxicity as discussed under acute toxicity. Therefore, **the sub-chronic NOEL used for risk assessment was 0.06 mg/kg/day, and the sub-chronic ENOEL was 0.006 mg/kg/day**. Both values were used in this document for calculating margins of exposure (MOE's) for potential sub-chronic exposure to deltamethrin.

3. Chronic Toxicity

In a two year oral toxicity and carcinogenicity study conducted in rats, Goldenthal (1980) reported a dose related increase in degeneration of sciatic, tibial, and plantar nerves. These effects were observed at 18 months but not at the 24-month study termination. As indicated in the toxicology profile section of this document, the lack of an effect at the 24-month period was likely due to an excessive background level for that time period. The critical NOEL for this study was established at 0.1 mg/kg/day based on peripheral nerve damage reported at 1.1 and 2.8 mg/kg/day. Assuming an oral absorption of approximately 60%, the adjusted critical **chronic NOEL for this risk assessment was 0.06 mg/kg/day.** This value was used in calculating margins of exposure for chronic exposure to deltamethrin.

4. Oncogenicity

On the basis of the data reviewed, no evidence of oncogenicity potential has been associated with deltamethrin exposure. Therefore, potency factors or other quantitative considerations of oncogenic risk were not calculated for deltamethrin.

5. Genotoxicity

Genotoxic potential has been reported in the open literature. Positive genotoxicity has been reported for deltamethrin technical and formulations containing deltamethrin as the active ingredient both *in vivo* (chromosomal aberrations and micronuclei) and *in vitro* (sister-chromatid exchange in human lymphocytes).

6. Reproductive Toxicity

A rat reproduction study submitted by the registrant indicated minor effects (reduced pup weight) but was considered unacceptable to DPR (Wrenn, 1980). Microscopic examinations were limited to F_{3b} weanlings and no parental microscopic data were collected. After a review of the open literature, a study was found that indicated a number of reproductive effects in rats treated with deltamethrin. Deltamethrin significantly decreased the weight of testes, seminal vesicle, and prostate glands. Significant decreases were also noted in sperm cell concentrations, percentage of live cells and sperm motility. Furthermore, plasma testosterone concentration was significantly decreased and the pregnancy rate was depressed (Abd El-Aziz, 1994).

7. Developmental Toxicity

In the studies submitted in support of registration, no significant developmental toxicity was reported in rats (Schardein, 1990a) or in rabbits (Schardein, 1990b). Effects in rats have been reported, however, in the open literature (Abd El-Khalik, et. al, 1993). These researchers reported that a 5% deltamethrin formulation results in dose-dependent early embryonic death, retardation of fetal growth, hypoplasia of the lungs, and dilation of the renal pelvis.

B. EXPOSURE ASSESSMENT

1. Pest Control Exposure

Exposure to deltamethrin from use in pest control has been evaluated, using surrogate data, by the Worker Health and Safety branch of DPR (Thongsinthusak, 1996). Anticipated California uses of deltamethrin include the treatment of cotton, professional pest control, and ready-to-use, do-it-your-self (residential) pest control. Table 17 presents average daily dosage estimates, in μg/kg/day, for acute, seasonal, annual, and lifetime potential exposures. For acute exposure, the mean and the upper-bound estimates, for absorbed daily dosage (ADD), are presented. The upper-bound values were used in this risk assessment because they represent appropriate estimates of maximum potential acute exposures. For seasonal average daily dosage (SADD), annual average daily dosage (AADD), and a lifetime average daily dosage (LADD), the mean potential exposure estimate was used because it was considered unlikely that a person would be exposed at the maximum, each day for the extended time periods. The LADD was estimated by multiplying the AADD times projected years of employment (40) and divided by projected lifetime (75 years).

Table 17: Estimated dosages for agricultural workers exposed to deltamethrin Decis 0.2 EC.

	Dosage (μg/kg/day)				
Worker Activity[a]	**$ADD_{(avg)}$**	**ADD**	**SADD**	**AADD**	**LADD**
Aerial Application[b]					
Mixer/Loader	0.46	1.12	0.37	0.06	0.03
Applicator	0.25	0.77	0.20	0.03	0.02
Flagger	0.03	0.06	0.03	0.005	0.002
Ground Boom Application[c]					
Mixer/Loader	0.42	0.74	0.14	0.02	0.01
Applicator	0.05	0.09	0.02	0.003	0.002
Mixer/Loader/Applicator	0.47	0.83	0.16	0.023	0.012
Cotton Scouts[d]					
Gloved	0.13	0.17	0.08	0.01	0.01
Not Gloved	0.22	0.29	0.14	0.02	0.01

a The following default factors were used in the estimation of exposures: adult male body weight = 75.9 kg, dermal absorption rate = 6.7%, years of employment = 40, life expectancy = 75 years (Thongsinthusak, 1996).
b Assumed 50 workdays in a 62-day season.
c Assumed 20 workdays in a 62-day season.
d Assumed 40 workdays in a 62-day season.
ADD Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others. The average ADD ($ADD_{(avg)}$) is also presented.
SADD Seasonal Average Daily Dosage based on mean exposure.
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.

As indicated in Table 17, upper bound acute (daily) deltamethrin exposure estimates, from use of Decis 0.2EC, range from 0.06 μg/kg/day for flaggers, to 1.12 μg/kg/day for mixer/loaders involved in aerial application. The average exposure values ranged from 0.05 to 0.47 μg/kg/day. Mixer/loaders also represented the group with the highest estimates for seasonal, annual, and lifetime exposures, 0.37, 0.06, and 0.03 μg/kg/day, respectively.

Estimates were also determined for occupational exposure to deltamethrin from Decis 1.5EC. These values are presented in Table 18.

Table 18: Estimated dosages for agricultural workers exposed to deltamethrin Decis 1.5 EC.

	Dosage (μg/kg/day)				
Worker Activity[a]	**$ADD_{(avg)}$**	**ADD**	**SADD**	**AADD**	**LADD**
Aerial Application[b]					
Mixer/Loader	0.70	1.68	0.56	0.10	0.05
Applicator	0.36	1.14	0.29	0.05	0.03
Flagger	0.05	0.09	0.04	0.007	0.004
Ground Boom Application[c]					
Mixer/Loader	0.64	1.11	0.21	0.03	0.02
Applicator	0.08	0.14	0.03	0.004	0.002
Mixer/Loader/Applicator	0.72	1.25	0.24	0.034	0.022
Cotton Scout[d]					
Gloved	0.19	0.25	0.12	0.02	0.01
Not Gloved	0.33	0.44	0.21	0.04	0.02

a The following default factors were used in the estimation of exposures: adult male body weight = 75.9 kg, dermal absorption rate = 6.7%, years of employment = 40, life expectancy = 75 years (Thongsinthusak, 1996).
b Assumed 50 workdays in a 62-day season.
c Assumed 20 workdays in a 62-day season.
d Assumed 40 workdays in a 62-day season.
ADD Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others. The average ADD ($ADD_{(avg)}$) is also presented.
SADD Seasonal Average Daily Dosage based on mean exposure.
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.

As indicated, upper bound acute deltamethrin exposure estimates, from use of Decis 1.5EC, range from 0.09 μg/kg/day for flaggers, to 1.68 μg/kg/day for mixer/loaders involved in aerial application. The average exposure values ranged from 0.05 to 0.72 μg/kg/day. Mixer/loaders also represented the group with the highest estimates for seasonal, annual, and lifetime exposures, 0.56, 0.10, and 0.05 μg/kg/day, respectively.
In addition to agricultural workers, exposure estimates were calculated for anticipated residential uses of deltamethrin.

Table 19 presents ADD, AADD, and LADD dosage estimates for pest control operators (PCOs), adult male and infant inhabitants.

Table 19: Estimated dosages from the residential use of deltamethrin for pest control operators (PCOs), adult male and infant inhabitants.

	Dosage (μg/kg/day)			
	$ADD_{(avg)}$	**ADD**	**AADD**	**LADD**
Home Application				
Residential PCO (M/L/A)[a]	43.20	61.00	26.40	14.10
Infants[b]	11.09	14.17	0.46	N/A
Adult Males[c]	7.10	9.02	0.29	0.16

a The workers were assumed to be wearing long-sleeved shirts, long pants, shoes, socks and rubber gloves. Results represent geometric mean values. Standard deviation could not be determined as individual data was not available. Inhalation rate per 8 hour work day was assumed to be 6.72 m^3. Exposure assumed 15 workdays in a 90-day season and 30 workdays per year (Thongsinthusak, 1996).

b Infant body weight was assumed to be 10.2 kg. The number of day exposed per year was assumed to be 15.

c The assumed number of days exposed per year was 15 (3 applications/year x 5 days/application).

ADD Absorbed Daily Dosage based on upper-bound estimate (i.e., upper limit of range for PCO mixer/loader/applicators, mean + 2SD for all others. The average ADD ($ADD_{(avg)}$) is also presented.

AADD Annual Average Daily Dosage based on mean exposure.

LADD Lifetime Average Daily Dosage based on mean exposure.

N/A Not applicable.

PCO Pest control operator.

M/L/A Mixer/Loader/Applicator.

The individuals with the highest estimated dosage, 61 μg/kg/day, following acute exposure, were PCO loader/applicators. These individuals were also shown to have the highest estimated dosages for annual and lifetime exposures, 26.4 and 14.1 μg/kg/day, respectively. No seasonal exposure was assumed for home application. For infants, the dosage estimates were 14.17 and 0.46 μg/kg/day for acute and annual exposures. For adult males, the dosage estimates were 9.02, 0.29, and 0.16 μg/kg/day for acute, annual, and lifetime exposures.

Deltamethrin dosage estimates were also generated for workers involved with the use of K-Othrine Dust on flowers and ornamentals (Table 20).

Table 20: Estimated dosages for loader/applicators involved with the use of K-Othrine Dust (0.05 % deltamethrin) on flowers and ornamentals.

	Dosage (μg/kg/day)			
Worker Activity	**ADD**	**SADD[b]**	**AADD[c]**	**LADD**
Loader/Applicator[a]	0.8	0.13	0.07	0.04

[a] Values represent geometric means as no data were available for upper-bound estimaes (Thongsinthusak, 1996)
[b] Fifteen workdays were assumed for a 90-day season
[c] Thirty workdays assumed in a year
ADD Absorbed Daily Dosage
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.

