

# New York State Department of Environmental Conservation

## Division of Solid and Hazardous Materials

Bureau of Pesticides Management, 11th Floor

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February 11, 2005

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Mr. E. David Lewis  
Mitsui Chemicals, Inc.  
c/o Lewis & Harrison, LLC  
122 C Street, N.W., Suite 740  
Washington, DC 20001

Dear Mr. Lewis:

**Re: Registration With Conditions of the New Active Ingredient Etofenprox Contained in the Pesticide Products Etofenprox Technical (EPA Reg. No. 33657-6) and 1% Etofenprox Aerosol (EPA Reg. No. 33657-9)**

The New York State Department of Environmental Conservation (Department) has completed a technical review of the applications and supplemental information submitted to date regarding registration of the referenced products in New York State. Etofenprox Technical (EPA Reg. No. 33657-6) and 1% Etofenprox Aerosol (EPA Reg. No. 33657-9) contain the new active ingredient etofenprox (Chemical Code 128965).

**The Department hereby accepts Etofenprox Technical (EPA Reg. No. 33657-6) and 1% Etofenprox Aerosol (EPA Reg. No. 33657-9) for registration subject to the following conditions:**

- **The expiration date of Etofenprox Technical (EPA Reg. No. 33657-6) and 1% Etofenprox Aerosol (EPA Reg. No. 33657-9) coincides with the federal expiration date of March 1, 2006.**
- **USEPA reviews and/or DERs for the acute, subchronic and developmental neurotoxicity studies and indoor dissipation and degradation studies must be submitted to this Department before March 1, 2006. Registration status is dependent upon USEPA's review and concurrence with the Department's evaluation of these same studies.**

Etofenprox Technical (97.0% etofenprox) is labeled as an insecticide for formulation into pesticide products intended for use in residential sites, commercial and industrial establishments and institutions.

1% Etofenprox Aerosol (1.00% etofenprox) is labeled to kill cockroaches, ants, fleas, ticks, spiders and other listed insects in homes, apartment buildings, and the nonfood/feed areas of hotels, stores, warehouses, office buildings, schools, nursing homes, hospitals and industrial buildings.

The registration package was deemed complete for purposes of technical review on September 4, 2002. Pursuant to the review time frame specified in Environmental Conservation Law (ECL) §33-0704.2, a registration decision date of February 1, 2003 was established. The decision date was subsequently waived in order to accommodate the review of the registrant's response to the Department's technical issues letter (12/13/02). The review ultimately focused on the acute, subchronic and developmental neurotoxicity studies as well as additional dissipation and degradation data required pursuant to the FIFRA sec. 3(c)(7)(A) conditional registration of 1% Etofenprox Aerosol and Etofenprox Technical issued on September 14, 2001. On March 1, 2004, the United States Environmental Protection Agency (USEPA) acknowledged receipt of the required studies and extended the conditional registrations of the subject products for two years establishing a new expiration date of March 1, 2006. While USEPA intends to review all relevant data and additional studies before March 1, 2006, a specific review date was not established. The NYSDOH agreed to review the neurotoxicity, dissipation and degradation studies prior to their review by the USEPA. By mutual agreement, a new registration decision date of February 18, 2005 was established.

Toxicological, ecotoxicity and environmental fate risk assessments were conducted for Etofenprox Technical and 1% Etofenprox Aerosol.

**TOXICOLOGICAL RISK ASSESSMENT:** Neither 1% Etofenprox Aerosol nor its active ingredient etofenprox (Etofenprox Technical is comprised of 97% etofenprox) was very acutely toxic to laboratory animals by the oral, dermal or inhalation routes of exposure. The 1% etofenprox product was not very irritating to animal eyes or skin (tested on rabbits). The active ingredient was not very irritating to the eyes, but was a moderate skin irritant. Neither of these materials was a skin sensitizer (tested on guinea pigs).

Rats exposed to etofenprox in a 90-day inhalation study showed an increase in weight of various organs (heart, lung, liver, kidney) as well as changes in blood parameters (decreased red blood cells and hemoglobin levels) at an air concentration of 0.2 milligrams per liter (mg/L), which is equivalent to a dose of about 52 milligrams per kilogram body weight per day (mg/kg/day). The no-observed-effect level (NOEL) was 0.04 mg/L (equivalent to 10.6 mg/kg/day).

