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R.E.D. FACTS

Amitraz

Pesticide Reregistration

All pesticides sold or distributed in the United States must be registered by EPA, based on scientific studies showing that they can be used without posing unreasonable risks to people or the environment. Because of advances in scientific knowledge, the law requires that pesticides which were first registered before November 1, 1984, be reregistered to ensure that they meet today's more stringent standards.

In evaluating pesticides for reregistration, EPA obtains and reviews a complete set of studies from pesticide producers, describing the human health and environmental effects of each pesticide. The Agency develops any mitigation measures or regulatory controls needed to effectively reduce each pesticide's risks. EPA then reregisters pesticides that can be used without posing unreasonable risks to human health or the environment.

When a pesticide is eligible for reregistration, EPA explains the basis for its decision in a Reregistration Eligibility Decision (RED) document. This fact sheet summarizes the information in the RED document for reregistration case 0234, amitraz.

Use Profile

Amitraz or BAAM is an insecticide and acaricide used primarily to control the pear psylla on Oregon pear crops. It also is used to control whiteflies and mites on cotton and pear crops; livestock ticks, lice, and mange mites on beef and dairy cattle and swine; and ticks on dogs. Formulations include a wettable powder, emulsifiable concentrate, soluble concentrate/liquid, and impregnated collar (for dogs). Amitraz is applied as an airblast and concentrate spray to pears; by ground boom or aircraft to cotton; as a dip or low pressure hand spray to cattle and swine; and through collars on dogs.

Regulatory History

Amitraz was registered as a technical grade pesticide in 1975. EPA received an application for registration of an end-use product for apples and pears in 1976. Before a registration decision was made, however, in 1977, the pesticide went into Special Review (then called Rebuttable Presumption Against Registration or RPAR) because it met the risk criteria for cancer effects--it was shown to cause cancerous tumors in mouse lymph systems.

At the end of the RPAR process in 1979, EPA concluded that there was "weakly positive evidence" that amitraz is a possible human carcinogen. The Agency conditionally registered the pear use in 1980 since there were no alternatives for controlling pear psylla, but rejected the apple use since alternative pesticides were available.

Part of the conditional registration requirements were satisfied by submission of a new mouse cancer study, which the Agency's Cancer Assessment Group (CAG) evaluated in 1986. CAG classified amitraz as a Group C, possible human carcinogen, a classification that still stands. In 1986, EPA registered amitraz to control ticks on cattle and lice on hogs.

Human Health Assessment

Toxicity

In acute toxicity studies, amitraz is moderately toxic by the dermal route, and has been placed in Toxicity Category II (the second highest of four categories) for this effect. It is slightly toxic by the oral and inhalation routes, and has been placed in Toxicity Category III for these effects. Amitraz is non-irritating to the eyes and skin and has been placed in Toxicity Category IV for these effects. Amitraz does not cause skin sensitization or cholinesterase inhibition.

In a subchronic toxicity study using mice, amitraz caused reduced body weight gain and liver toxicity at the higher doses. A study using Beagle dogs resulted in liver, kidney, and central nervous system effects. A study using rabbits resulted in skin reactions, anorexia, hyperglycemia, degeneration of the testes, and effects to the lymph nodes and various organs. A chronic toxicity study using dogs resulted in central nervous system depression, increased blood glucose levels, and hypothermia.

In a carcinogenicity feeding study using mice, amitraz produced lymphoreticular tumors in females at the highest dose level. In another study using mice, amitraz produced liver and lung tumors at the highest level studied. Based on these studies, EPA has classified amitraz as a Group C (possible human) carcinogen. Carcinogenic effects were not observed in a study using rats.

Amitraz caused both maternal and developmental effects at the highest dose level in a developmental toxicity study using rabbits. A multi-generation reproduction study using rats is unacceptable and must be replaced by confirmatory data regarding developmental neurotoxicity and reproductive toxicity. Amitraz is not mutagenic.

Data from an acute neurotoxicity study and a metabolism study using volunteer human subjects were used to establish the NOEL and LOEL. Neurotoxic signs were observed in chronic oral toxicity studies in rodents,

as well as in subchronic and chronic oral toxicity studies in non-rodents (dogs). Related acute signs also were observed in human volunteers.

Amitraz is rapidly metabolized in several species, including humans, to form six metabolites which are excreted primarily in the urine. EPA has established a Reference Dose (RfD) for amitraz at 0.0025 mg/kg/day based on results of the chronic oral toxicity study in dogs.

