June 2001 Update of the March 1991 Methoprene R.E.D. Fact Sheet

Environmental Protection Agency

PESTICIDE FACT SHEET

METHOPRENE

Methoprene is an insect growth regulator (IGR) with activity against a variety of insect species including horn flies, mosquitoes, beetles, tobacco moths, sciarid flies, fleas (eggs and larvae), fire ants, pharoah ants, midge flies and Indian meal moths. Controlling some of these insects, methoprene is used in the production of a number of foods including meat, milk, mushrooms, peanuts, rice and cereals. It also has several uses on domestic animals (pets) for controlling fleas. Methoprene products are sold under a number of trade names including Altosid®, Precor®, Kabat®, Pharorid®, Dianex®, Apex®, Fleatrol™, Ovitrol®, Extinguish® and Diacon®. Methoprene is considered a biochemical pesticide because rather than controlling target pests through direct toxicity, Methoprene interferes with an insect's life cycle and prevents it from reaching maturity or reproducing.

Regulatory History

Methoprene was first registered by EPA as a conventional, chemical pesticide in 1975. EPA issued a Registration Standard for Methoprene in February 1982. Subsequently, the Agency reclassified Methoprene as a biochemical pesticide. The Agency issued the Reregistration Eligibility Document (RED) in 1991 and reregistration of the active ingredient and all end-use products was completed in 1997. Tolerances (40 CFR 180.359) and exemption from tolerances (40 CFR 180.1033 and 185.4150) have been established for Methoprene in or on a number of food commodities. Methoprene is also recognized by FDA as a feed additive for use in cattle feeds to control horn flies (40 CFR 186.4150; formerly 21CFR 561.282).

Health Effects

An extensive safety data base has been generated for Methoprene since it was first registered in 1975. Toxicological data on file with the Agency includes an acute toxicity battery, irritation/sensitization studies, subchronic feeding studies, developmental and reproductive toxicity studies, mutagenicity studies, chronic feeding studies and lifetime carcinogenicity studies. In addition, special studies dealing with the metabolism and fate of Methoprene in several mammalian species and those dealing with the potential for endocrine effects have also been completed. Studies relating to the effect of Methoprene on the immune system were waived by EPA since there was no indication of the immune system being the potential target organ/system in any of the acute, subchronic, chronic, teratology, reproduction or special toxicity studies. Today, some of the submitted data would not even be required under the current guidelines for biochemical pesticides.

In addition to the studies mentioned above, the following data gaps identified in the March 1991 RED document have been completed:

1. Estuarine Invertebrate Life Cycle Study – MRID #44022101
2. Octanol/Water Partition Coefficient Study – MRID #42290001

The results from various toxicology studies for Methoprene are summarized below:

- The acute oral LD_{50} for racemic and (S)-Methoprene in rats is >10,000[1] and >5000[2] mg/kg, respectively. These doses were the highest doses tested (HDT) for both compounds. In dogs, the acute oral LD_{50} value for racemic Methoprene is between 5000 to 10,000[3] mg/kg. The acute dermal LD_{50} for both racemic[4] and (S)-Methoprene[5] in rabbits is >2000 mg/kg. The acute (4-hr) inhalation LC_{50} for racemic Methoprene in the rat[6] and guinea pig[7] is >210 mg/L. Primary eye and skin irritation studies have been conducted in rabbits for both racemic and (S)-Methoprene. Results from these studies indicate that both racemic[8, 9] and (S)-Methoprene[10, 11] are not likely to cause irritation to the skin or eyes of humans when exposed topically. Also, based on data generated for racemic Methoprene in guinea pigs[12], no potential for skin sensitization is expected for (S)-Methoprene. These data indicate an extremely low potential for acute toxicity to humans from overexposure to either racemic or (S)-Methoprene via the oral, dermal, ocular or inhalation routes of exposure. S-Methoprene is classified in toxicity categories III and IV.
  In order to evaluate health effects from short-term exposure, 90-day feeding studies[13] have been conducted with racemic Methoprene in rats given doses of 0, 250, 500, 1000 or 5000 ppm in diet and in dogs given doses of 0, 250, 500 or 5000 ppm in diet. The No-Observable-Effect Level (NOEL) for systemic effects was 500 ppm for both rats and dogs. Increased liver weights in rats and dogs and renal tubular degeneration effects in some rats were observed at higher dose levels but the significance of these effects are considered negligible since they were not observed in chronic feeding studies. A 30-day dermal toxicity study has been conducted in Japanese rabbits with undiluted Methoprene at doses of 0, 100, 300, 900 or 2700 mg/kg/day applied topically to the back of the rabbits[14]. The 300 mg/kg dose was concluded to be the NOEL for systemic effects and 100 mg/kg was considered to be the NOEL for local effects. The NOEL for racemic Methoprene was 20 mg/L (HDT) in a 21-day inhalation toxicity study in rats[15]. These data indicate that oral, dermal or inhalation exposure to Methoprene for an extended duration is not likely to cause adverse health effects in humans.