In a chronic feeding/oncogenicity study with etofenprox in mice, changes in kidney morphology (increased incidence of dilated basophilic renal cortical tubules) were reported at 80.9 mg/kg/day for females, and increased mortality and decreased body weight gain were reported at 10.4 mg/kg/day for males; the respective NOELs were 11.7 and 3.1 mg/kg/day. A rat

chronic feeding/oncogenicity study reported an increase in thyroid gland weights in males at 25.5 mg/kg/day, whereas in females an increase in liver weights and histopathological changes in liver and the thyroid were reported at 249 mg/kg/day; the respective NOELs were 3.7 and 34.3 mg/kg/day. In a one-year dog study, increased weights of the liver, kidney and pancreas along with serum chemistry changes (decrease in protein, albumin and cholesterol, increase in alkaline phosphatase levels) were reported at 352 and 340 mg/kg/day for males and females, respectively. The corresponding NOELs were 33 and 32 mg/kg/day. The USEPA calculated an oral reference dose (RfD) for etofenprox of 0.037 mg/kg/day based on the NOEL from the chronic feeding/oncogenicity rat study (3.7 mg/kg/day) and an uncertainty factor of 100. This value has not yet been adopted by the USEPA's Integrated Risk Information System.

In a rat developmental toxicity study, etofenprox caused some effects in the offspring of pregnant animals, but only at doses that also caused maternal toxicity. An increased incidence of malformations (facial defects, abnormal smallness of the eye) and visceral abnormalities was observed in offspring at a dose of 5,000 mg/kg/day; the NOEL was 250 mg/kg/day. Maternal toxicity characterized by an increased incidence of skin scabbing and fur staining also occurred at 5,000 mg/kg/day with a NOEL of 250 mg/kg/day. In rabbits, reduced fetal body weights and increased post-implantation loss were reported at 300 mg/kg/day; the NOEL was 100 mg/kg/day. Maternal toxicity (reduced body weights, body weight gains and food consumption rates) also occurred at 300 mg/kg/day with a NOEL of 100 mg/kg/day. In a multigeneration reproduction study in rats, no reproductive effects were observed at the highest dose tested, which was 245 mg/kg/day. However, paternal toxicity characterized by increased weight of liver, thyroid, kidney and histopathological changes in kidney occurred at a dose of 245 mg/kg/day; the NOEL was 35 mg/kg/day.

Etofenprox was oncogenic in rats, but not in mice. In both male and female rats there was a significant increase in combined thyroid follicular cell adenomas and carcinomas between controls and the highest dose group (187 mg/kg/day in males and 249 mg/kg/day in females). In addition, there was a significant dose-related positive trend of combined thyroid adenomas and carcinomas in both sexes. Based on this evidence, the USEPA's Health Effects Division Carcinogenicity Peer Review Committee classified etofenprox as a Group C, "possible human carcinogen" and assigned a cancer potency slope factor for this compound of  $5.1 \times 10^{-3}$  (mg/kg/day)<sup>-1</sup>. Etofenprox was negative in a number of genotoxicity studies.

The registration package contained several risk assessments conducted by the USEPA on exposure of workers and the general public (adults and children) to etofenprox. For application of the 1% Etofenprox product (as an aerosol spray) by workers using two cans per day, 30 times per year, the margin of exposure (MOE) for the active ingredient was estimated to be 29,000 by inhalation exposure. The NOEL used for estimating this MOE was 10.6 mg/kg/day from the 90-day rat inhalation study. For an exposure duration of 35 years for workers, the USEPA calculated an increased lifetime cancer risk of  $8.7 \times 10^{-7}$  using the cancer potency slope factor of  $5.1 \times 10^{-3}$  (mg/kg/day)<sup>-1</sup>. Generally, the USEPA considers MOEs of 100-fold or greater and cancer risks of  $1 \times 10^{-4}$  or less to provide adequate worker protection from noncancer and cancer effects, respectively. For adults in a nonoccupational setting, the combined MOE from handling and post-application exposures was estimated to be 2,200 and the estimated cancer risk was  $1.6 \times 10^{-6}$ . This cancer risk value is slightly above the level at which the USEPA generally