The dosage estimates for mixer/loaders using K-Othrine Dust were 0.8, 0.13, 0.07, and 0.04 μg/kg/day for acute, seasonal, annual, and lifetime exposure, respectively.

2. Dietary Exposure

DPR evaluates the risk of exposure to an active ingredient in the diet using two processes: (1) use of residue levels detected in foods to evaluate the risk from all dietary sources, and (2) use of tolerance levels to evaluate the risk from exposure to individual commodities (see the Tolerance Assessment of this document). For the evaluation of risk to detected residue levels, the total exposure in the diet is determined for all label-approved raw agricultural commodities, processed forms, and animal products (meat and milk) that have established U.S. EPA tolerances. The potential exposure from residues in the water and certain commodities without tolerances are also assessed in some cases. Tolerances may be established for the parent compound and associated metabolites. DPR considers these metabolites and other degradation products that may be of toxicological concern in the dietary assessment.

a. Residue Data

The sources of residue data for dietary exposure assessment include DPR and federal monitoring programs, field trials, and survey studies. In the absence of data, surrogate data from the same crop group as defined by U.S. EPA or theoretical residues equal to U.S. EPA tolerances are used. A commodity with a residue over an established tolerance is considered adulterated and illegal for sale. DPR evaluates the potential risk from consuming commodities with residues over tolerance levels using an expedited acute risk assessment process.

DPR has two major sampling programs: priority pesticide and marketplace surveillance. The priority pesticide program focuses on pesticides of health concern as determined by DPR Enforcement and Medical Toxicology Branches. Samples are collected from fields known to have been treated with the specific pesticides. For the marketplace surveillance program, samples are collected at the wholesale and retail outlets, and at the point of entry for imported foods. The sampling strategies for both priority pesticide and marketplace surveillance are similar and are weighted toward such factors as pattern of pesticide use; relative number and volume of pesticides typically used to produce a commodity; relative dietary importance of the commodity; past monitoring results; and extent of local pesticide use.

The United States Food and Drug Administration (FDA) has three monitoring programs for determining residues in food: (1) regulatory monitoring, (2) total diet study, and (3) incidence/level monitoring. For regulatory monitoring, surveillance samples are collected from individual lots of domestic and imported foods at the source of production or at the wholesale level. In contrast to the regulatory monitoring program, the total diet study monitors residue levels in the form that a commodity is commonly eaten or found in a prepared meal. The incidence/level monitoring program is designed to address specific concerns about pesticide residues in particular foods.

The U. S. Department of Agriculture (USDA) is responsible for the Pesticide Data Program (PDP), a nationwide cooperative monitoring program. The PDP is designed to collect objective, comprehensive pesticide residue data for risk assessments. Several states, including California, collect samples at produce markets and chain store distribution centers close to the consumer level. The pesticide and produce combinations are selected based on the toxicity of the pesticide as well as the need for residue data to determine exposure. In addition, USDA is responsible for the National Residue Program which provides data for potential pesticide residues in meat and poultry. These residues in farm animals can occur from direct application, or consumption of commodities or by-products in their feed.

The U.S. Department of Agriculture directs the Nationwide Food Consumption Survey (NFCS) and the Continuing Survey of Food Intakes by Individuals (CSFII). The NFCS is a geographically stratified probability sampling of the U.S. households and is conducted every 10 years (1977-1978 and 1987-1988). The CSFII is an annual survey which reflects the current consumption pattern and has a greater focus on consumption data for vulnerable population subgroups (e.g., infants and children).

Table 21 presents a summary of deltamethrin residue values used to assess acute and chronic dietary exposure.

Table 21: Summary of deltamethrin residue values in cottonseed oil, cottonseed mill, and soybeans used to assess acute and chronic dietary exposure

Commodity	Residue (ppm) Acute	Residue (ppm) Chronic	Data Source
Cottonseed Oil	0.089	0.085	Registrant studies
Cottonseed Meal	0.020	0.010	Registrant studies
Tomatoes Whole	0.200	0.200	US/EPA Tolerances
Tomatoes Puree	0.200	0.200	US/EPA Tolerances
Tomatoes Paste	0.200	0.200	US/EPA Tolerances
Tomatoes Catsup	0.200	0.200	US/EPA Tolerances
Tomatoes Dried	NC	0.200	US/EPA Tolerances

NC (no consumption was reported in the survey)

b. Acute Exposure

Estimates of potential acute (daily) dietary exposure use the highest measured residue values at or below the tolerance for each commodity. The following assumptions were used to estimate potential acute dietary exposure from measured residues: 1) the residue does not change over time, 2) the concentration of residue does not decrease when the raw agricultural commodity (RAC) is washed, 3) processing of RACs into various food forms does not reduce the residue, and 4) all foods that are consumed will contain the highest reported residue.

Acute dietary exposure analyses were conducted using the Exposure-4™ computer program developed by Technical Assessment Systems, Inc. (TAS, 1992a). This software estimates the distribution of single-day exposures for the overall U.S. population and specific population sub-groups. The analysis utilizes food consumption data, as reported by the U.S. Department of Agriculture (USDA, 1992). Exposure-4™ is designed to evaluate exposure to chemical residues as a function of consumer-days. A consumer-day is any day in which at least one commodity is consumed. For this document, all TAS dietary exposure values were adjusted for oral absorption.

Anticipated California use of deltamethrin on cotton is expected to be significant. Estimates of acute exposure from use on this commodity were, therefore, developed. Acute deltamethrin dosage (exposure x the estimated oral absorption of 60%) estimates, for various U.S. population sub-groups, are presented in Table 22.

Table 22: Potential dosage from acute dietary exposure to deltamethrin from residues in cotton.

Population Sub-group	Dosage (µg/kg/day)[a,b]
U.S. Population	0.008
Pacific Region - U.S. Population	0.006
U.S. Population (16+ years)	0.006
Seniors (55+ years)	0.005
Hispanics	0.006
Non-Hispanic Whites	0.008
Non-Hispanic Blacks	0.010
Non-Hispanic Other	0.007
All Infants	0.010
Nursing Infants (<1 year)	0.010
Non-Nursing Infants (<1 year)	0.010
All Infants	0.010
Children (1-6 years)	0.016
Children (7-12 years)	0.013
Females (13+/P[c]/NN[d])	0.006
Females (13+N[e])	0.009
Females (13-19 years/NP[f]/NN)	0.008
Females (20+/NP/NN)	0.005
Males (13-19 years)	0.009
Males (20+ years)	0.006

a = Exposure is evaluated as a function of user-days (i.e., day which at least one commodity containing deltamethrin is consumed).
b = Values represent the 95th percentile of consumer-day exposure.
c = pregnant
d = not nursing
e = nursing
f = not pregnant

On the basis of the 95th percentile of user-day exposures, the potential acute dietary exposure of from the use of deltamethrin, was approximately 0.008 µg/kg/day for the U.S. population (Table 22). Dosage estimates ranged from approximately 0.005 to 0.016 µg/kg/day. The population sub-group with the highest dosage estimate was children from the age group of 1 to 6 years.

It is anticipated that the primary dietary exposure to deltamethrin in the state of California would result from its use on cotton and tomatoes. While a petition for registration on tomatoes has not been submitted to California, the existence of a US/EPA tolerance allows for the sale and consumption of deltamethrin containing tomato products in the state. Since residue data has not been submitted to the state in support of registration, tolerance values have been used to develop dosage estimates for this commodity. Table 23

presents estimated acute dietary exposure to deltamethrin from potential residues in cotton, tomatoes, and byproducts of these commodities. Values were adjusted for 60% oral absorption.

Table 23: Potential acute dietary exposure to deltamethrin from residues in cotton and tomatoes.

Population Sub-group	Dosage (µg/kg/day)[a,b]
U.S. Population	1.3
Pacific Region - U.S. Population	1.2
U.S. Population (16+ years)	1.0
Seniors (55+ years)	0.7
Hispanics	1.8
Hispanics (16+ years)	1.3
Non-Hispanic Whites	1.3
Non-Hispanic Blacks	1.1
Non-Hispanic Other	1.4
All Infants	3.2
Nursing Infants (<1 year)	2.9
Non-Nursing Infants (<1 year)	2.2
Children (1-6 years)	2.4
Children (7-12 years)	1.7
Females (13+/P[c]/NN[d])	1.0
Females (13+N[e])	1.0
Females (13-19 years/NP[f]/NN)	1.3
Females (20+/NP/NN)	0.9
Males (13-19 years)	1.4
Males (20+ years)	1.1

a = Exposure is evaluated as a function of user-days (i.e., day which at least one commodity containing deltamethrin is consumed).
b = Values represent the 95th percentile of consumer-day exposure.
c = pregnant
d = not nursing
e = nursing
f = not pregnant

On the basis of the 95th percentile of user-day exposures, the potential acute dietary exposure to deltamethrin, from use on cotton and tomatoes, for the U.S. population, was approximately 1.3 µg/kg/day (Table 23). Dosage estimates ranged from approximately 0.7 to 3.2 µg/kg/day. The population sub-group with the highest dosage estimate was infants. Exposure for the U.S. population ages 16+ were estimated to predict the potential dietary component of total exposure to workers using deltamethrin. Since the Hispanic population

exposure estimate was larger than that of the U.S. population, the potential exposure for Hispanic Americans 16 years of age and older was also determined. The calculated value was 1.3 μg/kg/day.

c. Sub-chronic (seasonal) Exposure

Since dietary consumption of cotton and tomato products are not considered seasonal, i.e., consumption is year-round, sub-chronic dietary only exposure scenarios for deltamethrin are not addressed in this document.

d. Chronic (annual) Exposure

Estimates of potential chronic (annual) dietary exposure used the average of measured and "below detection limit" residue values for each commodity. The default procedure assumed that "below detection limit" residues were equal to one-half (50%) of the minimum detection limit (MDL) for each commodity. The following assumptions were used to estimate potential chronic dietary exposure from measured residues: 1) the residue level does not change over time, 2) residues are not reduced by washing the raw agricultural commodity (RAC), 3) processing of is assumed to be at a level equivalent to the RAC residue level that may be multiplied by an adjustment factor, and 4) exposures to a commodity at all reported residue levels do occur, i.e., a commodity with the average calculated residue is consumed every day at an annual average level (dosage).