Dietary Exposure

Tolerances or maximum residue limits are established for residues of amitraz in or on apples, pears, cotton seed, honey and comb, eggs, milk, and the meat, fat, and meat byproducts of cattle, hogs, horses, and poultry. These tolerances have been reassessed and most were found to be adequate. The 3.0 ppm tolerance for pears is being lowered to 2.0 ppm. Tolerances of 0.0 ppm for amitraz residues in apples and in horse fat, meat, and meat byproducts are being revoked. A tolerance for imported hops was proposed recently. No food/feed additive tolerances are established.

Adequate methods are available to enforce amitraz tolerances. Residues of amitraz and two of its metabolites are stable in several food commodities tested. Existing crop rotation restrictions for amitraz' cotton use are adequate.

A number of international Codex maximum residue limits (MRLs) are established for amitraz. However, compatibility between the Codex MRLs and U.S. tolerances cannot be achieved at present due to differences in tolerance definition/expression and analytical enforcement methods.

EPA assessed the chronic, carcinogenic, and acute dietary risks posed by amitraz. Most exposure to amitraz is attributed to one commodity, pears, which accounts for 58% of total exposure based on a 14-day preharvest interval (PHI).

EPA's chronic dietary risk assessment for amitraz indicates that with a 14-day PHI for pears, the Anticipated Residue Concentration (ARC) for the overall U.S. population is 1.1% of the Reference Dose (RfD) or amount believed not to cause adverse effects if consumed daily over a 70-year lifetime. The ARC for non-nursing infants less than one year old, the most highly exposed subgroup, is 4.5% of the RfD. In view of these low ARCs, it appears that chronic, non-cancer dietary risk from exposure to amitraz is minimal.

The upper bound cancer risk for the overall U.S. population is estimated at 1.4×10^{-6}, or 1.4 extra incidences of cancer per 1,000,000. This degree of risk is considered acceptable by the Agency.

Because neurotoxicity is the endpoint of concern, acute exposure and risk were calculated for all U.S. population subgroups. The Margins of Exposure (MOEs) are greater than 10 for all of these groups, which is considered acceptable.

Occupational and Residential Exposure

Workers may be exposed to amitraz during mixing, loading, and application of the pesticide, especially when liquid (emulsifiable concentrate) and wettable powder formulations are used. In addition, potential exposure risk exists for workers entering treated sites after application is complete, especially pear orchards and cotton fields.

A dermal and inhalation exposure assessment was conducted for the pear, cotton, and livestock uses of amitraz. Pear use is associated with the highest total exposure, followed by cotton use and, finally, livestock use. Pear handlers' exposure is highest when mixing/loading is accomplished using an open system and the application is by open cab/airblast. Post-application exposure is greatest during tasks requiring substantial dermal contact with treated foliage.

Handlers using amitraz to treat pear orchards, cotton fields, and livestock on a long-term basis may be at risk for carcinogenic effects. Pear use is associated with the highest cancer risk, followed by cotton use, and finally, livestock use. These handlers' upper bound cancer risks range from 2.7×10^{-8} to 1.2×10^{-5}; however, these risk levels are less than 1×10^{-4} which EPA finds acceptable.

In addition, certain handlers face neurotoxic risks from short-term exposure to amitraz. Margins of Exposure (MOEs) are less than 10, the margin generally considered acceptable, for three use scenarios in which wettable powder or liquid formulations of amitraz are mixed/loaded via open bag or open pour methods, and are applied to pear orchards or cotton crops using open cab/air blast or ground boom equipment.

Reentry workers involved on a long-term basis with post-application tasks requiring dermal contact with treated pear foliage also may be at risk for cancer effects, though these risks are considered acceptable. Pear and cotton reentry workers also encounter neurotoxicity risks from short-term exposure to amitraz residues. Post-application neurotoxicity risks resulting from use of amitraz on livestock and in pet collars are considered negligible.

Human Risk Assessment

Amitraz is of relatively low acute toxicity, but has been demonstrated to cause cancer in mice and is classified as a Group C "possible" human carcinogen. People may be exposed to residues of amitraz in pears and other foods. However, chronic exposure to amitraz in the diet is at a low level (only a small percent of the RfD), and is not a cause for concern at this time.

EPA is concerned that amitraz has the potential to cause reproductive, developmental, and neurological toxicity risks to the general population. The Agency also is concerned that handlers applying amitraz to pear orchards, cotton fields, and livestock on a long-term basis may be at risk for

cancer effects. Both handlers and reentry workers in pear orchards and cotton fields also may be at risk for acute neurotoxic effects.

