

Evidence on the Developmental and Reproductive Toxicity of Deltamethrin

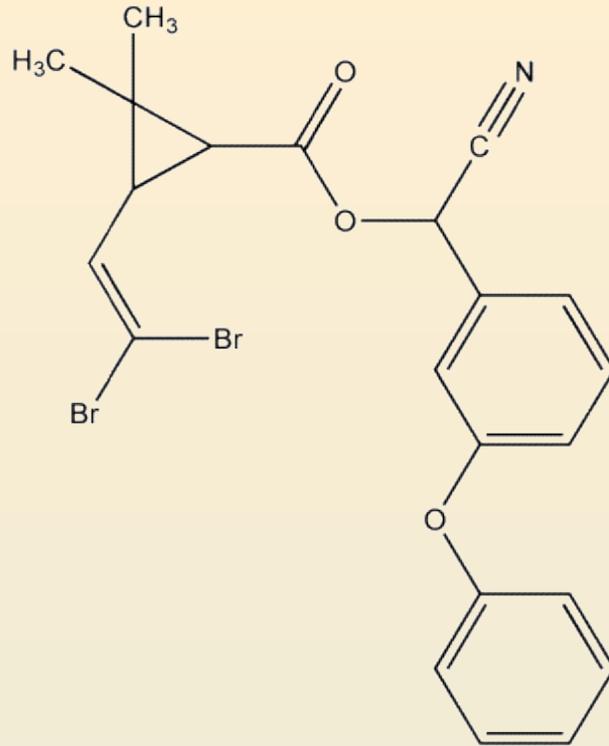
March 18, 2013

Developmental and Reproductive Toxicant
(DART) Identification Committee Meeting



Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency





Deltamethrin CAS registry number 52918-63-5

Synthetic pyrethroid insecticide

Formulations:

Emulsifiable concentrates, wettable powders, flowable formulations, granules

Use and Environmental Fate

- Largely used in structural pest control
- To control insect pests of field crops, potted plants, & ornamentals
- Primary metabolite of another pyrethroid, tralomethrin
- Environmental fate studies indicate that tralomethrin → deltamethrin

Deltamethrin Pharmacokinetics and Metabolism

- Absorption in the gastrointestinal tract and respiratory tract is > through the skin
- Oral absorption in humans - at least 50%
- Distributed to nerve tissues and all regions of the brain and fatty tissues
- Half-life in rat
 - blood 5.5 hours
 - brain 1-2 days
 - body fat 5 days
- Metabolized through ester hydrolysis, oxidation and conjugation.
- Only the parent compound is toxicologically significant

Non-DART Toxicity of Deltamethrin

- **Acute**

- Human: Paresthesia - acute dermal exposure in occupational studies
41 incidents of illness reports
- Animal: LD₅₀ values for rats: from 30 mg/kg (oil vehicle) to greater than 5000 mg/kg (aqueous vehicle)

- **Chronic**

- Human: No data for chronic health effects
- Animal: Dose-related ↑ in degeneration of sciatic, tibial, and plantar nerves

- **Cancer**

- Human: The U.S. EPA does not consider deltamethrin to be a mutagen or carcinogen
- Animal: No increase in tumor incidence in mice or rats in standard feeding studies

Male Reproductive Toxicity

- No studies examining male reproductive effects in humans
- Two animal studies (rats exposed to deltamethrin in diet) submitted to regulatory agencies
 - 3-gen reproduction study 0, 2, 20, 50 ppm (Wrenn, 1980)
No evidence of male reproductive toxicity
 - 2 gen reproduction study 0, 5, 20, 80 or 320 ppm (Hoberman, 1992)
 - ↓ absolute weights of male reproductive organs at 320 ppm (epididymis, testes)