The potential chronic dietary exposure was calculated using the Exposure-1™ computer program developed by TAS (Technical Assessment Systems, Inc., 1992b). The food consumption data for the chronic analysis was also based on the 1989-92 United States Department of Agriculture Nationwide Food Consumption Survey (USDA, 1992). The program estimates the annual average exposure for all members of a designated population subgroup.

The calculated dosages following chronic dietary exposure to deltamethrin from cotton byproducts was approximately 0.002 μg/kg/day for the U.S. population (Table 24). Values were adjusted for 60% oral absorption.

Table 24: Potential dosage from chronic (annual) dietary exposure to deltamethrin from residues in cotton

Population Sub-group	Dosage (µg/kg/day)[a]
U.S. Population	0.002
Pacific Region - U.S. Population	0.002
Seniors (55+)	0.001
Hispanics	0.001
Non-Hispanic Whites	0.002
Non-Hispanic Blacks	0.002
Non-Hispanic Other	0.002
All infants	0.001
Nursing Infants (<1 year)	0.001
Non-Nursing Infants (<1 year)	0.001
Children (1-6 years)	0.004
Children (7-12 years)	0.003
Females (13+/P[b]/NN[c])	0.001
Females (13+N[d])	0.002
Females (13-19 years/NP[e]/NN)	0.002
Females (20+/NP/NN)	0.001
Males (13-19 years)	0.002
Males (20+ years)	0.002

a = Exposure estimates were based on annual average daily consumption
b = pregnant
c = not nursing
d = nursing
e = not pregnant

The estimated dosages for the population subgroups examined ranged from approximately 0.001 to 0.004 µg/kg/day. The population sub-group with the highest exposure was children ages 1 through 6.

Chronic dietary exposure to deltamethrin was also estimated on the basis of predicted consumption of cotton byproducts, tomatoes, and tomato byproducts (Table 25). Values were adjusted for 60% oral absorption.

Table 25: Potential dosage from chronic (annual) dietary exposure to deltamethrin from residues in cotton and tomatoes.

Population Sub-group	Dosage (µg/kg/day)[a]
U.S. Population	0.27
Pacific Region - U.S. Population	0.25
Seniors (55+)	0.14
Hispanics	0.33
Non-Hispanic Whites	0.28
Non-Hispanic Blacks	0.21
Non-Hispanic Other	0.29
All Infants	0.13
Nursing Infants (<1 year)	0.10
Non-Nursing Infants (<1 year)	0.14
Children (1-6 years)	0.54
Children (7-12 years)	0.44
Females (13+/P[b]/NN[c])	0.23
Females (13+N[d])	0.28
Females (13-19 years/NP[e]/NN)	0.29
Females (20+/NP/NN)	0.19
Males (13-19 years)	0.32
Males (20+ years)	0.24

a = Exposure estimates were based on (annual average) daily consumption
b = pregnant
c = not nursing
d = nursing
e = not pregnant

As indicated, estimated deltamethrin dosages, based on consumption of cotton byproducts and tomatoes and their byproducts, for the U.S. population is 0.27g/kg/day. The range of dosage estimates for the population subgroups is approximately 0.10 to 0.54 µg/kg/day. The population sub-group with the highest exposure was children ages 1 through 6.

3. Combined (Aggregate) Exposure

a. Occupational (Agricultural Workers) and Dietary Exposure

In an effort to predict total (i.e., aggregate) exposure to agricultural workers using deltamethrin, estimated dietary exposure was combined with potential exposure from agricultural activities. The acute dietary component for the ADD (1.3 μg/kg/day) represents the estimated dosage to the Hispanic population ages 16 + (Table 23). The Hispanic population was chosen because it represented the population sub-group with the highest exposure estimate for potential workers. The population was restricted to those individuals 16 years and older to better represent the working population. For combined dosage estimates for seasonal, annual, and lifetime exposures, the dietary component (0.33 μg/kg/day) was also based on the annual exposure for the Hispanic population sub-group (Table 25). This population sub-group was chosen because it represented the population of potential workers with the highest potential exposure. Since the TAS dietary programs did not indicate substantial seasonal variability in potential exposure, the average daily exposure for the seasonal component was taken from chronic (annual) exposure estimates. The occupational components have been presented in Table 17. Table 26 presents the combined estimates for the ADD, SADD, AADD, and LADD. Note that for the combined LADD, the estimates assume that an individual would be exposed to the annual dietary exposure each successive year.

The estimated acute deltamethrin dosages based on occupational activities involved with the use of Decis 0.2EC, combined with estimated dietary exposures, range from 1.36 μg/kg/day for flaggers, to 2.42 μg/kg/day for mixer/loaders involved in aerial application (Table 26). Mixer/loaders also represented the group with the highest estimates for seasonal, annual, and lifetime exposures, 0.7, 0.39, and 0.36 μg/kg/day, respectively.

Table 26: Combined occupational and dietary dosages from the use of deltamethrin (Decis 0.2 EC).

	Dosage (μg/kg/day)[a]			
Worker Activity	**ADD**	**SADD**	**AADD**	**LADD**
Aerial Application[b]				
Mixer/Loader	2.42	0.7	0.39	0.36
Applicator	2.07	0.53	0.36	0.35
Flagger	1.36	0.36	0.34	0.33
Ground Boom Application[c]				
Mixer/Loader	2.04	0.47	0.35	0.34
Applicator	1.39	0.35	0.33	0.33
Mixer/Loader/Applicator	2.13	0.49	0.35	0.34
Cotton Scouts[d]				
Gloved	1.47	0.41	0.34	0.34
Not Gloved	1.59	0.47	0.35	0.34

a The following default factors were used in the estimation of exposures: adult male body weight = 75.9 kg, dermal absorption rate = 6.7%, years of employment = 40, life expectancy = 75 years (Thongsinthusak, 1996).
b Assumed 50 workdays in a 62-day season.
c Assumed 20 workdays in a 62-day season.
d Assumed 40 workdays in a 62-day season.
ADD Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others.
SADD Seasonal Average Daily Dosage based on mean exposure.
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.

Estimates were also determined for combined occupational and dietary exposure to deltamethrin from Decis 1.5EC (Table 27). The combined acute deltamethrin exposure estimates, from the occupational use of Decis 1.5EC and from dietary exposure to residues from cotton and tomatoes, ranged from 1.39 μg/kg/day for flaggers, to 2.98 μg/kg/day for mixer/loaders involved in aerial application. Mixer/loaders involved with aerial application also represented the group with the highest estimates for seasonal, annual, and lifetime exposures, 0.89, 0.43, and 0.38 μg/kg/day, respectively.

Table 27: Combined occupational and dietary dosages from the use of deltamethrin (Decis 1.5 EC).

	Dosage (μg/kg/day)[a]			
Worker	**ADD**	**SADD**	**AADD**	**LADD**
Aerial Application[b]				
Mixer/Loader	2.98	0.89	0.43	0.38
Applicator	2.44	0.62	0.38	0.36
Flagger	1.39	0.37	0.34	0.33
Ground Boom Application[c]				
Mixer/Loader	2.41	0.54	0.36	0.35
Applicator	1.44	0.36	0.33	0.33
Mixer/Loader/Applicator	2.55	0.57	0.36	0.35
Cotton Scout[d]				
Gloved	1.55	0.45	0.35	0.34
Not Gloved	1.74	0.54	0.37	0.35

a The following default factors were used in the estimation of exposures: adult male body weight = 75.9 kg, dermal absorption rate = 6.7%, years of employment = 40, life expectancy = 75 years (Thongsinthusak, 1996).
b Assumed 50 workdays in a 62-day season.
c Assumed 20 workdays in a 62-day season.
d Assumed 40 workdays in a 62-day season.
ADD Absorbed Daily Dosage based on upper-bound estimate (i.e., mean + 2SD for mixer/loaders and applicators involved with aerial application; upper limit of range all others.
SADD Seasonal Average Daily Dosage based on mean exposure.
AADD Annual Average Daily Dosage based on mean exposure.
LADD Lifetime Average Daily Dosage based on mean exposure.

b. Residential and Dietary Exposure

Combined dosage estimates for pest control operators, adult males and infants from the residential use of deltamethrin products and from dietary exposure from cotton byproducts, tomatoes and tomato byproducts are presented in Table 28. For PCO's and adult males, the acute dietary component for the ADD (1.3 μg/kg/day) represents the estimated dosage for the Hispanic population ages 16 and older (Table 23). For combined dosage estimates for seasonal, annual, and lifetime exposures, the dietary component (0.33 μg/kg/day) was also based on annual exposure estimates for the Hispanic population sub-group. For infants, the acute dietary component for the ADD (3.2 μg/kg/day) represents the estimated dosage for infants (Table 23). For combined annual exposure estimates, the estimated annual dietary component for infants was 0.13 μg/kg/day (Table 25).

The individuals with the highest estimated dosage, 62 μg/kg/day, following acute exposure, were PCO loader/applicators. These individuals were also shown to have the highest estimated dosages for annual and lifetime exposures, 27 and 14 μg/kg/day, respectively. No seasonal exposure was assumed for home application. For infants, the dosage estimates were 17 and 0.59 μg/kg/day for acute and annual exposures, respectively. For adult males, the dosage estimates were 10, 0.62, and 0.49 μg/kg/day for acute, annual, and lifetime exposures, respectively.

Table 28: Combined residential and dietary dosages from the use of deltamethrin.

