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Safety Review: Permethrin
[DRAFT - authors' names have been removed pending final edits and review]

Permethrin is one of a class of insecticides known as pyrethroids. Like other pyrethroids, permethrin kills insects by strongly exciting their nervous systems. In mammals it has been shown to cause a wide variety of neurotoxic symptoms including tremors, incoordination, elevated body temperature, increased aggressive behavior, and disruption of learning (*Cox 1998*).

Permethrin is classified as a ìpotential human carcinogenî by the EPA, and tests with human cells have shown it to be mutagenic. It is listed as a suspected endocrine disruptor, and both estrogen-like and antiandrogen-like effects have been observed in test animals. Studies have shown that pyrethroid exposure may be neurotoxic during development and that human newborns may be more sensitive to permethrin than adults. Children exposed to permethrin have developed immune-mediated respiratory and dermal irritation. It has also been shown to reduce cholinesterase activity in the kidneys and livers of test animals.

Permethrin is highly toxic to a wide variety of animals including honey bees (and other beneficial insects), fish, aquatic insects, crayfish, and shrimp. It is especially toxic to cats. Studies have shown that most cats (96%) exposed to permethrin develop toxic effects, including excitability, twitching, tremors, convulsions, muscular weakness, respiratory distress, vomiting, diarrhea, hypersalivation, and death.

The toxic effects of permethrin are often greatly increased when combined with other chemicals. Several studies have linked a variety of health problems (commonly referred to as Gulf War Syndrome) reported by 30,000 veterans who served in the Persian Gulf War, with exposure to a combination of permethrin, the anti-nerve gas drug pyridostigmine bromide, and the insect repellent DEET.

Permethrin

CAS Number

- 52645-53-1 (mixed isomers)
- 54774-45-7 (cis-isomer)
- 51877-74-8 (trans-isomer)

Class

- ***use type*** ñ insecticide (*PAN Database*)
- ***chem class*** ñ pyrethroid (synthetic insecticides structurally similar to pyrethrins, which are naturally occurring insecticidal compounds. Many pyrethroids are suspected endocrine disruptors.) (*PAN Database*)

European Classification

- ***hazard symbols***
  - Xn (harmful)
  - N (dangerous for the environment) (*EC Annex II; Gestis Database*)
- ***risk phrases***
  - R20/22 (harmful by inhalation and if swallowed)
  - R43 (may cause sensitization by skin contact)
  - R50/53 (very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment) (*EC Annex III*; *Gestis Database*)
- ***safety phrases***
  - S(2) (keep out of the reach of children)

    - S13 (keep away from food, drink and animal feeding stuffs)
    - S24 (avoid contact with skin)
    - S36/37/39 (wear suitable protective clothing, gloves and eye/face protection)
    - S60 (this material and its container must be disposed of as hazardous waste)
    - S61 (avoid release to the environment) (*EC Annex IV*; *Gestis Database*)

WHO (World Health Organization) Classification

- moderately hazardous (*PAN Database*)

Toxicity (selected LD_{50}s and LC_{50}s)

- **Inhalation** LC_{50} Rat : 485 mg/m„ (*MP Biomedicals MSDS*)
- **Inhalation** LC_{50} Mouse : 685 mg/m„ (*MP Biomedicals MSDS*)
- **Oral** LD_{50} Rat : 383 mg/kg (*MP Biomedicals MSDS*)
- **Oral** LD_{50} Mouse : 424 mg/kg (*MP Biomedicals MSDS*)
- **Dermal** LD_{50} Rabbit : >2 gm/kg (*MP Biomedicals MSDS*)

Health Effects (Warnings)