Male Reproductive Toxicity in Animals

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|--|--|--|
| Salem et al., 1988 (Decis®) | Rabbits 5 groups (3 animals/group) 2 groups - deltamethrin at 1/10 th LD ₅₀ and 1/100 th LD ₅₀ orally via gelatin capsule. (LD ₅₀ not stated in study) 6 weeks - pretreatment 6 weeks - exposure 6 weeks - recovery period Semen collected (method not stated) twice weekly from all the animals for 18 weeks. | Deltamethrin alone: ↓ Body weight, libido, ejaculate volume, sperm concentration ↑ % of dead spermatozoa Similar effects were seen for dimethoate |
| Abd el-Aziz et al., 1994 (Butox®) | Rat deltamethrin for 65 days (1, 2 mg/kg-day). (Oral) Mated with non-treated females | ↓ Testosterone levels ↓ Weight of male reproductive organs and sperm motility ↑ % of dead spermatozoa (↓ conception in non-treated females) |
| El-Gohary et al., 1999 (Deltamethrin technical) | Rat 1 mg/kg-day (Intraperitoneal) deltamethrin for 21 days | Vacuoles in Sertoli cells Apoptosis in testes |

Male Reproductive Toxicity in Animals (continued)

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|--|---|--|
| Andrade et al., 2000 (Deltamethrin technical) | Rats (females) were treated daily by oral gavage with deltamethrin. 0, 1.0, 2.0, or 4.0 mg/kg from day 1 of pregnancy to day 21 of lactation. Male offspring examined. | <p>↓ absolute testis & epididymis weights</p> <p>Subtle changes in reproductive behavior and physiology of male offspring</p> <p>No effect on sexual development landmarks or daily sperm production</p> |
| Shukla and Taneja, 2000 (Decis®) | Mouse Dominant-lethal (Oral) Control 0 (corn oil), 0.36, 0.72 and 1.08 mg/kg) deltamethrin dissolved in corn oil for 2 wks. Control and treated males, mated with untreated females, every week for 6 weeks. All mated females sacrificed on the 13th day of separation. | <p>↑ Post-implantation losses at medium and high doses</p> <p>Slight ↑ in dominant –lethal mutation rate in early weeks but ↓ in later weeks</p> |

Male Reproductive Toxicity in Animals (continued)

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|---|--|---|
| Issam et al., 2009 (Deltamethrin technical) | Rat (sub-cutaneous) 30 days: 0.003 mg/kg for 30 days 45 days: 0.003 mg/kg for 30 days & 0.03 mg/kg for 15 days 60 days: 0.003 mg/kg for 30 days & 0.03 mg/kg for 15 days & 0.3 mg/kg for 15 days Control: 30, 45, 60 days equivalent volume of ethanol | Arrest in spermatogenesis, Disharmony in sex hormones |
| Ben Abdallah et al., 2009 (Deltamethrin SEPCM) | Mouse: oral by gavage for 21 days dimethoate (5 mg/kg-day) and dimethoate + deltamethrin mixture (5 mg/kg-day) | Deltamethrin and mixture ↓ Motility & viability of sperm ↑ % abnormal sperm |
| Ben Abdallah et al., 2010 | Rat spermatozoa Incubated with 0, 10, 50, 100 and 200 µM for 3 hours at 37 °C <i>in vitro</i> | ↓ Motility & viability of sperm ↑ abnormal sperm morphology |

Male Reproductive Toxicity in Animals (continued)

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|----------------------------------|---|---|
| Oda and El Maddawy 2011 (Butox®) | Rats (oral gavage) 0.6 mg/kg alone or 0.6 mg/kg-day and 1.2 mg/kg twice per week s/c Viteselen (Vit E & Selenium mixture) | <p>↓ Relative weight of testis, epididymis, and accessory sex organs; ↓ epididymal sperm count, motility, and viability, and ↓ serum levels of testosterone</p> <p>Severe degenerative histopathological changes in the testis, prostate, epididymis and seminal vesicles</p> <p>Effects attenuated by Vit E & Selenium mixture</p> |
| Ben Slima et al., 2012 | Dimethoate, deltamethrin (5mg/kg-day) and combination to pregnant mice on GD 3 – 21(oral gavage) | <p>Deltamethrin alone: ↓ Testis weights, epididymal sperm count, motility, and viability ↑ Abnormal morphology of epididymal sperm vacuolization in Sertoli cells, degeneration and loss of some cells</p> |