	Dosage (μg/kg/day)[a]		
	ADD	**AADD**	**LADD**
Home Application			
Residential PCO (M/L/A)[b]	62	27	14
Infants[c]	17	0.59	N/A
Adult Males[d]	10	0.62	0.49

a All values have been rounded to 2 significant digits.

b The workers were assumed to be wearing long-sleeved shirts, long pants, shoes, socks and rubber gloves. Results represent geometric mean values. Standard deviation could not be determined as individual data was not available. Inhalation rate per 8 hour work day was assumed to be 6.72 m^3. Exposure assumed 15 workdays in a 90-day season and 30 workdays per year (Thongsinthusak, 1996).

c Infant body weight was assumed to be 10.2 kg. The number of day exposed per year was assumed to be 15.

d The assumed number of days exposed per year was 15 (3 applications/year x 5 days/application).

ADD Absorbed Daily Dosage based on upper-bound estimate (i.e., upper limit of range for PCO mixer/loader/applicators, mean + 2SD for all others).

AADD Annual Average Daily Dosage based on mean exposure.

LADD Lifetime Average Daily Dosage based on mean exposure.

N/A Not applicable.

PCO Pest control operator.

M/L/A Mixer/Loader/Applicator.

c. Flowers/Ornamentals and Dietary Exposure

Combined occupational and dietary dosage estimates were also generated for the use of deltamethrin (e.g., K-Othrine Dust) on flowers and ornamentals (Table 29). For loader/applicators, the acute dietary component for the ADD (1.3 μg/kg/day) represents the estimated dosage for the Hispanic population 16+ (Table 23). For combined dosage estimates for seasonal, annual, and lifetime exposures, the annual dietary component (0.33 μg/kg/day) was based on the Hispanic population sub-group. The dosage estimates for loader/applicators were 2.1, 0.46, 0.40, and 0.37 μg/kg/day for acute, seasonal, annual, and lifetime exposure estimates, respectively.

Table 29: Combined occupational and dietary dosages from the use of deltamethrin (K-Othrine Dust) on flowers and ornamentals.

	Dosage (μg/kg/day)[a]			
Worker Activity	**ADD**	**SADD[b]**	**AADD[c]**	**LADD**
Loader/Applicator	2.1	0.46	0.40	0.37

[a] Occupational values from Table 20 were based on geometric means. No upper-bound estimate was presented (Thongsinthusak, 1996).

[b] Fifteen workdays were assumed for a 90-day season

[c] Thirty workdays assumed in a year.

C. RISK CHARACTERIZATION

In order to characterize the potential risks associated with exposure to deltamethrin, margins of exposure (MOEs) were calculated for exposures resulting from pest control usage (agricultural, professional pest control operators, and do-it-yourself residential pest control), dietary exposure, and combined pest control and dietary exposures. An MOE is defined as the ratio of the No-Observed-Effect-Level (NOEL) to the estimated human absorbed dosage. Experimentally determined NOELs or ENOELs (estimated NOELs) were described in the Toxicology Profile and Hazard Identification sections of this document. Dosage estimates were determined by the Worker Health and Safety Branch of DPR (Thongsinthusak, 1996) and summarized in the Exposure Section of this document.

When the NOEL for an adverse effect is derived from a laboratory animal study, a calculated MOE of 100 is generally considered adequate for protection against potential toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for intraspecies variability, as well as an uncertainty factor of 10 for inter-species variability. This latter uncertainty factor assumes that the least sensitive human is 10 times more sensitive to the effects of a toxin than are laboratory animals (Davidson et al., 1986; Dourson and Stara, 1983,1985; USEPA, 1986b). If the critical NOEL is from a human study, a benchmark of 10 is used, incorporating a single uncertainty factor which assumes there is only a 10-fold difference between the least sensitive and most susceptible human.

As indicated in the Hazard Identification Section of this document, in the process of the DPR internal review, a consensus on the biological relevance of low dose effects was not established for acute and sub-chronic toxicity testing. Two sets of MOE estimations are, therefore, presented for potential acute and sub-chronic human exposures. For potential acute exposures, MOEs are presented for the ENOEL of 0.006 mg/kg/day and the NOEL of 0.06 mg/kg/day. For potential sub-chronic exposures, MOEs are presented for the ENOEL of 0.006 and the NOEL of 0.06 mg/kg/day. For potential chronic exposures, MOE's are presented for the NOEL of 0.06 mg/kg/day.

1. Occupational/Residential Exposure

In Tables 30-33, margins of exposure are presented for deltamethrin exposures related to agricultural, professional pest control, and residential use (exclusive of dietary exposure). Acute exposures used in MOE calculations were based on the upper limit (i.e., either the maximum value or the mean plus 2 standard deviations) of potential average daily exposures. This risk assessment assumes that it is unlikely, however, that an individual would be exposed to a maximum or upper bound potential daily exposures over a repeated exposure scenario. Margins of exposure calculations for seasonal, and annual exposures were, therefore, based on the mean "average daily dosage" rather than an upper limit. Since lifetime exposure estimates were less than estimated potential annual exposures, and the same NOEL (0.06 mg/kg/day) was assumed for the two time-points, lifetime MOEs would by default be higher than annual MOEs (i.e., health protective measures used to ensure the health and safety from annual exposure would be protective under a lifetime exposure scenario). MOE calculations were not, therefore, considered necessary for lifetime exposures.

Table 30a: Margins of exposure based on estimated daily, seasonal, and annual deltamethrin exposures for agricultural workers involved in the treatment of cotton with Decis 0.2 EC. For this table, the estimated NOEL's for daily and seasonal exposures were 0.006 mg/kg/day. The NOEL for annual exposure was 0.06 mg/kg/day.

	Margins of Exposure[a]		
Worker Activity	**Daily[b]**	**Seasonal[c]**	**Annual[d]**
Aerial Application			
Mixer/Loader	5	16	1,000
Applicator	8	30	2,000
Flagger	100	200	12,000
Ground Boom Application			
Mixer/Loader	8	43	3,000
Applicator	67	300	20,000
Mixer/Loader/Applicator	7	38	2,600
Cotton Scout			
Gloved	35	75	6,000
Not Gloved	21	43	3,000

a Margin of Exposure defined as the ratio of the NOEL/dosage. Dosages were presented in Table 17. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.

b The ENOEL = 0.006 mg/kg/day based on autonomic nervous system dysfunction in dogs.

c The ENOEL = 0.006 mg/kg/day based on autonomic nervous system dysfunction in dogs.

d The NOEL = 0.06 mg/kg/day based on nerve damage in rats.

Table 30b: Margins of exposure based on estimated daily and seasonal deltamethrin exposures for agricultural workers involved in the treatment of cotton with Decis 0.2 EC (Note: annual MOE is presented in Table 30a). For this table, the estimated NOEL's for daily and seasonal exposures were 0.06 mg/kg/day

	Margins of Exposure[a]	
Worker Activity	**Daily**[b]	**Seasonal**[c]
Aerial Application		
Mixer/Loader	54	160
Applicator	78	300
Flagger	1000	2000
Ground Boom Application		
Mixer/Loader	81	430
Applicator	670	3000
Mixer/Loader/Applicator	72	380
Cotton Scout		
Gloved	350	750
Not Gloved	210	430

a Margin of Exposure defined as the ratio of the NOEL/dosage. Dosages were presented in Table 17. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.

b The NOEL = 0.06 mg/kg/day based on autonomic nervous system dysfunction in dogs.

c The NOEL = 0.06 mg/kg/day based on autonomic nervous system dysfunction in dogs.

Table 31a: Margins of exposure based on estimated daily, seasonal, and annual exposures to deltamethrin for agricultural workers involved in the treatment of cotton with Decis 1.5 EC. For this table, the estimated NOEL's for daily and seasonal exposures were 0.006 mg/kg/day. The NOEL for annual exposure was 0.06 mg/kg/day.

	Margins of Exposure[a]		
Worker Activity	**Daily[b]**	**Seasonal[c]**	**Annual[d]**
Aerial Application			
Mixer/Loader	4	11	600
Applicator	5	21	1,200
Flagger	67	150	8,600
Ground Boom Application			
Mixer/Loader	5	29	2,000
Applicator	43	200	15,000
Mixer/Loader/Applicator	5	25	1,800
Cotton Scout			
Gloved	24	50	3,000
Not Gloved	14	29	1,500

a Margin of Exposure defined as the ratio of the NOEL/dosage. Dosages were presented in Table 18. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.

b The ENOEL = 0.006 mg/kg/day based on autonomic nervous system dysfunction in dogs.

c The ENOEL = 0.006 mg/kg/day based on autonomic nervous system dysfunction in dogs.

d The NOEL = 0.06 mg/kg/day based on nerve damage in rats.

Table 31b: Margins of exposure based on estimated daily and seasonal exposures to deltamethrin for agricultural workers involved in the treatment of cotton with Decis 1.5 EC (Note: MOEs for annual exposure are presented in Table 31a). For this table, the estimated NOEL's for daily and seasonal exposures were 0.06 mg/kg/day.

	Margins of Exposure[a]	
Worker Activity	**Daily[b]**	**Seasonal[c]**
Aerial Application		
Mixer/Loader	36	110
Applicator	53	210
Flagger	670	1500
Ground Boom Application		
Mixer/Loader	54	290
Applicator	430	2000
Mixer/Loader/Applicator	48	250
Cotton Scout		
Gloved	240	500
Not Gloved	140	290

a Margin of Exposure defined as the ratio of the NOEL/dosage. Dosages were presented in Table 18. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.

b The NOEL = 0.06 mg/kg/day based on autonomic nervous system dysfunction in dogs.

c The NOEL = 0.06 mg/kg/day based on autonomic nervous system dysfunction in dogs.

Table 32a: Margins of exposure based on estimated daily and annual exposures to deltamethrin for pest control operators (PCOs), residents, and do-it-your-self home applicators. For this table, the estimated NOEL for daily exposure was 0.006 mg/kg/day. The NOEL for annual exposure was 0.06 mg/kg/day.

	Margins of Exposure[a]	
Exposure Population	**Daily[b]**	**Annual[c]**
Home Application		
Residential PCO	<1	2
Infants	<1	130
Adult Males	1	207

a Margin of Exposure defined as the ratio of the NOEL/dosage. Dosages were presented in Table 19. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.

b The ENOEL = 0.006 mg/kg/day based on autonomic nervous system dysfunction (diarrhea/liquid feces).

c The NOEL = 0.06 mg/kg/day based on nerve damage.