To reduce risks of cancer and neurotoxicity to the general public and amitraz handlers, EPA is taking a number of risk mitigation measures described in greater detail below. For example, the Agency is requiring an increase in the interval between amitraz applications to pears; an increase in the restricted-entry interval (REI) for pears and cotton; and engineering controls for the pear and cotton uses. EPA also is specifying minimum, baseline personal protective equipment (PPE) for workers, and is requiring the registrant to submit a new combined developmental, neurological, and reproductive toxicity study as confirmatory data.

Environmental Assessment

Environmental Fate

The Agency has performed a comprehensive qualititative environmental fate assessment for parent amitraz. The review of available studies submitted indicates that parent amitraz rapidly degrades in the environment to form two primary transformaton products BTS 27271, BTS 27919 and a secondary transformation product BTS 24868. Because of its rapdi degration in the environment, parent amitraz is not expected to pose a concern for ground or surface waters. In contrast to parent amitraz, amitraz transformation products have been shown to be moderately persistent in aquatic and terrestrial environments and appear to be relative immobile in soil column and field dissipation studies. An accurate quantitative assessment of these products in ground and surface water, though, cannot be made until additonal mobility studies (batch equilibrium) are completed.

Ecological Effects

In acute toxicity studies, amitraz is slightly toxic to mallard ducks. BTS-27271 is moderately toxic and BTS-27919 is slightly toxic to the bobwhite quail. In subacute dietary studies, parent amitraz is practically nontoxic to the mallard duck and slightly toxic to the bobwhite quail. Its two primary degradates are practically nontoxic to the mallard duck. BTS-27271 is slightly toxic and BTS-27919 is practically nontoxic to the bobwhite quail. Parent amitraz causes effects on avian reproduction including eggshell cracking and reductions in the number of viable embryos, embryos that survive to hatching, and 14-day old survivors.

Parent amitraz is highly toxic to freshwater fish while BTS-27271 and BTS-27919 are slightly toxic to practically nontoxic, respectively. Parent amitraz also is very highly toxic to aquatic invertebrates while BTS-27271 and BTS-27919 are moderately toxic and practically nontoxic, respectively. Parent amitraz is highly toxic to oysters, moderately toxic to the sheepshead minnow, and slightly toxic to grass shrimp. BTS-27271 is slightly toxic and BTS-27919 is practically nontoxic to the sheepshead minnow and eastern oyster; both are moderately toxic to the mysid shrimp.

Amitraz is slightly toxic to small mammals on an acute oral basis, and is practically nontoxic to bees.

Ecological Effects Risk Assessment

Regarding acute risks, parent amitraz does not appear to pose a risk to endangered or non-endangered terrestrial organisms from either the cotton or pear uses. However, BTS-27271 may pose an acute hazard to birds since it is more acutely toxic and more persistent in the environment than the parent. Due to the presence of BTS-27271, use of amitraz on cotton and pears may pose an acute risk to endangered birds feeding on insects or short grass. Since parent amitraz dissipates rapidly in the environment, it should pose minimal acute risk to aquatic organisms.

Regarding chronic effects, use of amitraz on cotton and pears may adversely affect avian reproduction. In addition, endangered small mammals may be affected when amitraz is used on cotton. Because parent amitraz is short-lived in the environment, the potential for chronic effects to nontarget aquatic organisms is expected to be minimal. However, the chronic toxicity of amitraz degradates is of concern because they are more persistent in aquatic environments than parent amitraz. While the cotton use pattern does not appear to pose a chronic risk to aquatic organisms, the pear use pattern is of concern since it involves a higher application rate. Chronic adverse effects to aquatic invertebrates may be expected from the use of amitraz on pears.

Use of amitraz on cattle and swine is expected to result in minimal exposure to aquatic organisms.

Risk Mitigation

EPA has determined that amitraz is a valuable tool to control pear psylla, whiteflies, and mites. Considering the limited acreage involved in its use on pears and cotton, and the risk mitigation measures required, amitraz' risk potential is reduced.

The following risk mitigation measures, combined with generic worker protection labeling, should mitigate the unacceptable neurotoxicity risks to amitraz handlers:

- ***For the Pear Use:***

  Closed system mixing and loading;

  Applications from within an enclosed cab; and

  Minimal (baseline) personal protective equipment (PPE).

- ***For the Cotton Use:***

  Closed system mixing and loading;

  Mechanical flagging; and

  Minimal (baseline) PPE.