Female Reproductive Toxicity

- No studies examining female reproductive effects in humans
- No studies evaluating effects of deltamethrin on the estrous cycle
- Two animal studies (rats exposed to deltamethrin in diet) submitted to regulatory agencies
 - 3-gen reproduction study 0, 2, 20, 50 ppm (Wrenn, 1980)
No evidence of female reproductive toxicity
 - 2 gen reproduction study 0, 5, 20, 80 or 320 ppm (Hoberman, 1992)
↓ absolute weights of non-gravid uterus at 320 ppm (P1 and F1 animals)

Female Reproductive Toxicity in Animals

Rats:

Lemos et al., (2011) Effect of deltamethrin formulation (Decis® 25CE) at 1.0, 2.0 or **4.0** mg/kg on the response of blastocyst-endometrium interactions

- Implantation process affected
Histopathological alterations in the implantation sites
↓ in the number of sites

Lemos et al., (2012) At sub-lethal doses deltamethrin formulation (Decis® 25CE) at 1.0, 2.0 or **4.0** mg/kg with no clinical signs, in dams

- Histopathology in dams - inflammatory reaction in kidneys, liver and lungs
- ↓ number of pups and ↓ fertility
- No malformations

Developmental Effects

- Neurodevelopment
- Other Developmental Effects

TIMING AND SEQUENCE OF BRAIN DEVELOPMENT ACROSS MAMMALS

- Timing and sequence of early events in brain development are remarkably conserved across mammals; but timing of birth is not
- For general, limbic and cortical events in the brain, PND 1–10 in the rat pup corresponds to the *in utero* period in humans
- For some cortical events in the brain, PND 10–13 in the rat pup corresponds to the third trimester in humans
- Lactational exposure in rodents may also be relevant for premature human infants

Translating Brain Development Across Species (Days)

| rat | mouse | limbic | general | cortex |
|-------------------------|-------------------------|--------|---------|--------|
| 19 | 16.4 | 69 | 75 | 91 |
| 20.5 | 17.6 | 79 | 86 | 104 |
| Birth (21.5) | Birth (18.5) | 84 | 91 | 110 |
| PND 2 | PND 1.5 | 94 | 101 | 123 |
| PND 4 | PND 3.1 | 103 | 112 | 136 |
| PND 10 | PND 8.3 | 127.7 | 138 | 175.3 |
| PND 13 | PND 10.8 | 141.4 | 152.7 | 194.2 |

Gestational length in humans = 270 days

Days *in utero* in blue

Postnatal days (PND) in black

Studies examining neurodevelopment

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|---|---|--|
| <p>Andrade et al., 2000 (Deltamethrin technical)</p> | <p>Rats/Prenatal and Postnatal From day 1 of pregnancy to day 21 of lactation 0, 1.0, 2.0, or 4.0 mg/kg Oral</p> <p>Male offspring examined</p> | <p>For male offspring: No changes in mount, intromission, ejaculatory latency, number of intromissions up to ejaculation or ejaculatory frequency</p> <p>(A trend toward a ↓ in the number of animals with ejaculate)</p> |
| <p>Aziz et al., 2001 (Decis®)</p> | <p>Rat/Prenatal Neurodevelopmental GD 14-20 Oral 1 mg/kg-day</p> | <p>Alterations in biochemical & behavioral parameters</p> <p>↑ Hippocampal cholinesterase activity</p> <p>Impairment in cholinergic receptors in hippocampus</p> <p>↓ in learning and memory performance observed at both 6 and 12 weeks age</p> |

Studies examining neurodevelopment

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|---|---|---|
| Lazarini et al., 2001 (Deltamethrin technical) | Rat/Prenatal Neurodevelopmental Oral, GD 6-15 0.08 mg/kg-day At PND 60: an anxiogenic swimming procedure followed by open-field behavior testing | Emotionality as demonstrated by: <ul style="list-style-type: none"> - decreased locomotion frequency - increased immobility in open field - reduced latency to float in response to swimming test ↑ in emotional state |
| Johri et al., 2006 (Decis®) | Rat/Prenatal (GD 5-21) Oral 0, 0.25, 0.5 , 1.0 mg/kg | ↑ expression Cytochrome P450 – CYP alterations ↓ spontaneous locomotor activity Persistent effects |