Table 32b: Margins of exposure based on estimated daily exposures to deltamethrin for pest control operators (PCOs), residents, and do-it-your-self home applicators (Note: MOEs for annual exposure are presented in Table 32a). For this table, the estimated NOEL for daily exposure was 0.06 mg/kg/day.

	Margins of Exposure[a]
Exposure Population	**Daily[b]**
Home Application	
Residential PCO	1
Infants	4
Adult Males	7

a Margin of Exposure defined as the ratio of the NOEL/dosage. Dosages were presented in Table 19. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.

b The NOEL = 0.06 mg/kg/day based on autonomic nervous system dysfunction (diarrhea/liquid feces).

Table 33a: Margins of exposure based on estimated daily, seasonal, and annual exposures to deltamethrin for loader/applicators using K-Othrine Dust (0.05% deltamethrin) on flowers and ornamentals. For this table, estimated NOEL's for daily and seasonal exposures were 0.006 mg/kg/day. The NOEL for annual exposure was 0.06 mg/kg/day.

Margins of Exposure[a]			
Worker Activity	**Daily[b]**	**Seasonal[c]**	**Annual[d]**
Loader Applicator[a]	8	230	430

a Margin of Exposure defined as the ratio of the NOEL/dosage. Dosages were presented in Table 20. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.
b The ENOEL = 0.006 mg/kg/day based on autonomic nervous system dysfunction in dogs.
c The ENOEL = 0.006 mg/kg/day based on autonomic nervous system dysfunction in dogs.
d The NOEL = 0.06 mg/kg/day based on nerve damage.

Table 33b: Margins of exposure based on estimated daily, seasonal, and annual exposures to deltamethrin for loader/applicators using K-Othrine Dust (0.05% deltamethrin) on flowers and ornamentals (Note: MOEs for annual expsoure are presented in Table 33a). For this table, the estimated NOEL's for daily and seasonal exposures were 0.06 mg/kg/day.

Margins of Exposure[a]		
Worker Activity	**Daily[b]**	**Seasonal[c]**
Loader Applicator[a]	75	2300

a Margin of Exposure defined as the ratio of the NOEL/dosage. Dosages were presented in Table 20. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.
b The NOEL = 0.06 mg/kg/day based on autonomic nervous system dysfunction in dogs.
c The NOEL = 0.06 mg/kg/day based on autonomic nervous system dysfunction in dogs.

a. Acute Exposure

For Decis, 0.2 EC, using an ENOEL of 0.006 mg/kg/day, the estimated acute (daily) margin of exposure for flaggers is 100 (Table 30a). For all other worker activities, MOE's are less than 100. For mixer/loaders and applicators, involved with the aerial application of the product, estimated MOE's are 5 and 8, respectively. With ground boom application, the MOE's for mixer/loaders, applicators, and mixer/loader/applicators are 8, 67, and 7, respectively. MOE's for cotton scouts are 35 and 21 for gloved and not gloved workers, respectively. When the MOE's are based on the average acute exposure rather than the upper-bound estimate, the values range from 13 to 200. The MOE's are greater than 100 for flaggers and applicators involved with ground boom application. The MOE's are less than 100 for all other activities. When the MOE's are based on a NOEL of 0.06 (Table 30b), values are elevated 10-fold.

For Decis 1.5 EC, using an ENOEL of 0.006 mg/kg/day, all estimated MOE's for acute exposure to deltamethrin are less than 100 (Table 31a). The MOE's range from 4 (mixer/loaders involved with aerial application) to 67 (flaggers). When the MOE's are based on the average acute exposure rather than the upper-bound estimate, the values range from 8 to 120. The MOE for flaggers is 120. The MOE's are less than 100 for all other activities. When the MOE's are based a NOEL of 0.06 mg/kg/day (Table 31b), values are elevated 10-fold.

For the residential use of deltamethrin products, using an ENOEL of 0.006 mg/kg/day, calculated MOE's are less than 100 for PCO's, infants, and adult males (<1, <1, and 1, respectively)(Table 32a). When the MOE's are based on the average acute exposure rather than the upper-bound estimate, the values are the same. When the MOE's are based a NOEL of 0.06 mg/kg/day (Table 32b), values are elevated 10-fold.

For acute exposure associated with the use of K-Othrine Dust on flowers and ornamentals, using an ENOEL of 0.006 mg/kg/day, the calculated MOE is 8 for loader/applicators (Table 33a). When the MOE's are based a NOEL of 0.06 mg/kg/day (Table 33b), The MOE is increased to 8.

b. Seasonal Exposure

For seasonal exposure to deltamethrin from the use of Decis 0.2 EC and Decis 1.5 EC, and using an ENOEL of 0.006 mg/kg/day, the calculated MOE's are greater than 100 for flaggers and applicators involved with ground boom application (Tables 30a and 31a). The MOE's for all other worker activities are less than 100. When the MOE's are based a NOEL of 0.06 mg/kg/day (Tables 30b and 31b), values are elevated 10-fold.

Seasonal exposure does not apply to residential PCO or home applications; therefore, margins of exposure were not calculated for these activities.

For seasonal exposure associated with the use of K-Othrine Dust, the calculated margins of exposure are greater than 100 (Table 33a and 33b) for both NOEL's.

c. Annual Exposure

On the basis of annual exposure estimates, calculated margins of exposure for all agricultural and residential activities were greater than 100, except for residential PCO's. Their MOE was 2 (Tables 30a, 31a, 32a and 33a).

d. Life-time Exposure

As indicated in Tables 17-20, all estimated life-time exposure to deltamethrin, from agricultural and residential use, were less than annual exposures. MOE calculations were not performed.

2. Dietary Exposure

a. Acute (daily) Exposure

Margins of exposure for potential acute dietary exposure to deltamethrin residues and cotton and tomato products, were calculated as the ratio of the NOEL to the potential dietary dosage (Tables 34a and 34b). Using an ENOEL of 0.006 mg/kg/day, margins of exposure are less than 100 for all population sub-groups examined (Table 34a). Using a NOEL of 0.06 elevates the MOE's by 10-fold, however, all estimated MOE's are still less than 100 (Table 34b).

Table 34a : Margins of exposure based on potential acute dietary exposure from residues in cotton and tomato products. For this table, the estimated NOEL for acute exposure was 0.006 mg/kg/day.

Population Sub-group	MOE[a]
U.S. Population	5
Pacific Region - U.S. Population	5
U.S. Population (16+ years)	6
Seniors (55+ years)	9
Hispanics	3
Hispanic Population (16+ years)	5
Non-Hispanic Whites	5
Non-Hispanic Blacks	6
Non-Hispanic Others	4
All Infants	2
Nursing Infants (<1 year)	2
Non-Nursing Infants (<1 year)	2
Children (1-6 years)	2
Children (7-12 years)	3
Females (13+/P[b]/NN[c])	6
Females (13+N[d])	6
Females (13-19 years/NP[e]/NN)	5
Females (20+/NP/NN)	7
Males (13-19 years)	4
Males (20+ years)	5

a = Margin of exposure defined as the ratio of the NOEL to the dosage. The ENOEL used for acute exposure was 0.006 mg/kg based on autonomic nervous system dysfunction in dogs. Dosage presented in Table 23. All values have been rounded to 2 significant digits.
b = pregnant
c = not nursing
d = nursing
e = not pregnant

Table 34b : Margins of exposure based on potential acute dietary exposure from residues in cotton and tomato products. For this table the estimated NOEL for acute exposure was 0.06 mg/kg/day.

Population Sub-group	MOE[a]
U.S. Population	46
Pacific Region - U.S. Population	50
U.S. Population (16+ years)	60
Seniors (55+ years)	91
Hispanics	34
Hispanic Population (16+ years)	46
Non-Hispanic Whites	47
Non-Hispanic Blacks	57
Non-Hispanic Others	43
All Infants	19
Nursing Infants (<1 year)	21
Non-Nursing Infants (<1 year)	27
Children (1-6 years)	25
Children (7-12 years)	35
Females (13+/P[b]/NN[c])	63
Females (13+N[d])	59
Females (13-19 years/NP[e]/NN)	63
Females (20+/NP/NN)	70
Males (13-19 years)	44
Males (20+ years)	54

a = Margin of exposure defined as the ratio of the NOEL to the dosage. The NOEL used for acute exposure was 0.06 mg/kg based on autonomic nervous system dysfunction in dogs. Dosage presented in Table 23. All values have been rounded to 2 significant digits.
b = pregnant
c = not nursing
d = nursing
e = not pregnant

b. Chronic (annual) Exposure

Margins of exposure for potential annual dietary exposures are presented in Table 35. The lowest MOE's are 64 and 80 for children 1-6 and children 7-12, respectively. All other population sub-groups have MOE's greater than 100.

Table 35: Margins of exposure based on potential chronic (annual) dietary exposure from residues in cotton and tomato products.

Population Sub-group	MOE[a]
U.S. Population	130
Pacific Region - U.S. Population	140
Hispanics	110
Non-Hispanic Whites	130
Non-Hispanic Blacks	170
Non-Hispanic Others	120
Nursing Infants (<1 year)	350
Non-Nursing Infants (<1 year)	250
All Infants	270
Females (13+/P[b]/NN[c])	150
Females (13+N[d])	130
Children (1-6 years)	64
Children (7-12 years)	80
Males (13-19 years)	110
Females (13-19 years/NP[e]/NN)	120
Males (20+ years)	140
Females (20+/NP/NN)	180

a = Margin of exposure defined as the ratio of the NOEL to the dosage. The NOEL used for chronic exposure was 0.06 mg/kg/day based on a nerve damage in rats. Values have been rounded to 2 significant digits.
b = pregnant
c = not nursing
d = nursing
e = not pregnant

3. Combined Occupational/Residential and Dietary Exposure

Margins of exposure were calculated for potential deltamethrin exposures related to occupational/residential use (i.e., agricultural, professional pest control, and residential) combined with potential dietary exposure (Tables 36-39).

Table 36a: Margins of exposure based on estimated daily, seasonal, and annual exposures for agricultural workers involved in the treatment of cotton using Decis 0.2 EC. Dietary exposure is included. For this table, the estimated NOEL's for daily and seasonal exposures were 0.006 mg/kg/day. The NOEL for annual exposure was 0.06 mg/kg/day.