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requires mitigative measures. MOEs also were determined for children from post-application exposure (inhalation and ingestion from hand-to-mouth and object-to-mouth activity) to etofenprox. For short-term exposure, using the NOEL of 100 mg/kg/day from the rabbit developmental toxicity study, the estimated MOE was 7,100. For intermediate exposure, the MOE was estimated to be 2,200 using the NOEL of 10.6 mg/kg/day from the 90-day rat inhalation study.

There are no chemical specific federal or State drinking water/groundwater standards for etofenprox. Based on its chemical structure, etofenprox falls under the 50 microgram per liter general New York State drinking water standard for “unspecified organic contaminants” (10 NYCRR Part 5, Public Water Systems). Using the USEPA cancer potency slope factor of  $5.1 \times 10^{-3}$  (mg/kg/day)<sup>-1</sup> and 6 NYCRR Part 702.4 procedures for deriving ambient water quality standards and guidelines based on oncogenic effects, the ambient water quality value associated with a one in a million increased lifetime cancer risk is 7 micrograms per liter for etofenprox.

Neither etofenprox nor 1% Etofenprox Aerosol was very toxic, irritating or caused skin sensitization following acute exposures in laboratory animals. Also, etofenprox did not cause any significant developmental or reproductive effects. However, etofenprox caused several noncancer effects at relatively low doses, including effects on the thyroid gland. In addition, this active ingredient caused thyroid tumors in rats exposed over their lifetime and the USEPA classified etofenprox as a Group C, “possible human carcinogen” and developed a cancer potency slope factor for the quantification of risk. While the estimated occupational and nonoccupational risks posed by etofenprox and 1% Etofenprox Aerosol are relatively low, the New York State Department of Health has concerns for registering a pesticide product or technical grade active ingredient that has carcinogenic potential unless either the needs for the product/active ingredient are significant or it replaces those that pose greater risks.

Before 1% Etofenprox Aerosol could be considered further for registration, information comparing the risks of this product to those of alternate products registered for the same uses was required. This comparison should also address the dissipation and degradation of etofenprox and alternative active ingredients in indoor environments. In addition, the federal registration of both 1% Etofenprox Aerosol and Etofenprox Technical is conditional (until March 1, 2004) upon the registrant submitting acute, subchronic and developmental neurotoxicity studies as well as additional exposure data. The NYSDOH requested that the registrant submit any such data that has been developed thus far along with the comparison information indicated above.

The additional information submitted in response to the Department’s technical issues letter, dated December 13, 2002, partially mitigated the above-stated concerns. Specifically, the comparative data submitted indicated that etofenprox may be a reasonable alternative to the other active ingredients it may replace, as these other chemicals have significant toxicological concerns (e.g., acute toxicity, carcinogenic potential, neurotoxicity). The registrant did not, however, submit USEPA Data Evaluation Reports (DERs) on the acute, subchronic and developmental neurotoxicity studies on etofenprox, nor reports on the dissipation and degradation of this compound.

According to the terms of the FIFRA sec. 3(c)(7)(A) conditional registration of Etofenprox Technical and 1% Etofenprox Aerosol issued on September 14, 2001, the registrant was required to submit acute, subchronic and developmental neurotoxicity studies as well as additional dissipation and degradation data by September 1, 2003. On March 1, 2004, USEPA acknowledged receipt of the required studies and extended the conditional registrations for two years establishing a new expiration date of March 1, 2006. While USEPA intends to review all relevant data and additional studies before March 1, 2006, a specific review date was not established. The NYSDOH reviewed the neurotoxicity, dissipation and degradation studies prior to their review by the USEPA.

The acute, subchronic and developmental neurotoxicity studies submitted by the agent for the registrant appear to have been conducted in accordance with USEPA Health Effect Test Guidelines OPPTS 870.6200 for acute and subchronic neurotoxicity screening and OPPTS 870.6300 for developmental neurotoxicity studies.

