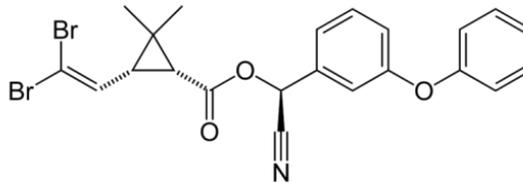




# Bayer CropScience



## Deltamethrin: Consideration for Listing as a Reproductive Toxicant (Prop 65)

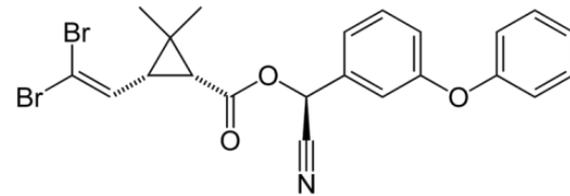
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# Deltamethrin: Toxicology Profile

- Pyrethroid Insecticide
  - Registrations since 1974



- Mode of Action (Insects & Vertebrates)
  - Affect Na<sup>+</sup> channels in nerve membrane
  - Acute neurotoxicity (acute and chronic exposure)

# Guideline Studies: Pesticides

- **GLP** – Rigorous documentation and oversight (QAU)
  - Sufficient to re-construct the study and know the information in the report accurately reflects the data
- **Study Design:** In accordance with guideline requirements
  - Suited for hazard identification & risk assessment
  - >99% purity with verified doses
  - 3 dose levels (minimum): NOEL, mid- and high-dose (MTD)
  - Appropriate
    - Controls (concurrent & historical for reference)
    - Sample size
    - Route & duration of exposure
    - Selection of endpoints

# Guideline Studies: Deltamethrin

- **Developmental and Reproductive Toxicity**
  - Two- and three-generation reproduction (rat)
  - Developmental Toxicity (rat & rabbit): implantation → gestation
  - Developmental Neurotoxicity (rat): GD6 – LD21
- **Adult** (rat, mouse & dog): 28- and/or 90-day and 1-year
  - Reproductive organ wts & histopathology
  - These tissues were not affected

# Two-generation reproduction study

Hoberman & Christian (Argus Labs, 1992)

- 12 weeks pre-mating (P-gen) → LD21 of F1 (F2 pups to weaning)
- 30 rats/sex/dietary level: 0, 5, 20, 80 & 320 ppm (HDT ~26 mg/kg/day)
- P-generation (high-dose; excessive toxicity/neurotoxic signs)
  - Mortality & neurotoxic signs during lactation (↑ dosage)
  - ↓tissue wts in F only (with ↓bwt); **No histopathological effects**
  - **No effect on reproduction or litter parameters**
- F1-generation (high-dose; excessive toxicity/neurotoxic signs)
  - Acute toxicity: post-weaning / high dose + ↑sensitivity juvenile rat
    - ↑mortality; neurotoxic signs
  - ↓tissue wts in M and F (with ↓bwt) – **No histopathological effects**
  - **No effect on reproduction or litter parameters**
- F2-generation: ↓bwt with no effect on viability

# 2-gen study: Findings cited in the HID

## Female and Male Reproductive Toxicity

- **Uterine and Pituitary Weights in Females**
  - ↓absolute wt of non-gravid uterus & pituitary
- **Testicular effects and reproductive behavior in Males**
  - ↓absolute wt of epididymis & testis (F1) & relative to brain wt
- Findings associated with ↑mortality & ↓bwt (↑ relative wt); with no evidence of histopathology
- **Conclude:** General toxicity at a lethal dose level (EPA & other Agency reviews) and not reproductive toxicity

# DPR evaluation: Two-generation reproduction study

	NOAEL	Findings at LOAEL
<b>Parental</b>	80 ppm	Clinical signs, increased mortality, lower bwt, & ↓ food consumption at 320 ppm (HDT)
<b>Reproductive</b>	320 ppm	No treatment-related effects on reproductive parameters at the HDT
<b>Developmental</b>	80 ppm	Lower pup bwt (F1 & F2) and ↑ mortality (F1) during lactation period at 320 ppm

- *California Dept. of Pesticide Regulation (2000): Review of Hoberman, 1992; CDPR concluded this study has no major deficiencies;*
- *Consistent with determinations by US EPA, EU and WHO*

# Female Reproductive Toxicity

- **Implantation and Fertility (Lemos 2011 & 2012)**
  - ↓# implantation sites w/ histopathology in rat (2011); ↓# pups and ↓fertility in rat (2012)
    - **Decis 25CE**: Oral 1, 2 & 4 mg/kg x GD 0-6 or GD 0-LD1
    - 97.5% formulating agents (aromatic hydrocarbons ); 2.5% DLM
    - **Controls received water** (vs. formulating agents)
    - Reproductive toxicity only at HDT, with ↑fetal death
- **Conclude**: Findings with formulation (2.5% DLM) at dose lethal to the fetus, without appropriate control for reference; No effect in guideline DART studies at much higher doses

# Male Reproductive Toxicity

- **Decrease in live sperm & plasma testosterone**
  - ↓live sperm, conception rate & T; Degenerative pathology in testis & accessory glands in rat (Abd el-Aziz, 1994)
    - Oral 1 or 2 mg/kg **Decis 5F** x 65 d to adult (n=5 for histopath)
    - 95% formulating agents (aromatic hydrocarbons) + 5% DLM
    - **Controls received water** (vs. formulating agents)
  - Arrest in spermatogenesis and ↓FSH in rat (Issam, 2009)
    - **Subcutaneous** dose 0.003 mg/kg DLM x 45-60 days (n=6)
    - **Unknown TM purity, one dose** & relevance via s.c. route;
- Flawed studies; Inconsistent with no histopathology in 2-generation and adult studies (90-day & 1-year exposure)