- Chronic feeding studies have been conducted in rats[16] and mice[17]. Rats exposed to Methoprene technical at 0, 250, 1000, or 5000 ppm in the diet daily for two years did not exhibit any adverse health effects even at the highest dose as compared to control animals[16]. No increase in tumor incidence was observed. The NOEL for systemic effects was 5000 ppm, the highest dose tested in the study. No potential for increase in tumors was observed in another chronic study using CD-1 mice fed diets containing 0, 250, 1000 or 2500 ppm of Methoprene daily for 18 months[17]. No significant health effects were observed in treated groups. The NOEL for systemic effects in mice was concluded to be 250 mg/kg/day due to the presence of brown pigmentation of the liver in some animals at higher doses. It can therefore be concluded that Methoprene is not an oncogenic compound based on the chronic toxicity studies summarized above.

- Complete data are available for evaluating the developmental and reproductive effects of Methoprene in animals. Methoprene is not a developmental toxicant as evaluated in rabbits (NOEL 2000 mg/kg, the highest dose tested)[18] and mice (NOEL 600 mg/kg/day, the highest dose tested)[19]. The three-generation reproduction study conducted in rats also revealed a NOEL of 2500 ppm (HDT) for reproductive effects[20]. With such high NOELs for Methoprene in these studies at the highest doses tested, no developmental toxicity can be expected in humans from exposure to the residues of Methoprene either during pregnancy or during early childhood.

- Methoprene is not a mutagenic compound based on negative results obtained in the Ames test and several other mutagenicity assays[21, 22, 23, 24].

- Special studies relating to mammalian metabolism[25] indicate that Methoprene is metabolized rapidly and extensively into endogenous products such as acetate molecules and these are incorporated into the biosynthesis of naturally occurring constituents of the body such as cholesterol and bile acids.

- Screening studies relating to endocrine effects indicate that Methoprene has no potential for an estrogenic, androgenic, anabolic or a glucocorticoid effect[26]. In addition, any potential for these effects would have been revealed in the developmental studies and/or the three-generation reproduction study where animals were exposed to high levels of Methoprene technical.

Routes of Human Exposure

Through the Diet

Dietary exposure to Methoprene is minimal and would only be expected to occur from treatment of mushrooms, stored grains, peanuts and cereals or low-level residues in cattle meat, fat or milk from feed-through applications. Methoprene has been in use for over two decades. The stored grain uses are at a maximum 5 ppm rate. No health hazards have been reported that could be related to the ingestion of Methoprene residues. Residues of Methoprene are at negligible levels particularly with respect to the NOEL levels in the developmental and reproductive toxicity studies. Due to the high toxicological endpoints and low levels of residues, risk from consumption of treated commodities is considered negligible for the general population and infants and children.

Through Drinking Water

Exposure to Methoprene residues is not expected from drinking water. In aqueous solutions, Methoprene degrades rapidly under sunlight into at least 50 minor photolysis products[27, 28]. Methoprene is rapidly metabolized in soil both under aerobic and anaerobic conditions (half-life 10-14 days) with CO_2 as the major product[29]. Degradation in surface water is due to both microbial metabolism and photolysis[27, 30]. By the time surface water reaches drinking water treatment plants, residues of Methoprene are unlikely to be present and in the unlikely event that residues are present, these would be mitigated by water treatment procedures. In view of these points, drinking water is not considered an additive factor in exposure of the human population to Methoprene.

During Application

Non-Dietary Exposure is considered minimal with respect to mixers, loaders and applicators since exposure via dermal and inhalation routes are negligible and Methoprene is classified in toxicity category III and IV for dermal and inhalation toxicity, respectively. Furthermore, no evidence exists for neurotoxic, oncogenic, reproductive or developmental adverse effects that can be attributed to Methoprene. EPA considers Methoprene to pose no risks to people who are occupationally exposed to this biopesticide.

