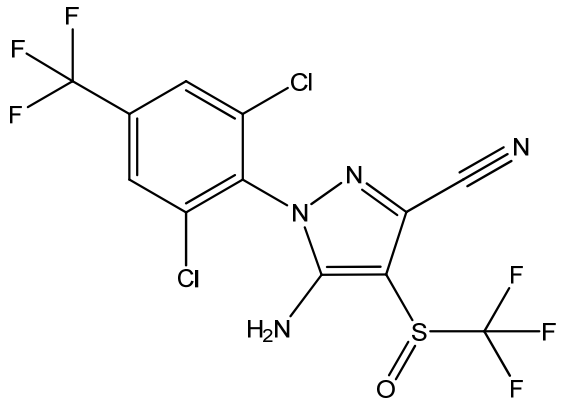
Fipronil [CASRN: 120068-37-3]

Materials for the July 28-29, 2009 Meeting of the California Environmental Contaminant Biomonitoring Program (CECBP) Scientific Guidance Panel (SGP)

Agenda Item: "Potential Designated Chemicals: Pesticides"



<u>Exposure or potential exposure to the public or specific subgroups:</u>

Fipronil is a phenylpyrazole insecticide that was first approved for use by U.S. EPA in 1996. The California Department of Pesticide Regulation (CDPR, 2009) listed 37 products currently registered for use in California that contain fipronil. CDPR (2007) reported the use of 64,721 pounds in 2007, with use almost exclusively related to structural pest control and no use on agricultural crops in California (CDPR, 2007). Fipronil is also used for ant and cockroach control in household and garden products and as a topical flea and tick treatment for dogs and cats.

After flea and tick treatment, fipronil collects in the oils of the skin and hair follicles of an animal and is continuously released onto the animal's skin and coat for weeks (Jennings et al., 2002). Fipronil is not easily absorbed dermally, but human exposure can occur through hand-to-mouth transfer after petting treated animals.

Gunasekara et al. (2007) reported that the U.S. Geological Survey found fipronil and its degradation products at low concentrations (in the ppb range) in urban creeks feeding into the Sacramento and San Joaquin Rivers. A recent U.S. EPA study conducted between 2005-2006 found fipronil residues (on floor wipes) in approximately 40% of homes studied (Stout et al., 2009).

<u>Known or suspected health effects:</u>

Fipronil acts by preventing the passage of chloride ions through γ-aminobutyric acid (GABA) - gated chloride channels. It is considered a selective GABA antagonist because it shows a greater binding affinity to insect than to mammal GABA receptor chloride channels. However, signs of neurotoxicity have been found in subchronic and chronic studies in mammals (U.S. EPA, 1997). U.S. EPA (1997; 1998a; 1998b) reported that a developmental neurotoxicity study had positive

findings. The U.S. EPA Health Effects Division's Hazard ID Assessment Review Committee (HIARC) concluded that "the apparent increased susceptibility in the developmental neurotoxicity study was not supported by the overall weight-of-the-evidence" (U.S. EPA, 1998b). More recently, fipronil was found to cause neurodevelopmental toxicity in a cell line used to study neuronal development (Lassiter et al., 2009). Stehr et al. (2006) reported that fipronil affected neurodevelopment in zebrafish by a mechanism unrelated to its effect on the GABA receptor.

U.S. EPA has classified fipronil as a possible human carcinogen (Group C) based on increases in thyroid tumors in rats. Fipronil treatment also caused a decrease in thyroid hormone (T4) levels, an increase in thyroid stimulating hormone (TSH), and an increase in liver and thyroid gland weight (U.S. EPA, 1994). Leghait et al. (2009) concluded that, in the rat, thyroid disruption resulted from increased T4 elimination which the authors suggest may be related to a fipronil-dependent increase in liver enzymes.

Potential to biomonitor:

Physical and chemical properties (HSDB)*:*
Molecular weight: 437.15
Vapor pressure: 2.78×10^{-9} mm Hg
Water solubility: 1.9 mg/L at 25ºC
Octanol/water partition coefficient: Log K_{ow} = 4.0

Metabolism and pharmacokinetics. A study in rats found fipronil in the carcass, GI tract, liver, adrenals and abdominal fat after a single dose or repeated oral doses. Most of the dose was excreted in feces (45-75%), while urinary excretion accounted for 4-25%. (U.S. EPA, 1998b). Studies in mice and rats found that fipronil is metabolized almost exclusively to fipronil-sulfone (Hainzl and Casida, 1996; Leghait et al., 2009). In mice, fipronil-sulfone was found in brain, liver, and kidney seven hours after i.p. administration; it was also retained in fat (Hainzl and Casida, 1996). *In vitro* studies suggest that fipronil-sulfone is also the major metabolite in humans and that metabolism to fipronil-sulfone is generally greater in rats than in humans (Tang et al., 2004). Tang et al. (2004) reported a 40-fold variation in the formation of fipronil-sulfone in human liver microsomes.

Persistence: Fipronil is generally regarded as persistent and slowly degrades in soil through microbial processes (Tingle et al., 2003). In the presence of sunlight, fipronil undergoes rapid photochemical degradation, with the major breakdown product being desulfinyl-fipronil (Hainzl and Casida, 1996; Raveton et al., 2006). Desulfinyl-fipronil has a half-life in soil of 630-693 days, depending on the soil (Gunasekara et al., 2007).

Bioaccumulation: BCF = 240 (predicted using PBT Profiler). Studies in rainbow trout indicate that fipronil is rapidly accumulated but also rapidly metabolized and excreted (Konwick et al., 2006). Studies with desulfinyl-fipronil and fipronil-sulfone suggest that these degradation products may have the potential to bioaccumulate (U.S. EPA, 1998b; Konwick et al., 2006).

Need to assess efficacy of public health actions:

Fipronil poses potential concerns for developmental neurotoxicity, carcinogenicity and hormone effects. It is a relatively new pesticide with the potential for increased household use. Biomonitoring fipronil will help the State to assess the extent of exposure in California and determine the need for further study.

Availability of analytical methods:

A method coupling solid-phase microextraction (SPME) with GC-MS has been developed for determination of fipronil in human urine (Vilchez et al., 2001). A GC-MS/MS method has been developed for determining fipronil residue in ovine plasma (Bichon et al., 2008).

Availability of adequate biospecimens: Blood or urine.

Incremental analytical cost: Separate analytical methods will need to be developed by CECBP laboratories. This chemical cannot likely be bundled with other analytes.

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