- ***For the Livestock Spray/Dip Use:***

  Minimal (baseline) PPE.

The following risk mitigation measures, combined with generic worker protection labeling, should mitigate the unacceptable neurotoxicity and cancer risks to post-application workers (those exposed to amitraz residues after application is complete).

- ***For the Pear Use:***

  Minimum of 35 days between applications; and

  Restricted-entry interval of 28 days (increased from 24 hours).

- ***For the Cotton Use:***

  Mechanical harvesting; and

  Restricted-entry interval of 48 hours (increased from 24 hours).

The following risk mitigation measures are required to reduce exposure to birds and small mammals:

- ***For the Pear Use:***

  Deletion of pre-bloom use; and

  Limit use to two applications per season.

Additional Data Required

EPA is requiring the following additional generic data for amitraz to confirm its regulatory assessments and conclusions:

- Life-Cycle Aquatic Invertebrate study for the pear use;
- Concurrent Dislodgeable Foliar Residue and Dermal Exposure data;
- Batch Equilibrium studies for BTS 27271 and BTS 27919;
- Droplet Size Spectrum and Field Drift studies;
- Dermal Exposure and Inhalation Exposure studies for spray/dip treatment of livestock.

An additional confirmatory study not part of the target database for amitraz is also required:

- Combined Developmental/Neurological/Reproduction Toxicity study in rats.

EPA also is requiring product-specific data including product chemistry and acute toxicity studies, as well as revised Confidential Statements of Formula (CSFs) and revised labeling for reregistration.

Product Labeling Changes Required

All amitraz end-use products must comply with EPA's current pesticide product labeling requirements and those summarized below. For a complete description of amitraz labeling requirements, please refer to the RED document.

Personal Protective Equipment (PPE) Requirements

<u>For Occupational Use Products</u> - Minimum/baseline PPE requirements are:

- ***For Pear Uses*** - Applicators and other handlers must wear:
  - Coveralls over long-sleeved shirt and long pants;

- Chemical-resistant footwear plus socks;
- Chemical-resistant gloves;
- Chemical-resistant headgear for overhead exposure;
- Chemical-resistant apron when cleaning equipment, mixing, or loading.

• ***For Cotton Uses*** - Mixers, loaders and others exposed to the concentrate must wear:

- Coveralls over long-sleeved shirt and long pants;
- Chemical-resistant footwear plus socks;
- Chemical-resistant gloves;
- Chemical-resistant headgear for overhead exposure;
- Chemical-resistant apron.

Applicators and other handlers exposed to the dilute must wear:

- Long-sleeved shirt and long pants;
- Chemical-resistant gloves;
- Shoes plus socks.

• ***For Livestock Spray or Dip Uses*** - Applicators and other handlers must wear:

- Coveralls over long-sleeved shirt and long pants;
- Chemical-resistant footwear plus socks;
- Chemical-resistant gloves;
- Chemical-resistant headgear for overhead exposure;
- Chemical-resistant apron when cleaning equipment, mixing, or loading.

• ***For Livestock Impregnated Collar Uses*** - Applicators and other handlers must wear:

- Long-sleeved shirt and long pants;
- Chemical-resistant gloves;
- Shoes plus socks.

For Homeowner Use Products - The Agency is not establishing minimum/baseline PPE for end-use products intended primarily for homeowner use. PPE requirements, if any, will be established based on the acute toxicity of the end-use product.

Entry Restrictions

For Occupational Use Products:

Restricted-Entry Interval (REI) - An REI is specified for uses within the scope of the Worker Protection Standard (WPS) for all end-use products.

• ***For Pear Uses*** - The REI is 28 days.

- ***For Cotton Uses*** - The REI requirement must state:

  "Do not enter of allow workers entry into the treated area during the restricted-entry interval of 48 hours. Note: mechanical harvesting may be performed during the restricted-entry interval ONLY if the harvesters will have no dermal or inhalation contact with treated surfaces, including both the treated foliage and the residues in airborne dusts generated by the mechanical harvesting. Crop advisors may enter if they are wearing full early entry personal protective equipment (PPE) as described below."

Early-Entry Personal Protective Equipment (PPE)

- ***For Pear and Cotton Uses*** - The PPE is:
  - Coveralls over long-sleeved shirt and long pants;
  - Chemical-resistant gloves;
  - Chemical-resistant footwear plus socks;
  - Chemical-resistant headgear for overhead exposures.

For Home Use Products - No restrictions are being established for products intended primarily for home use.