	Margins of Exposure[a]		
Worker Activity	**Daily[b]**	**Seasonal[c]**	**Annual[d]**
Aerial Application			
Mixer/Loader	2	9	150
Applicator	3	11	170
Flagger	4	17	180
Ground Boom Application			
Mixer/Loader	3	13	170
Applicator	4	17	180
Mixer/Loader/Applicator	3	12	170
Cotton Scout			
Gloved	4	15	180
Not Gloved	4	13	170

a Margin of Exposure defined as the ratio of the NOEL to the dosage. Dosages were presented in Table 26. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.

b The ENOEL = 0.006 mg/kg/day based on autonomic nervous system dysfunction in dogs.

c The ENOEL = 0.006 mg/kg/day based on autonomic was based on autonomic nervous system dysfunction in dogs.

d The NOEL = 0.06 mg/kg/day based on nerve damage in rats.

Table 36b: Margins of exposure based on estimated daily and seasonal exposures for agricultural workers involved in the treatment of cotton using Decis 0.2 EC. Dietary exposure is included. For this table, the estimated NOEL's for daily and seasonal exposures were 0.06 mg/kg/day.

	Margins of Exposure[a]	
Worker Activity	**Daily[b]**	**Seasonal[c]**
Aerial Application		
Mixer/Loader	25	86
Applicator	29	110
Flagger	44	170
Ground Boom Application		
Mixer/Loader	29	130
Applicator	43	170
Mixer/Loader/Applicator	28	120
Cotton Scout		
Gloved	41	150
Not Gloved	38	130

a Margin of Exposure defined as the ratio of the NOEL to the dosage. Dosages were presented in Table 26. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.

b The NOEL = 0.06 mg/kg/day based on autonomic nervous system dysfunction in dogs.

c The NOEL = 0.06 mg/kg/day based on autonomic was based on autonomic nervous system dysfunction in dogs.

Table 37a: Margins of exposure based on estimated daily, seasonal, and annual exposures for agricultural workers involved in the treatment of cotton using Decis 1.5 EC. Dietary exposure is included. For this table, the estimated NOEL's for daily and seasonal exposures were 0.006 mg/kg/day. The NOEL for annual exposure was 0.06 mg/kg/day.

	Margins of Exposure[a]		
Worker Activity	**Daily[b]**	**Seasonal[c]**	**Annual[d]**
Aerial Application			
Mixer/Loader	2	7	140
Applicator	2	10	160
Flagger	4	16	180
Ground Boom Application			
Mixer/Loader	2	11	170
Applicator	4	17	180
Mixer/Loader/Applicator	2	11	170
Cotton Scout			
Gloved	4	13	170
Not Gloved	3	11	160

a Margin of Exposure defined as the ratio of the NOEL to the dosage. Dosages were presented in Table 27. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.

b The ENOEL = 0.006 mg/kg/day based on autonomic nervous system dysfunction in dogs.

c The ENOEL = 0.006 mg/kg/day based on autonomic was based on autonomic nervous system dysfunction in dogs.

d The NOEL = 0.06 mg/kg/day based on nerve damage in rats.

Table 37b: Margins of exposure based on estimated daily, seasonal exposures for agricultural workers involved in the treatment of cotton using Decis 1.5 EC. Dietary exposure is included. For this table, the estimated NOEL's for acute and seasonal exposures were 0.06 mg/kg/day.

	Margins of Exposure[a]	
Worker Activity	**Daily[b]**	**Seasonal[c]**
Aerial Application		
Mixer/Loader	20	67
Applicator	25	97
Flagger	43	160
Ground Boom Application		
Mixer/Loader	25	110
Applicator	42	170
Mixer/Loader/Applicator	24	100
Cotton Scout		
Gloved	39	130
Not Gloved	34	110

a Margin of Exposure defined as the ratio of the NOEL to the dosage. Dosages were presented in Table 27. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number. All other values have been rounded to two significant digits.

b The NOEL = 0.06 mg/kg/day based on autonomic nervous system dysfunction in dogs.

c The NOEL = 0.06 mg/kg/day based on autonomic was based on autonomic nervous system dysfunction in dogs.

Table 38a: Margins of exposure based on estimated daily and annual exposures for pest control operators (PCOs), residents, and do-it-your-self home applicators. Exposure includes dietary contribution from residues from cotton and tomatoes. For this table, the estimated NOEL for acute exposure was 0.006 mg/kg/day. For annual exposure the NOEL was 0.06mg/kg/day.

	Margins of Exposure[a]	
Person Exposed	**Daily[b]**	**Annual[c]**
Home Application		
Residential PCO	<1	2
Infants	<1	100
Adult Males	1	97

a Margin of Exposure defined as ratio of the NOEL to the dosage. Dosages were presented in Table 28. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number, all other values have been rounded to two significant digits.
b The ENOEL = 0.006 mg/kg/day was based on autonomic nervous system dysfunction in dogs.
c The NOEL = 0.06 mg/kg/day was based on nerve damage in rats.

Table 38b: Margins of exposure based on estimated daily exposures for pest control operators (PCOs), residents, and do-it-your-self home applicators. Exposure includes dietary contribution from residues from cotton and tomatoes. For this table, the estimated NOEL for daily exposure was 0.06 mg/kg/day.

	Margins of Exposure[a]
Person Exposed	**Daily[b]**
Home Application	
Residential PCO	1
Infants	3
Adult Males	6

a Margin of Exposure defined as ratio of the NOEL to the dosage. Dosages were presented in Table 28. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number, all other values have been rounded to two significant digits.
b The NOEL = 0.06 mg/kg/day was based on autonomic nervous system dysfunction in dogs.

Table 39a: Margins of exposure based on estimated daily, seasonal, and annual exposures for loader/applicators using K-Othrine Dust (0.05% deltamethrin) on flowers and ornamentals. Exposure includes dietary contribution from residues from cotton and tomatoes. For this table, the estimated NOEL's for daily and seasonal exposures were 0.006 mg/kg/day. For annual exposure, the NOEL was 0.06 mg/kd/day.

	Margins of Exposure[a]		
Worker Activity	**Daily[b]**	**Seasonal[c]**	**Annual[d]**
Loader Applicator[a]	3	13	150

a Margin of Exposure defined as the ratio of the NOEL to the dosage. Dosages were presented in Table 29. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number, all other values have been rounded to two significant digits.
b The ENOEL = 0.006 mg/kg/day was based on autonomic nervous system dysfunction in dogs.
c The ENOEL = 0.006 mg/kg/day was based on autonomic nervous system dysfunction in dogs.
d The NOEL = 0.06 mg/kg/day was based on nerve damage in rats

Table 39b: Margins of exposure based on estimated daily and seasonal exposures for loader/applicators using K-Othrine Dust (0.05% deltamethrin) on flowers and ornamentals. Exposure includes dietary contribution from residues from cotton and tomatoes. For this table, the estimated NOEL's for daily and seasonal exposures were 0.06 mg/kg/day.

	Margins of Exposure[a]	
Worker Activity	**Daily[b]**	**Seasonal[c]**
Loader Applicator[a]	29	130

a Margin of Exposure defined as the ratio of the NOEL to the dosage. Dosages were presented in Table 29. NOELs were discussed in the Hazard Identification section. All values less than 10 have been rounded to the nearest whole number, all other values have been rounded to two significant digits.
b The NOEL = 0.06 mg/kg/day was based on autonomic nervous system dysfunction in dogs.
c The NOEL = 0.06 mg/kg/day was based on autonomic nervous system dysfunction in dogs.

a. Combined Acute Exposure

When potential acute occupational exposure to deltamethrin was combined with potential dietary exposure, all margins of exposure based on an acute ENOEL of 0.006 mg/kg/day or an acute NOEL of 0.06 mg/kg/day were less than 100 (Tables 36-39).

b. Combined Seasonal Exposure

When potential seasonal occupational exposure to deltamethrin was combined with potential dietary exposure, all margins of exposure based on a sub-chronic ENOEL of 0.006 mg/kg/day were less than 100 for Decis 0.02 EC and Decis 1.5 EC (Tables 36a and 37a), and for flower and ornamental use (Table 39a). When margins of exposure were based on a sub-chronic NOEL of 0.06 mg/kg/day, the MOEs were less than 100 for mixer/loaders involved with aerial application of Decis 0.02 EC and Decis 1.5 EC (Tables 36b and 37b) and applicators involved with the aerial application of Decis 1.5 EC (Table 37b).

c. Combined Annual Exposure

When potential annual occupational exposure to deltamethrin was combined with potential dietary exposure, all margins of exposure based on a chronic NOEL of 0.06 mg/kg/day were greater than 100 except for those involved in home uses. The MOE for pest control operators was 2. For Adult males it was 97 and for infants the calculated MOE was 100. (Table 38a).

V. RISK APPRAISAL

A. Introduction

This risk assessment was conducted to examine the potential risk associated with exposure of deltamethrin to agricultural workers, pest control operators, those who come in contact due to home use, and the general public from dietary sources (cotton and tomato products). The routes of exposure considered were dermal, inhalation, and oral. Where applicable, acute, seasonal, annual, and life-time exposure conditions were considered.

Risk assessment is the process used to evaluate the potential for human exposure to a substance and the likelihood that that potential exposure will cause adverse health effects in humans under specific conditions. Every risk assessment is affected by inherent limitations in the data base used in predicting potential risk to the human population. As a consequence of these limitations, the incorporation of certain assumptions and extrapolations is deemed necessary. The result is a level of uncertainty in the conclusions of the risk characterization. Qualitatively, risk assessments for all chemicals have similar uncertainties. The degree or magnitude of the uncertainty, however, can vary depending on the availability and quality of the data. The uncertainty is also affected by the types of exposure scenarios being assessed. Areas of uncertainty specific to this risk assessment are presented in the following discussion.