- ***ingestion***
    - harmful if swallowed (*Sigma-Aldrich MSDS*)
    - burning sensation, diarrhea, vomiting (*NIOSH - ICSC 0312*)
- ***inhalation***Ý
    - may be irritating to mucous membranes and upper respiratory tract; harmful if inhaled (*Sigma-Aldrich MSDS*).
    - cough (*NIOSH - ICSC 0312*).
    - can cause skin or respiratory reactions in people with hay fever or in people sensitive to ragweed or pollen; reactions may include irritation or inflammation of the skin (contact dermatitis), sneezing, nasal stuffiness, or asthmatic breathing (*NPIC 1997*).
- ***eye***Ý
    - may cause eye irritation (*Sigma-Aldrich MSDS*)
    - redness, pain (*NIOSH - ICSC 0312*)
    - risk of serious damage to eyes (*MP Biomedicals MSDS*)
- ***skin***
    - may be harmful if absorbed through the skin (*Sigma-Aldrich MSDS*)
    - may cause allergic skin reaction (*Sigma-Aldrich MSDS*)
    - redness, burning sensation (*NIOSH - ICSC 0312*)
    - acute exposure in adults has been shown to result in skin irritation (*EPA 2006b; EPA-TEACH 2007; HHS 2003*)
    - exposure to permethrin may occasionally produce temporary numbing, tingling, and burning sensations of the skin (*NPIC 1997*)
    - can cause skin or respiratory reactions in people with hay fever or in people sensitive to ragweed or pollen; reactions may include irritation or inflammation of the skin (contact dermatitis), sneezing, nasal stuffiness, or asthmatic breathing (*NPIC 1997*)
- ***immunity***
    - experiments with laboratory animals indicate that the immune system ìappears to be a sensitive target for permethrin activity.î ÝIngestion of permethrin reduces the ability of immune system cells called T-lymphocytes to recognize and respond to foreign proteins (*Cox 1998*).
    - doses equivalent to 1/100 of the LD_{50}, have been shown to inhibit T-lymphocytes over 40 percent (*Cox 1998*).
    - permethrin ingestion has also been shown to reduced the activity of a second type of immune system cell, natural killer cells, by about 40 percent.(*Blaylock et al. as cited by Cox 1998*).
- ***neurotoxicity***
    - studies in adult humans and experimental animals have demonstrated that permethrin, like other pyrethroids, alters nerve function by altering the

biochemistry of nerve membrane sodium channels (*EPA 2006a, 2006b, EPA-TEACH 2007*).
    - acute exposure in adults has been shown to result in dizziness, twitching, and nervous disorders (*EPA 2006b*; *EPA-TEACH 2007*; *HHS 2003*).
    - has complex effects on the nervous system in mammals; causes repetitive nerve impulses, and also inhibits a variety of nervous system enzymes:
        - ATPase: whose inhibition results in increased release of the neurotransmitter acetylcholine (*Al-Rahji 1990 as cited by Cox 1998*).
        - monoamine oxidase-A: the enzyme which maintains normal levels of three other neurotransmitters (*Rao & Rao 1993 as cited by Cox 1998*).
        - acetylcholinesterase: the enzyme that breaks down acetylcholine (*Rao & Rao 1995 as cited by Cox 1998*).
    - inhibits the $GABA_A$ receptor (a nervous system receptor) producing excitability and convulsions (*Ramadan et al. 1988a as cited by Cox 1998*).
    - inhibits respiration in a manner similar to other neurotoxic drugs (*Gassner et al. 1997 as cited by Cox 1998*).
    - at relatively high doses, neurotoxic symptoms of permethrin include tremors, incoordination, hyperactivity, paralysis, and an increase in body temperature, these symptoms can persist up to three days (*IPCS 1989 as cited by Cox 1998*).
- ***cholinesterase activity***
    - shown to reduce cholinesterase activity in the kidneys and livers of test animals (*Khan et al. 2003*).
- ***other chronic effects***
    - the liver is a sensitive target for permethrin effects. In an EPA summary of 17 medium-term and long-term laboratory studies that exposed test animals to permethrin, effects on the liver were noted at the ìlowest effect levelî in all of them (*EPA 1997 as cited by Cox 1998*).
    - enlarged adrenal glands and increased kidney weights have been demonstrated in laboratory tests (*EPA 1997 as cited by Cox 1998*).
- ***carcinogenicity*** Ý
    - possible (*PAN Database*)
    - classified by EPA as ìLikely to be Carcinogenic to Humansî by the oral route (this classification was based on two reproducible benign tumor types (lung and liver) in the mouse, equivocal evidence of carcinogenicity in Long-Evans rats, and supporting structural activity relationships (SAR) information) (*EPA 2006b*)
    - IARC (International Agency for Research on Cancer) Classification:
        - Group 3: unclassifiable because the data are incomplete or ambiguous (*PAN Database*).
    - U.S. EPA Office of Pesticide Programs (OPP) Carcinogen List:
        - Suggested: Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential. This descriptor is appropriate when the evidence from human or animal data is suggestive of carcinogenicity, which raises a concern for carcinogenic effects, but is judged not sufficient for a conclusion as to human carcinogenic potential (*PAN Database*).
    - EPA found that permethrin increased the frequency of lung tumors in female mice, and increased the frequency of liver tumors in male and female mice (*EPA 1997 as cited by Cox 1998*).
    - WHO (World Health Organization) reports that permethrin increased the frequency of lung tumors in females in two out of the three mouse studies it reviewed (*WHO 1990 as cited by Cox 1998*).
    - two proposed molecular mechanisms could explain permethrinís carcinogenicity:
        1. permethrin reduces the activity of an enzyme involved in the breakdown of the amino acid tryptophan. This can lead to the buildup of carcinogenic tryptophan breakdown products (*El-Touky et al. 1989 as cited by Cox 1998*).