Other Labeling Requirements

Application Restrictions:

- "Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application."
- "For livestock spray or dip applications in enclosed areas: Apply only in well-ventilated areas."
- "For pear applications, allow a minimum of 35 days between applications."
- "Do not rotate to root and leafy vegetables for 44 days or to small grains and other crops for 60 days following application."

Engineering Controls:

- "When handlers use closed systems, enclosed cabs, or aircraft in a manner that meets the requirements listed in the Worker Protection Standard (WPS) for Agricultural Pesticides, ...the handler PPE requirements may be reduced or modified as specified in the WPS."

  "No human flaggers allowed. Mechanical flaggers are required."
- "Cotton must be harvested mechanically. No hand harvesting is allowed."
- "For pear uses, this product must be mixed and loaded using a closed system and the applicator must be inside an enclosed cab during application. The closed mixing/loading system and enclosed cab must meet the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides... When these engineering controls

are used correctly, the handler PPE requirements may be reduced or modified as specified in the WPS."

- "For cotton uses, this product must be mixed and loaded using a closed system (water-soluble bags are considered a closed mixing/loading system). The closed mixing/loading system must meet the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides..

When these engineering controls are used correctly, the handler PPE requirements may be reduced or modified as specified in the WPS."

User Safety Requirements:

"Follow manufacturer's instructions for cleaning/ maintaining PPE. If no such instructions exist for washables, use detergent and hot water. Keep and wash PPE separately from other laundry."

User Safety Recommendations:

- "Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet."
- "Users should remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing."
- "Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing."

Notification Requirement for WPS Uses:

- "Notify workers of the application by warning them orally and by posting warning signs at entrances to treated areas."

Fish and Wildlife Hazard Statements: Amitraz labels must bear the following Precautionary Statements under the subheading Environmental Hazards:

- Emulsifiable Concentrate and Wettable Powder Formulations:

  "This pesticide is toxic to fish and aquatic invertebrates. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean water mark. Drift and runoff from treated areas may be hazardous to aquatic organisms in adjacent sites. Do not contaminate water when disposing of equipment washwaters or rinsate."

- Products Other than Those Described Above, and the 10% A.I. Dairy Collar:

  "This pesticide is toxic to fish and aquatic invertebrates. Do not contaminate water when disposing of equipment washwaters or rinsate."

The MITAC WP label's Use Directions should be revised to include the following restrictions:

> "PEAR PSYLLA: Apply a maximum or 1 1/2 pounds MITAC WP per acre. Do not exceed 3 lbs of MITAC WP per acre per season. Do not make more than two applications of MITAC WP per season."

Regulatory Conclusion

The use of currently registered products containing amitraz in accordance with approved labeling will not pose unreasonable risks or adverse effects to humans or the environment. Therefore, all uses of these products are eligible for reregistration.

Amitraz products will be reregistered once the required confimatory generic data, product specific data, revised Confidential Statements of Formula (CSFs) and revised labeling are revised and accepted by EPA.

For More Information

EPA is requesting public comments on the Reregistration Eligibility Decision (RED) document for [name] during a 60-day time period, as announced in a Notice of Availability published in the Federal Register. To obtain a copy of the RED document or to submit written comments, please contact the Pesticide Docket, Public Response and Program Resources Branch, Field Operations Division (7506C), Office of Pesticide Programs (OPP), US EPA, Washington, DC 20460, telephone 703-305-5805.

Electronic copies of the RED and this fact sheet can be downloaded from the Pesticide Special Review and Reregistration Information System at 703-308-7224. They also are available on the Internet on EPA's gopher server, *GOPHER.EPA.GOV*, or using ftp on *FTP.EPA.GOV*, or using WWW (World Wide Web) on *WWW.EPA.GOV*.

Printed copies of the RED and fact sheet can be obtained from EPA's National Center for Environmental Publications and Information (EPA/NCEPI), PO Box 42419, Cincinnati, OH 45242-0419, telephone 513-489-8190, fax 513-489-8695.

Following the comment period, the [name] RED document also will be available from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161, telephone 703-487-4650.

For more information about EPA's pesticide reregistration program, the [name] RED, or reregistration of individual products containing [name], please contact the Special Review and Reregistration Division (7508W), OPP, US EPA, Washington, DC 20460, telephone 703-308-8000.

For information about the health effects of pesticides, or for assistance in recognizing and managing pesticide poisoning symptoms, please contact the National Pesticides Telecommunications Network (NPTN). Call toll-free 1-800-858-7378, between 9:30 am and 7:30 pm Eastern Standard Time, Monday through Friday.