B. Hazard Identification

The primary effects associated with acute deltamethrin exposure are consistent with autonomic nervous system dysfunction. These effects included excessive salivation, vomiting, diarrhea/liquid feces, uncoordinated body movements, tremors, convulsions, and death. The effects of deltamethrin have been reported in a variety of species, e.g., excessive salivation occurred in rats, mice, and dogs; diarrhea/liquid feces have been reported in rats, dogs, and rabbits; uncoordinated movements have been reported in rats, mice, dogs, rabbits, and hens; and tremors and or convulsions have been reported in mice and dogs. The basic assumption used in this risk assessment was that the signs of autonomic nervous system dysfunction reported in various animal species can occur in humans at comparable dosages and exposure durations. This assumption is consistent with reports of autonomic nervous system dysfunction in humans following exposure to deltamethrin due to accidental or suicidal poisonings (He, et al., 1989). It is not known if the use of animal data over or under estimates the potential risk to humans from deltamethrin exposure. In the absence of applicable human data, however, this assumption and the resulting extrapolation are necessary.

The estimated critical acute NOELs used in this assessment were based on signs reported during the first week of a 13-week dog study. Since the signs of autonomic nervous system dysfunction were observed within hours of exposure, they were assumed to be the result of acute toxicity. The dog study was chosen because this animal was the most sensitive species. In the absence of adequate human data, the use of the most sensitive species is assumed to be the most health protective approach. The actual human sensitivity to deltamethrin may be greater or less than that of the reported animal subjects; however, the general default assumption used in the risk assessment process is that the least sensitive human is 10-fold more sensitive than the most sensitive animal. For example, the dog study used for the acute NOEL determination utilized polyethylene glycol (PEG) as the

solvent (carrier) for deltamethrin. A dog study conducted with technical grade deltamethrin, in the absence of any solvent, required higher doses to elicit signs of autonomic nervous system dysfunction. These studies demonstrate that the toxicity of deltamethrin can be dramatically affected by the use of a solvent such as PEG. Based on the chemical and physical properties of technical grade deltamethrin, (crystalline compound that is extremely lipophilic) this risk assessment assumes that the use of a solvent, such as PEG, likely increases the bioavailability of this highly water-insoluble compound. Furthermore, this risk assessment assumes that sufficient data does not exist to determine absorbed dosage from dog studies utilizing non-solubilized technical grade deltamethrin. Therefore, toxicology studies conducted without the aid of solvents may significantly underestimate potential dosages because of the general limitation for systemic bioavailability. In the dog study utilizing PEG as the solvent for deltamethrin, signs of autonomic nervous system dysfunction were reported at the lowest dose tested. The primary specific signs reported in this study included liquid feces, vomiting, and tremors and/or uncoordination. During the first week of the study, a statistically significant increase in liquid feces was reported at all treatment levels (0.1, 1.0, 2.5, and 10 mg/kg./day). The increase was apparent in both the incidence and the percent of animals involved. Since liquid feces was assumed to be indicative of autonomic nervous system dysfunction, it appeared that the LOEL was the lowest dose tested (0.1 mg/kg/day). However, in the process of DPR internal review of the risk assessment, a consensus on the biological relevance of the effects at 0.1 mg/kg/day could not be established. Consequently, margins of exposure were calculated using 0.1 mg/kg/day as both a NOEL and a LOEL, with a resultant estimated NOEL (i.e., ENOEL) of 0.01 mg/kg/day. The ENOEL was calculated by using the default approach of dividing the LOEL by an uncertainty factor of 10.). This adjustment may over or underestimate the actual NOEL. Since oral absorption has been estimated to be approximately 60% (actual mean value was 58.4%), the acute NOEL of 0.1 mg/kg/day was adjusted to 0.06 mg/kg/day, and the acute ENOEL 0.01 mg/kg/day was adjusted to 0.006 mg/kg/day. Both values were used in this document for calculating margins of exposure (MOE's) for potential acute exposure to deltamethrin.

The sub-chronic NOEL was established from the same 13-week dog study as used for the acute NOEL (Chesterman, 1977). The primary specific signs reported throughout the 13 week of the study included liquid feces, vomiting, and tremors and/or uncoordination. Increases in liquid feces and vomiting were reported at doses of 0.1, 1.0, 2.5, and 10 mg/kg./day. For liquid feces a positive trend was reported at all doses with statistical significance observed at 10 mg/kg/day. For vomiting, a positive trend was reported at all doses with statistical significance observed at 1, 2.5, and 10 mg/kg/day. In addition to the an increase in reported incidences, the number of animals having vomiting episodes increased at all doses. Since liquid feces and vomiting were assumed to be indicative of autonomic nervous system dysfunction, it appeared that the LOEL was the lowest dose tested (0.1 mg/kg/day). However, as previously discussed, in the process of DPR internal review of the risk assessment, a consensus on the biological relevance of the effects at 0.1 mg/kg/day could not be established. Consequently, margins of exposure were calculated using 0.1 mg/kg/day as both a NOEL and a LOEL, with resultant estimated NOEL (i.e., ENOEL) of 0.01 mg/kg/day. The ENOEL was calculated by using the default approach of dividing the LOEL by an uncertainty factor of 10. This adjustment may over or underestimate the actual NOEL. Since oral absorption has been estimated to be 58%, the acute NOEL of 0.1 mg/kg/day was adjusted to 0.06 mg/kg/day, and the acute ENOEL of 0.01 mg/kg/day was adjusted to 0.006 mg/kg/day. Both values were used in this document for calculating margins of exposure (MOE's) for potential seasonal exposure to deltamethrin.

The primary effect associated with chronic deltamethrin exposure was nerve degeneration. As reported by Godenthal (1980), a statistically significant increase, over controls, in nerve degeneration was reported in rats after 18 months exposure to deltamethrin. After 24 months, however, a significant increase over control levels was not observed. After extensive review of the data, this risk assessment concluded that an elevated background level at 24 months prevented detection of induced lesions. The effects reported at 18 months were, therefore, assumed to be related to deltamethrin exposure. It is noted that the estimated NOELs for acute and chronic exposures to deltamethrin were lower than calculated NOEL for chronic exposure. This is primarily due to the fact that the effects are observed at different sites and in different species. Furthermore, estimated NOELs for acute and chronic involved an additional factor of 10 because they were based on LOELs. This additional uncertainty factor is considered helth protective and is a product of dose selection.

Since lifetime exposure estimates were less than potential annual exposures, and the same NOEL (0.06 mg/kg/day) was assumed for the two time-points, lifetime MOEs would by default be higher than annual MOEs (i.e., health protective measures used to ensure the health and safety from annual exposure would be protective under a lifetime exposure scenario). MOE calculations were not, therefore, considered necessary for lifetime exposure.

It is important to note that genotoxic potential has been identified in the open literature for this compound. While it is believed that genotoxicity can lead to such adverse effects as tumor formation, no evidence of oncogenicity has been associated with deltamethrin exposure. At the current time, the potential consequence of the reported genotoxicity is unknown.

In reviewing the developmental studies for deltamethrin, adults appear to be more sensitive than pups. This raises the question of increased sensitivity for children exposed to deltamethrin when compared to adults. On the basis of the Abd El-Khalik, et al., 1993 study, the LOEL for fetuses would be 1 mg/kg/day. Since the NOELs used for acute exposure for adults and children were at least 10 fold less than 1 mg/kg/day, the estimated MOEs are assumed to be health protective for both adults and children.

C. Exposure assessment

1. Occupational/Residential exposure

For occupational and residential exposure, a number of assumptions and extrapolations were necessary. In some cases, actual exposure data from deltamethrin use was not available. The exposure estimation for cotton scouts, applicators of dust formulation to ornamentals, and adults and children playing in treated homes were derived mainly from surrogate data (see Thongsinthusak , 1996 for complete discussion). In using the surrogate data, it was assumed that deltamethrin exposure would be proportional to surrogate pesticides based upon application rates, monitoring period, efficiency of residue transfer and vapor pressure. While the intent in this risk assessment has been to protect public health, it is not known for certain if the extrapolations made in the occupational/residential exposure assessment resulted in over or under estimates of potential exposures. For acute exposure, mean and upper-bound estimates were made for

all exposure scenarios except for those involved with the treatment of flowers and ornamentals. For risk characterization, however, only MOEs for acute exposure, based on upper-bound estimates, were considered appropriate estimates of maximum potential exposures. The one exception was the treatment of flowers and ornamentals. The average value was used as no estimate of variability was presented. The value is likely an underestimate of potential acute exposure. For chronic exposure scenarios, the average estimated exposure values were used. This was based on the assumption that an individual is unlikely to be exposed to the maximum potential exposure each day for an extended period of time.

It should be noted that deltamethrin exposure estimates were based solely on potential deltamethrin exposures and did not include the concurrent use of other pesticides.

2. Dietary exposure

In addition to the occupational and residential exposures, potential dietary exposure to deltamethrin was evaluated. Dietary exposure was based on a national consumption survey conducted by the U.S. Department of Agriculture. The dietary exposure data used to estimate the potential combined (occupational plus dietary) exposure for workers was based on those survey respondents who were reported to be of Hispanic origin ages 16 and older. This population sub-group was chosen because it was the most highly exposed group of potential workers and had a sufficient number of respondents. Furthermore, inherent in the use of the national survey is the assumption that the exposure is representative of California residents.

In the dietary assessment, since neither table top nor market basket data were available, residue estimates were based on field trials and tolerance values. These field studies were conducted to establish tolerances for specific raw agricultural commodities and, therefore, were designed to obtain the highest potential residue under the conditions indicated on the product label. When field study data were inadequate or non-existent, residue values were assumed at tolerance levels. The resulting estimate of exposure was likely an overestimate of actual exposure from dietary sources. Furthermore, it was assumed that residue levels were stable; i.e., residue values do not change over time, the concentration does not decrease when the commodity is washed, the residue concentration is not reduced by processing of the commodity, and all consumed commodities contain the highest reported residue.

D. Risk characterization

In order to characterize the potential risks associated with exposure to deltamethrin, margins of exposure (MOE's) were calculated. An MOE is defined as the ratio of the NOEL to the absorbed dosage.