2. permethrin inhibits what is called ìgap junctional intercellular communicationî (GJIC), chemical communication between cells. GJIC plays an important role in the growth of cells, and some cancer promoting chemicals inhibit GJIC (*Tateno et al. 1993 as cited by Cox 1998*).

- ***mutagenicity***
  - shown to be mutagenic (damaging to genetic material) in tests with human cell cultures, hamster cells, and fruit fly larvae (*Cox 1998*).
  - in cultures of human lymphocytes (white blood cells), permethrin exposure caused an increase in chromosome aberrations, chromosome fragments (*Barrueco et al. 1992 as cited by Cox 1998*), and DNA lesions (*Surralles et al. 1995 as cited by Cox 1998*).
  - in hamster ovary cell cultures, permethrin exposure caused chromosome aberrations (*Barrueco et al. 1994 as cited by Cox 1998*).
- ***developmental or reproductive toxin***
  - no available weight-of-the-evidence summary assessment (*PAN Database*).
  - evidence is accumulating that pyrethroid exposure may be neurotoxic during development (*Shafer et al. as cited by EPA -TEACH 2007*).
  - there is concern for developmental neurotoxicity based on evidence of neurotoxicity at high doses in a subchronic neurotoxicity study (*EPA 2006b*).
  - affects both male and female reproductive systems (*Cox 1998*). Ý
  - shown to cause reduced testes weights in a long term feeding study of mice (*EPA 1997 as cited by Cox 1998*).Ý
  - in females, permethrin exposure has caused embryo loss in pregnant rabbits (*EPA 1997 as cited by Cox 1998*) and in pregnant rats (*Spencer & Berhane 1982 as cited by Cox 1998*).Ý
- ***endocrine disruptor***Ý Ý
  - suspected (*PAN Database*)
  - binds to receptors for androgen, a male sex hormone, in skin cells from human males, causing researchers to ìadvise protection from any form of contact or ingestion of the pyrethroidsî (*Eil & Nisula 1990 as cited by Cox 1998*).
  - binds to a different receptor, called the peripheral benzodiazepine receptor, that stimulates production of the male sex hormone testosterone (*Ramadan et al. 1988b as cited by Cox 1998*).
  - test results suggest that permethrin may cause mitochondrial membrane impairment in Leydig cells and disrupt testosterone biosynthesis by diminishing the delivery of cholesterol into the mitochondria and decreasing the conversion of cholesterol to pregnenolone in the cells, thus reducing subsequent testosterone production (*Zhang et al. 2007*).
  - test results showed estrogen-like effects in female rats, but antiandrogen-like effects in males (*Kim et al. 2005*).
- ***children***Ý
  - results of animal studies suggest that human newborns may be more sensitive to permethrin than adults (*NPIC 1997*).
  - recent studies of children have reported immunotoxic effects following exposure to pyrethroids, with increased incidence of anti-nuclear antibodies associated with autoimmune disease (*Rosenberg et al. 1999 as cited EPA -TEACH 2007*).
  - permethrin exposure may impact the immune system in children (*EPA -TEACH 2007*); case reports indicated that children exposed to permethrin developed immune-mediated respiratory and dermal irritation (*Fuortes 1999 as cited by EPA -TEACH 2007*).
  - exposure of toddlers to permethrin exceeded the U.S. EPA Level of Concern (LOC) when combined chronic exposure via dietary sources (food and drinking water) and short-term exposure via contact with permethrin-treated lawns and indoor surfaces (particularly with carpets in treated rooms) was taken into account (*EPA 2006b as cited by EPA -TEACH 2007*); this led to new EPA risk