Studies examining neurodevelopment

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|--|---|--|
| Gilmore et al., 2006 (Deltamethrin technical) | Rat/Developmental Neurobehavioral Test (DNT) GD 6-PND 21 In diet 0, 20, 80, 200 ppm | ↓ Post-natal body weight ↓ fixed female brain weight ↑ resistance at removal from cage with vocalization at 200 ppm |

Studies examining other developmental effects

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|--|--|--|
| Kavlock et al., 1979 (Deltamethrin technical) | Rat - 0, 1.25, 2.5, 5 mg/kg-day Mouse - 0, 3, 6, 12 mg/kg-day Prenatal – oral gavage | No adverse effects |
| Schardein, 1990a (Deltamethrin technical) | Rat - 0, 1, 3.3, 7, 11 mg/kg-day GD 6-15 Prenatal – oral gavage | No adverse effects |
| Schardein, 1990b (Deltamethrin technical) | NZW Rabbit - 0, 10, 25, 100 mg/kg-day GD 6-28 Prenatal – oral gavage | Retardation of bone ossification in offspring and other variations |

Studies examining other developmental effects

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|---|---|---|
| Abdel-Khalik et al., 1993 (Butox®) | Rat -1, 2.5 or 5 mg/kg GD 6 -15 Prenatal – oral gavage | Growth retardation Hypoplasia of the lungs Dilatation of the renal pelvis ↑ placental weight |
| Andrade et al., 2000 (Deltamethrin technical) | Rat - 0, 1.0, 2.0, 4.0 mg/kg from day 1 of pregnancy to day 21 of lactation - oral gavage Prenatal and Postnatal exposure | No effect on sexual development landmarks or daily sperm production ↓ absolute testis & epididymis weights in male offspring |

Studies examining other developmental effects

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|---|--|--|
| Richard, 2001 (Deltamethrin technical) | Rabbit - 0, 3, 10, 32 mg/kg-day GD 6-28 Prenatal – oral gavage | ↓ Body weight and food consumption in does (pregnant females) No adverse developmental effects |
| Kandil, 2006 | Rat- GD 8-16 and to another set of animals from GD 1-20 0, 5.35, 13.38 , 26.75 mg/kg-day Prenatal – oral gavage No statistical analyses presented | ↑ % of resorbed fetuses malformed fetuses (paralysis of forelimbs) ↓ in fetal body weight and incomplete ossification ↓ uterine weight ↓ maternal body weight gain and signs of lethargy |

Studies examining other developmental effects

| REFERENCE | SPECIES/STUDY DESIGN | EFFECTS |
|---|---|--|
| Gilmore et al., 2006 (Deltamethrin technical) | Rat/Developmental Neurobehavioral Test (DNT) GD 6-PND 21 In diet 0, 20, 80, 200 ppm Prenatal and Postnatal exposure | Delay in mean age of attainment of preputial separation of male pups |
| Lazarini et al., 2007 (Deltamethrin technical) | Rat/Developmental Oral, GD 6-15 0.08 mg/kg-day | Delay in day of eyes opening for male Early vaginal channel opening in female offspring |

Summary of Developmental Effects (Neurodevelopment)

- ↓ fixed female brain weight in F1 rats at termination and increased resistance at removal with vocalization in males at the high dose group of 200 ppm
(Gilmore et al., 2006)
- No adverse effects for auditory startle habituation, learning and memory (passive avoidance after weaning and water maze task)
(Gilmore et al., 2006)
- After maternal exposure during the organogenesis period:
 - ↓ locomotion frequency with ↑ immobility in male rats interpreted as high levels of emotionality
(Lazarini et al., 2001)

Summary of Developmental Effects (Other)

- Effects on developmental landmarks – prenatal and a combination of prenatal and postnatal exposure (Gilmore et al., 2006; Lazarini et al., 2007)
- Other developmental effects – prenatal exposure (Abdel-Khalik et al., 1993; Kandil, 2006)
- Some of the studies reported no adverse developmental effects (Kavlock et al., 1979; Wrenn, 1990; Schardein 1990 a,b; Richard, 2001)