# Male Reproductive Toxicity

- **Testicular effects and reproductive behavior**
  - Testicular apoptosis in rat (El-Gohary, 1999)
    - Intraperitoneal 1 mg/kg/day DLM (purity unknown) x 21 days
    - **Severe / arrested spermatogenesis**
    - **One dose, inappropriate route, unknown TM purity**
    - **Conclude:** Flawed study, inconsistent with repro & adult studies
  - ↓# rats with ejaculate, ↓testicular and epididymal abs wt, and ↓diameter seminiferous tubules (Andrade, 2002 )
    - Oral 1, 2 & 4 mg/kg/day DLM (98.8% purity) GD1 – LD21
    - **# w/ ejaculate (n.s. or dose-related); ↓tissue wts with ↓bwt; s. tubule diameter at HDT 5.7% less than control (historical control not shown)**
    - **No effect:** Testosterone, sperm morphology or sexual maturation
    - **“Subtle changes”; flawed statistics (litter); no historical control**
    - **Conclude:** Insufficient evidence of an effect

# Male Reproductive Toxicity

- **Sperm Motility and Abnormalities**

- ↓ Sperm count, motility & viability, with ↑% morphologically-abnormal spermatozoa in mice (Abdallah, 2010)
  - Oral 5 mg/kg DLM (**one dose, purity unknown**) x 21 days
  - No effect on testis or epididymal wts; histopathology not done
- ↓ ejaculate vol. & sperm conc. with ↑ dead sperm in rabbit (Salem, 1988)
  - Oral: 'Decis' 1/10 and 1/100 LD50) x 6 weeks
  - **Doses and test material purity undefined**
  - **Insufficient sample (n=3)** to show slight effect

- **Conclude:** Flawed studies (dose, TM purity & sample size); no reference to historical control; 2-gen study had no histopathological effect in testis or epididymis or ↓ fertility

# Developmental Toxicity

- **Developmental Neurotoxicity**

- ↓fixed brain wt in F & ↑handling resistance in M rat (Gilmore, 2006)
  - Guideline DNT: HDT 16 m/k/d (>99%) x GD6 – LD21
  - **No effect on fresh brain wt (F or M) or fixed brain wt in M**
  - No histopathology or effect on microscopic brain measures
- ↓locomotion and ↑immobility in open field in rat; Alterations in motor & dopaminergic activity in rat (Lazarini, 2001)
  - Oral 0.08 mg/kg x GD 6-15 (Unclear what material was tested)
  - **One dose level / one age: Biological variability? (no historical control)**
  - Inconsistent: Across measures & sex (other measures not affected); **Inconsistent with guideline DNT study** (no effect on motor activity at much higher doses)

- **Conclude:** No clear or credible evidence for concern

# Developmental Toxicity

- **Offspring Viability, Growth and Malformations**

- One rat and rabbit study report no adverse developmental effects (Schardein, 1990; Richard, 2001)
  - Guideline developmental toxicity studies (HDT: 11 & 32 mg/kg/day)
  - Consistent with 2-gen, 3-gen, DNT & teratology studies (mouse & rabbit; Kavlock (USEPA), 1979)
- Delay eye opening (M) & early vaginal opening rat (Lazarini, 2007)
  - Oral: 0.08 mg/kg/day x GD 6-15; **Unknown TM purity**
  - **One dose** / small differences from control (**biological variability**);
  - **Inconsistent: VO not affected in guideline DNT study** (16 mg/kg/day x GD6 - PND21); **eye opening not affected to 5 mg/kg/day x GD 7-21** (Kavlock, 1979)

# Developmental Toxicity

- **Offspring Viability, Growth & Malformations (Cont'd)**
  - Delay in preputial separation in rat (Gilmore, 2006)
    - Guideline DNT: 16.1 mg/kg/day GD6 – PND21
    - **Some delay is common** with ↓BWG (No effect on VO)
  - ↓Uterine wt + ↑resorbed & malformed fetuses, incomplete ossification w/ ↓fetal wt & ↓maternal BWG (gestation) + lethargy (Kandil, 2006)
    - 13.38 and 26.75 mg/kg/day (**controls treated with water**)
    - **EC: 5% DLM** + form. agents (**aromatic hydrocarbons**)
  - **Conclude:** General toxicity with a formulation at a lethal dose; Inappropriate control for reference;

# Weight-of-Evidence

- **Male and Female Reproductive Toxicity**
  - DART studies in accordance with GLP & global standards have determined deltamethrin is not a reproductive toxicant;
  - Findings from other sources are generally unreliable and are insufficient to challenge this determination
- **Developmental Toxicity**
  - DART studies in accordance with GLP & global standards have determined deltamethrin is not a developmental toxicant;
  - Findings from other sources are generally unreliable or associated with general toxicity to the mother & offspring

# Reviews by Agencies & Organizations

- **DPR and US EPA:** Evaluations did not classify DLM as a developmental or reproductive toxicant. (various dates)
- **World Health Organization:** “... no evidence of genotoxic, carcinogenic, mutagenic, teratogenic or reproductive effects ...,” when approving DLM for bed net treatment / impregnation for vector control in developing countries (2005)
- **European Union:** No effect on mating or fertility and no developmental toxicity (2011)