mitigation measures (EPA 2006a, *2006b as cited by EPA -TEACH 2007*); mitigation measures include discontinued use of sponge applications; discontinued use of broadcast, crack and crevice sprays on all residential indoor surfaces (except for aerosol sprays); and concentration limits on aerosol and total release fogger formulations (*EPA 2006a as cited by EPA -TEACH 2007*).

Synergy with other chemicals

- synergy between two or more chemicals occurs when their combined exposure causes more adverse effects than the sum of their individual effects (*as defined by Cox 1998*). Several studies have linked health problems reported by 30,000 veterans who served in the Persian Gulf War, to exposure to a combination of permethrin, the anti-nerve gas drug pyridostigmine bromide, and the insect repellent DEET (*Abdel-Rahman et al. 2001; Abdel-Rahman et al. 2002; Abdel-Rahman et al. 2004*; *Abou-Donia et al. 1996*; *Abou-Donia et al. 2001*; *Baynes et al. 2002*; *Cox 1998*; etc.)
- neurotoxic symptoms, including decreased activity, diarrhea, shortness of breath, tremors, inability to walk, and damage to nerves, were observed in hens exposed to all three chemicals, but not in hens exposed to permethrin alone. Permethrin with just pyridostigmine bromide or just DEET also caused tremors and inability to walk, but symptoms were not as severe (*Abou-Donia et al. 1996 as cited by Cox 1998*).

Animal toxicity

- toxic to honey bees and other beneficial insects, fish, aquatic insects, crayfish, and shrimp; for many species, concentrations of less than one part per billion are lethal; causes deformities and other developmental problems in tadpoles, and reduces the number of oxygen-carrying cells in the blood of birds (*Cox 1998*).
- ***cats*** - highly toxic to cats.
    - inappropriate use of PSOs (permethrin spot-on products) on cats can cause severe toxicity, and frequently result in convulsions and fatalities (*Meyer 1999, Bates 2000, Gray 2000, Martin and Campbell 2000 as cited by Sutton et al. 2007*).
    - most cats (over 96%) exposed to permethrin develop toxic effects (*Sutton et al. 2007*); clinical signs of feline permethrin toxicosis usually present within 3 hours of exposure but may be delayed up to 72 hours (*Merola and Dunayer 2006 as cited by Sutton et al. 2007*).
    - symptoms of toxicity include excitability, twitching, tremor, hyperaesthesia, convulsions, muscular weakness, fasciculations, hyperthermia, respiratory distress, vomiting, diarrhea, hypersalivation, anorexia, tachypnoea, death (*Sutton et al 2007: Whittem 1995 as cited by Sutton 2007*).
- ***bees*** - highly toxic to honeybees, as well as other beneficial insects (*EPA 2006a*).

Aquatic toxicity

- ***fish*** ñ Ýhighly toxic to both freshwater and estuarine aquatic organisms (*EPA 2006a*).

Ecological Toxicity

- classified as ìhazardous wasteî under the European Waste Catalogue Ordinance (AVV) (*Gestis Database*).
- classified as ìdangerous for the environmentî under European labeling (*Gestis Database*).
- classified as ìvery toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environmentî under European labeling (*Gestis Database*).
- ***ground water contaminant*** - prevent escape into water, drainage, sewer, or ground (*Gestis Database*); hazard for drinking water sources when only small quantities get into groundwater (*Gestis Database*); classified as WGK 3 ìsevere hazard to watersî under the European Administrative Regulation of Substances Hazardous to Water (VwVwS) (*Gestis Database*).

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- Annex III ñ risk phrases http://ec.europa.eu/environment/dansub/pdfs/annex3_en.pdf
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