The potential neurotoxicity of etofenprox was evaluated in several rat studies designed to evaluate such effects. Administration of etofenprox in either the acute neurotoxicity rat gavage study and the 13-week neurotoxicity rat feeding study did not cause any functional or pathological neurotoxic effects at the highest doses tested, which were 2,000 milligrams per kilogram body weight per day (mg/kg/day) and 690 mg/kg/day for the acute and subchronic studies, respectively. In the 13-week study, stained fur, which is considered to be a behavioral effect, was noted in all dose groups including the lowest dose level of 149 mg/kg/day. In the developmental neurotoxicity study, female rats were treated with etofenprox from day six of gestation to day 20 postpartum. The results presented showed that overall there were some effects in offspring from their prenatal and postnatal exposures to etofenprox. These effects were characterized primarily by an increase in movement to a sound stimulus (auditory startle test) at a dose of 238 mg/kg/day; the NOEL was 79 mg/kg/day. However, no effects were observed on the rats' learning/memory capabilities, nor were there treatment-related histopathological alterations in the tissues of the central and peripheral nervous systems of these offspring, even at the highest dose tested (238 mg/kg/day).

The registrant conducted an indoor air dissipation study using a total-release fogger product that contains 1% etofenprox (the subject product is a 1% spray). The indoor air measurements indicated that residues of etofenprox, following the simulated residential usage of the 1% total-release fogger, were no longer detectable in air beyond six hours. Thus, dissipation of this active ingredient from air was relatively rapid, even after dispersion as a total-release fogger. Dissipation of a spray product would likely occur more rapidly. The measured indoor air level of etofenprox averaged 0.00073 milligrams per cubic meter (mg/m<sup>3</sup>) over the initial six-hour period which is about half the airborne level (0.0015 mg/m<sup>3</sup>) used by USEPA in conducting a risk assessment on the post-application exposures of adults and children. In that risk assessment, MOEs were determined to be above the level of 100-fold or greater normally considered by the USEPA as adequate to protect the general public from noncancer effects.

To measure transfer of etofenprox from residential surfaces such as carpeting and vinyl floors, several transfer techniques were used either over a seven-day sampling period for carpeting or over a three-day period for vinyl flooring. Again, the product used was a total-

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release fogger containing 1% etofenprox, not the spray product. In regard to the carpet dissipation study, the average removal of etofenprox residues ranged over this period from 1.28 to 3.90% of the initially-deposited surface residue, whereas for vinyl flooring, the average removal of etofenprox residues ranged from about 0.73 to 1.36%. Based on application rates of 0.00313 milligrams per square centimeter ( $\text{mg}/\text{cm}^2$ ) and 0.00203  $\text{mg}/\text{cm}^2$  for carpet flooring and vinyl flooring respectively, the respective highest average measured dislodgeable etofenprox residue levels were 0.00012  $\text{mg}/\text{cm}^2$  and 0.0000276  $\text{mg}/\text{cm}^2$ . Using these values, and assuming that each day all of the dislodgeable material was available for dermal contact, was completely transferred to and absorbed by the hands and forearms of an adult weighing 70 kg and to the torso, arms and legs of a child weighing 10 kg, dose levels can be estimated. The highest dermal doses so calculated from post-application exposures to etofenprox residues from carpet flooring for adults and children would be 0.00446  $\text{mg}/\text{kg}/\text{day}$  and 0.0624  $\text{mg}/\text{kg}/\text{day}$ , respectively. For vinyl flooring, the respective post-application dermal exposure doses would be 0.00103  $\text{mg}/\text{kg}/\text{day}$  and 0.0144  $\text{mg}/\text{kg}/\text{day}$ . Using a NOEL of 10.6  $\text{mg}/\text{kg}/\text{day}$  from a 90-day rat inhalation study, MOEs of 170 and 2,300 can be calculated for children and adults, respectively from exposure to dislodgeable etofenprox residues from carpet flooring. In regard to vinyl flooring, the respective calculated MOEs are 700 and 10,000. All these MOEs are above the level of 100-fold or greater generally considered by the USEPA as adequate to protect the general public from noncancer effects. In addition, no systemic effects were noted at doses up to 1,000  $\text{mg}/\text{kg}/\text{day}$  (the highest dose tested) in a 28-day dermal exposure study in rats (skin lesions occurred at 400  $\text{mg}/\text{kg}/\text{day}$ , the lowest dose tested). Finally, for adults in a nonoccupational setting, the estimated cancer risk from a lifetime average daily dose of dislodgeable etofenprox residues from either carpet or vinyl flooring would be less than  $1.0 \times 10^{-6}$  based on the cancer potency slope factor of  $5.1 \times 10^{-3} (\text{mg}/\text{kg}/\text{day})^{-1}$  for thyroid tumors in rats. This cancer risk value is below the level at which the USEPA generally requires mitigative measures.