When the NOEL for an adverse effect is derived from a laboratory animal study, a calculated MOE of 100 is generally considered adequate for protection against potential toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for intraspecies variability, as well as an uncertainty factor of 10 for inter-species variability. This latter uncertainty factor assumes that the least sensitive human is 10 times more sensitive to the effects of a toxin than are laboratory animals (Davidson et al., 1986;

Dourson and Stara, 1983,1985; USEPA, 1986b). If the critical NOEL is from a human study, a benchmark of 10 is used, incorporating a single uncertainty factor which assumes there is only a 10-fold difference between the least sensitive and most susceptible human.

VI. TOLERANCE ASSESSMENT

A. BACKGROUND

A tolerance is the maximum, legal amount of a pesticide residue that is allowed on a raw or processed agricultural commodity, or in an animal tissue used for human consumption. The U.S. EPA tolerance program was developed as an enforcement mechanism to identify illegal residue concentrations resulting from potential non-compliance with the product label requirements (e.g., improper application rates or methods, inadequate pre-harvest intervals, direct or indirect application to non-approved commodities). Tolerances are enforced by the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state enforcement agencies (e.g., Pesticide Enforcement Branch of DPR).

Current pesticide tolerances are generally set at levels that are not expected to produce deleterious health effects in humans from chronic dietary exposure. The data requirements for establishing a specific tolerance include: 1) toxicology data for the parent compound, major metabolites, degradation products and impurities, 2) product chemistry, 3) analytical methods(s) that are readily available, accurate and precise, 4) measured residues in crops used for animal feeds, 5) measured residues in animal tissues (e.g., meat, milk, and eggs) from direct or indirect (feed) applications, 6) measured residue levels from field studies. The minimum requirements for the field study include: 1) an application rate at or above the highest rate on the product label, 2) the greatest number of allowable repeat applications, 3) the shortest pre harvest interval listed on the product label. Generally, the registrant of the pesticide requests a commodity-specific tolerance, which is equal to the highest measured residue, or some multiple of that value, from the field trial using the specific pesticide.

Assembly Bill 2161 (Bronzan and Jones, 1989) requires the DPR to "conduct an assessment of dietary risks associated with the consumption of produce and processed food treated with pesticides." In the situation where "any pesticide use represents a dietary risk that is deleterious to the health of humans, the DPR shall prohibit or take action to modify that use or modify the tolerance". As part of the tolerance assessment, a theoretical dietary exposure for a specific commodity and specific population sub-groups can be calculated from the product of the tolerance and the daily consumption rate.

B. ACUTE EXPOSURE

An acute exposure assessment using the residue level equal to the tolerance is conducted for each individual label-approved commodity. The TAS Exposure-4™ software program and the USDA consumption data base are used in the assessment. The acute tolerance assessment does not routinely address multiple commodities at tolerance levels since the probability of consuming multiple commodities at these levels decreases as the number of commodities included in the assessment increases.

A dietary exposure assessment for deltamethrin was conducted using tolerance levels as assumed residue values. Table 40 shows the calculated margin of exposure (MOE) range for each label approved commodity.

Table 40: Deltamethrin tolerances and corresponding margins of exposure (MOEs) following acute dietary exposure. (NOTE: MOEs are based on residues at tolerance levels)

Commodity	Tolerance (ppm)	Margins of Exposure	
		low	high
Cottonseed	0.04	58	195
Tomatoes	0.20	1	4

On the basis of acute exposure deltamethrin from tomatoes, all population sub-groups had calculated margins of exposure of less than 100 when residue levels were based on tolerance. When tolerance levels of deltamethrin were assumed for exposure from use on cottonseed, margins of exposure less than 100 for non-Hispanic blacks (88), nursing infants (91), non-nursing infants (93), all infants (89), children ages 1-6 (58), and children ages 7-12 (68). All other population sub-groups had MOE's greater than 100.

C. CHRONIC EXPOSURE

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations or commodities has not been conducted because it is highly improbable that an individual would chronically consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from CDFA pesticide monitoring programs that indicate that less than one percent of all sampled commodities have residue levels at or above the established tolerance (CDFA, 1990).

VII. CONCLUSIONS

In order to characterize the potential risks associated with exposure to deltamethrin, margins of exposure (MOE's) were calculated for each of the exposure scenarios previously described. An MOE is defined as the ratio of the No-Observed-Effect-Level (NOEL) to the absorbed dosage. When the NOEL for an adverse effect is derived from a laboratory animal study, a calculated MOE of 100 is generally considered adequate for protection against potential toxicity of a chemical. This benchmark of 100 includes an uncertainty factor of 10 for intraspecies variability, as well as an uncertainty factor of 10 for inter-species variability. This latter uncertainty factor assumes that the least sensitive human is 10 times more sensitive to the effects of a toxin than the most sensitive laboratory animals (Davidson et al., 1986; Dourson and Stara, 1983,1985; USEPA, 1986b). If the critical NOEL is from a human study, a benchmark of 10 is used, incorporating a single uncertainty factor which assumes there is only a 10-fold difference between the least sensitive and most susceptible human. Margins of exposure for deltamethrin exposure were all based on NOEL's from laboratory animal data.

The following is a summary of the MOEs for the various exposure scenarios:

Acute Occupational Exposure Excluding Dietary Contribution: For Decis, 0.2 EC, using an ENOEL of 0.006 mg/kg/day, the estimated acute (daily) margin of exposure for flaggers was 100 (Table 30a). For all other worker activities, MOE's were less than 100. For mixer/loaders and applicators, involved with the aerial application of the product, estimated MOE's are 5 and 8, respectively. With ground boom application, the MOE's for mixer/loaders, applicators, and mixer/loader/applicators were 8, 67, and 7, respectively. MOE's for cotton scouts were 35 and 21 for gloved and not gloved workers, respectively. When the MOE's were based on the average acute exposure rather than the upper-bound estimate, the values ranged from 13 to 200. The MOE's were greater than 100 for flaggers and applicators involved with ground boom application. The MOE's were less than 100 for all other activities. When the MOE's were based on a NOEL of 0.06 mg/kg/day, the respective values were elevated 10-fold.

For Decis 1.5 EC, using an ENOEL of 0.006 mg/kg/day, all estimated MOE's for acute exposure to deltamethrin were less than 100. The MOE's range from 4 (mixer/loaders involved with aerial application) to 67 (flaggers). When the MOE's were based on the average acute exposure rather than the upper-bound estimate, the values ranged from 8 to 120. When the MOE's are based a NOEL of 0.06 mg/kg/day, the respective values were elevated 10-fold.

For the residential use of deltamethrin products, using an ENOEL of 0.006 mg/kg/day, calculated MOE's were less than 100 for PCO's, infants, and adult males (<1, <1, and 1, respectively). When the MOE's were based on the average acute exposure rather than the upper-bound estimate, the values remained the same. When the MOE's were based a NOEL of 0.06 mg/kg/day, respective values were elevated 10-fold.

For acute exposure associated with the use of K-Othrine Dust on flowers and ornamentals, using an ENOEL of 0.006 mg/kg/day, the calculated MOE was 8 for loader/applicators. When the MOE's were based a NOEL of 0.06 mg/kg/day, The MOE was increased to 8.

Acute Dietary Exposure: Using an ENOEL of 0.006 mg/kg/day, margins of exposure were less than 100 for all population sub-groups examined. Using a NOEL of 0.06 mg/kg/day the MOE's increased by 10-fold, however, all estimated MOE's were still less than 100.

Combined Acute Occupational and Dietary Exposure: When potential acute occupational exposure to deltamethrin was combined with potential dietary exposure, all margins of exposure based on an acute ENOEL of 0.006 mg/kg/day or an acute NOEL of 0.06 mg/kg/day were less than 100.

Seasonal Occupational Exposure Excluding Dietary Contribution: For seasonal exposure to deltamethrin from the use of Decis 0.2 EC and Decis 1.5 EC, and using an ENOEL of 0.006 mg/kg/day, the calculated MOE's were greater than 100 for flaggers and applicators involved with ground boom application. The MOE's for all other worker activities are less than 100. When the MOE's were based a NOEL of 0.06 mg/kg/day, values were elevated 10-fold.

Seasonal exposure does not apply to residential PCO or home applications; therefore, margins of exposure were not calculated for these activities.

For seasonal exposure associated with the use of K-Othrine Dust, the calculated margins of exposure were greater than 100 for both NOEL's.

Combined Seasonal Occupational and Dietary Exposure: When potential seasonal occupational exposure to deltamethrin was combined with potential dietary exposure, all margins of exposure based on a sub-chronic ENOEL of 0.006 mg/kg/day were less than 100 for Decis 0.02 EC and Decis 1.5, and for flower and ornamental use. When margins of exposure were based on a sub-chronic NOEL of 0.06 mg/kg/day, the MOEs were less than 100 for mixer/loaders involved with aerial application of Decis 0.02 EC and Decis 1.5 EC and applicators involved with the aerial application of Decis 1.5 EC.

Annual Occupational Exposure Excluding Dietary Contribution: On the basis of annual exposure estimates, calculated margins of exposure for all agricultural and residential activities were greater than 100, except for residential PCO's. Their MOE was 2.

Annual Dietary Exposure: The lowest annual dietary MOE's were 64 and 80 for children 1-6 and children 7-12, respectively. All other population sub-groups had MOE's greater than 100.

Combined Annual Occupational and Dietary Exposure: When potential annual occupational exposure to deltamethrin was combined with potential annual dietary exposure, all margins of exposure based on a chronic NOEL of 0.06 mg/kg/day were greater than 100 except for those involved in home uses. The MOE for pest control operators was 2. For adult males the MOE was 97 and for infants the calculated MOE was 100.

Life-time exposure; On the basis of the toxicology data base evaluated, the NOEL for life-time exposure to deltamethrin was the same as that used for annual exposure, i.e., 0.06 mg/kg/day. The average daily dosage for life-time exposure was estimated by taking the average daily dosage for annual exposure and amortizing over a lifetime. This assumes 40 years of exposure over a lifetime of 70 years. Since the amortization reduces the potential exposure by approximately 57% (40/70), MOE estimations were not considered necessary

for life-time deltamethrin exposures (i.e., risk estimates considered acceptable for annual exposure would by default be acceptable for life-time exposures).

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