Domestic Animals

The Agency is reviewing submitted data regarding the safety of Methoprene use on domestic animals. It is used on pets (dogs and cats) and in pet areas (bedding). Incidents of toxicity to cats from the use of products containing Methoprene have been reported to the Agency. EPA is investigating these incidents and evaluating domestic animal safety data for Methoprene to determine if the cause of the reported incidents is due to Methoprene or another ingredient in the products. Once the cause of the adverse effect incidents is known the Agency will take appropriate regulatory action.

Environmental Hazards

Environmental Fate

All the environmental fate data requirements for Methoprene have been satisfied. The available information indicates that Methoprene will not result in unreasonable adverse effects on the environment since Methoprene degrades rapidly in sunlight[27], both in water[28] and on inert surfaces. Methoprene is also metabolized rapidly in soil and does not leach[29]. Thus, Methoprene is not expected to persist in soil or contaminate ground water.

Ecological effects

Methoprene has been shown to be practically non-toxic to terrestrial species including mallard ducks[31] and quail[32] and Methoprene had no effect on mallard[33] or quail[34] reproduction.

Ecological effects studies on aquatic species either on file with the Agency or submitted by the registrant between 1993 and 1996, indicate minimal acute and chronic risk to freshwater fish [35,36,37], freshwater invertebrates[38,39] and estuarine species [40,41,42,43] from exposure to Methoprene mosquito products.

Extensive research has addressed the effects of Methoprene on non-target aquatic and terrestrial organisms. Acute, short-term and subchronic effects studies on non-target immature and adult arthropods [Crustacea, Insecta and Mollusca, including shrimp, damselfly, beetle, tadpole] demonstrate 24- and 48- hour LC_{50} values >900 ppb[44,45]. Confirming these studies, other researchers have demonstrated that sensitive life stages of nontarget organisms, *i.e.,* nymph and larvae, and

nontarget aquatic organisms that are highly related to mosquitoes, *i.e.,* dragonfly, are not affected by Methoprene up to 1,000 ppb [46].

Preliminary investigations by Cliburn[47] were reported on the effects of Methoprene on various life stages of different amphibian species (*B. woodhousei*, *R. catesbeiana* and *R. pipiens*). Acute studies on *R. catesbeiana* and *R. pipiens* larvae indicate LC_{50} values >10,000 ppb and *B. woodhousei* adult LC_{50} values >1,000 ppb (highest dose tested). Chronic studies on *B. woodhousei* indicate a 22 day LC_{50} >1,000 ppb and LC_{50} > 1,000 ppb for *R. catesbeiana* and *R. pipiens*. No other adverse effects were reported.

Rate of release and data generated under laboratory and field conditions with Methoprene mosquito product formulations, including slow release briquet formulations, indicate a maximal rate of release of ≤ 4 ppb. Data on nontarget organism support margins of safety of >200 for nearly all organisms tested. Therefore, exposure to Methoprene will not reach levels which are toxic to aquatic non-target species either after acute or chronic exposure [48,49,50].

Based upon review of the data submitted to the Agency between 1993 and 1996, EPA concluded in 1996 that the following label changes should be implemented on all solid Methoprene mosquito products:

- Remove the label restriction "do not use in fish-bearing waters" from all briquet and pellet labels and
- Add the label warning "this product is toxic to aquatic dipteran (mosquitoes) and chironomid (midge) larvae" to all briquet and pellet labels.

Additional Data Required

Reregistration of the active ingredient Methoprene and all end-use products was completed in 1997.

Product Labeling Changes Required

All labeling changes with regard to fish and aquatic invertebrates were completed in 1996. No additional label changes are required.

Regulatory Conclusions

- The studies available to EPA indicate that the biochemical insect growth regulator Methoprene is of low toxicity and poses very little hazard to people and other non-target species.

- Ecological concerns contained in the 1991 Methoprene R.E.D. FACTS document related to toxicity to estuarine invertebrates have been alleviated as a result of submission of the estuarine invertebrate life cycle toxicity study in 1996, which indicated minimal chronic risk to Mysid Shrimp.

- All Methoprene end-use products completed the reregistration process in 1997 and all reregistration data requirements and label changes have been completed.

End Notes

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