Neurotoxicity studies indicate that etofenprox caused only limited indicators of neurotoxicity in adult and developing laboratory animals exposed to this chemical pre- and post-natally. The endpoints and effect levels of these studies do not provide a more stringent basis for characterizing risks from the use of the etofenprox products than do the other toxicity studies conducted. In addition, the air dissipation studies indicate that the potential for exposure to this chemical rapidly decreases after its introduction into indoor air from a total-release fogger product. It is expected that the labeled use of the subject 1% etofenprox product, which is a spray to be applied as a spot, crack and crevice treatment, would result in even lower inhalation exposure potential to etofenprox residues. Furthermore, the etofenprox residue studies show that there is a relatively small amount of this chemical that has the potential to dislodge from surfaces, thus indicating a low degree of transfer to skin from dermal contact with these surfaces. The air and surface monitoring dissipation studies both show that the levels of released etofenprox residues that are available for either inhalation or dermal exposures should not result in any significant nonoccupational health risks (occupational risks were previously evaluated) either to adults or children.

**ECOTOXICITY and ENVIRONMENTAL FATE RISK ASSESSMENTS:** There are no anticipated risks to fish, wildlife or groundwater resources since Etofenprox Technical and 1% Etofenprox Aerosol are labeled for indoor uses only. However, etofenprox is highly toxic to

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aquatic organisms. Any products containing this active ingredient bearing outdoor use patterns would require a full suite of environmental fate studies and USEPA DERs to support such uses.

**DISCUSSION:** Given the unique circumstances under which the NYSDOH reviewed the neurotoxicity and dissipation studies (i.e., no USEPA DERs), and that USEPA has not yet reviewed these data, the NYSDOH recommended that these products be registered conditionally pending USEPA's review and concurrence with their evaluation of these same studies.

**REGISTRATION ACTION:** The Department hereby accepts Etofenprox Technical (EPA Reg. No. 33657-6) and 1% Etofenprox Aerosol (EPA Reg. No. 33657-9) for registration subject to the following conditions:

- The expiration date of Etofenprox Technical (EPA Reg. No. 33657-6) and 1% Etofenprox Aerosol (EPA Reg. No. 33657-9) coincides with the federal expiration date of March 1, 2006.
- USEPA reviews and/or DERs for the acute, subchronic and developmental neurotoxicity studies and indoor dissipation and degradation studies must be submitted to this Department before March 1, 2006. Registration status is dependent upon USEPA's review and concurrence with the Department's evaluation of these studies.

Enclosed for your files are the Certificates of Pesticide Registration and New York State stamped "ACCEPTED" labels.

Please note that a proposal by Mitsui Chemicals, Inc., or any other registrant, to register a product containing etofenprox, whose labeled uses are likely to increase the potential for significant exposure to humans or impact to the environment, would constitute a major change in labeled (MCL) use pattern. Such an application must be accompanied by a new application fee and meet the requirements specified in 6 NYCRR Part 326.17.

Please contact Samuel Jackling, Chief of our Pesticide Product Registration Section, at (518) 402-8768, if you have any questions.

Sincerely,

Maureen P. Serafini  
Director  
Bureau of Pesticides Management

Enclosures

cc: w/enc. - N. Kim/D. Luttinger, NYS Dept. of Health  
R. Zimmerman/R. Mungari, NYS Dept. of Ag. & Markets  
W. Smith, Cornell University, PSUR