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R.E.D. FACTS

Warfarin

Pesticide Reregistration

All pesticides sold or used 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 years ago be reregistered to ensure that they meet today's more stringent standards.

In evaluating pesticides for reregistration, EPA obtains from pesticide producers and reviews a complete set of studies showing the human health and environmental effects of each pesticide. The Agency imposes any regulatory controls that are needed to effectively manage each pesticide's risks. EPA then reregisters pesticides that can be used without posing undue hazards to human health or the environment.

When a pesticide is eligible for reregistration, EPA announces this and explains why in a Reregistration Eligibility Document, or RED. This fact sheet summarizes the information in the RED for warfarin and its sodium salt.

Warfarin

Warfarin and its sodium salt are registered for use in controlling commensal rodents (rats and mice) in and around homes, animal and agricultural premises, and commercial and industrial sites. Warfarin is a blood anticoagulant; its sodium salt is used medically to treat people with blood hypercoagulation problems. These compounds used as rodenticides cause internal bleeding and hemorrhaging which ultimately is fatal in rats and mice. They are applied as dry and liquid baits, and as a dust which acts as a tracking powder. All uses of warfarin and its sodium salt are eligible for reregistration.

Regulatory History

Warfarin and its sodium salt were first Federally registered for use in the United States as rodenticides in 1952. EPA issued a Registration Standard for these pesticides in August 1981, and required certain additional data. In April 1989, after reviewing the studies submitted, the Agency issued a "Draft Warfarin Reregistration Document" for public comment. Rather than issue a final version of that document, EPA has developed the RED on warfarin and its sodium salt.

Health Effects

All of EPA's toxicology data requirements for warfarin and its sodium salt have been satisfied. Because a great deal of information about warfarin's effects on people is available, animal toxicity studies were not needed or required.

Warfarin's toxicology and mechanism of action, as well as the methods for treating warfarin overdose in humans, are well understood. A synthetic analogue of Vitamin K, warfarin is a member of the coumarin family of blood anticoagulant chemicals. Its sodium salt has been used by doctors for years in treating people with hypercoagulation problems.

Because of its high degree of acute oral toxicity, technical warfarin has been placed in Toxicity Category I (the most toxic category). However, the dermal and inhalation toxicity of warfarin are not significant. Warfarin does not cause allergic or sensitization problems in people exposed to it orally or through injections.

Warfarin has been established clearly as a human teratogen, as it causes birth defects in the offspring of women receiving clinical doses of the compound during any trimester of pregnancy. (However, the amount of warfarin contained in the rodenticide bait products registered for use by homeowners is very low. A single ingestion of warfarin-treated bait by an adult female would not be likely to cause teratogenic effects.)

Routes Of Exposure

Through the Diet

Historically, none of warfarin's rodenticide uses were considered food or feed uses, so residue chemistry data were not required and tolerances (legal residue limits) or exemptions from the requirement of a tolerance were not established. Similarly, no international Codex Maximum Residue Levels were set.

More recently, EPA has decided that the use of warfarin tracking powder formulations in food and feed handling establishments has the potential to contaminate food and feed. Therefore, warfarin tracking powder products will have to bear new label language that limits the placement of tracking powder to inaccessible areas within such establishments. If this new label language is not adopted, residue chemistry data will be required and warfarin tolerances may have to be established.

During Application

Warfarin's use patterns do not trigger data requirements for applicator or reentry exposure studies.

Incidents

Poison control centers report thousands of incidents or suspected incidents of human exposure to anticoagulant rodenticides each year. However, accidental ingestion of warfarin seldom results in life-threatening or disabling symptoms. Pet exposure incidents also are reported (most involving dogs), and deaths occur in some of these animal exposure incidents.

These human and pet poisoning incidents point to the need for use of tamper-resistant bait stations when warfarin baits are applied in areas accessible to children and nontarget animals, as required by current product labeling.

Environmental Hazards

All the previously required studies needed to assess the environmental impact of warfarin and its sodium salt have been submitted to EPA and found acceptable, except two fish toxicity studies and one invertebrate toxicity study using the sodium salt. However, while these studies are being required, warfarin's sodium salt is eligible for reregistration, since its use in and around buildings is expected to result in little exposure to fish and aquatic invertebrates.

Environmental Fate

The environmental fate data requirements for warfarin and its sodium salt were waived. Based on the use patterns and label recommendations of warfarin rodenticide products, significant residues of concern are not expected to be introduced into the environment.

Ecological Effects

Information available to EPA on the acute avian toxicity of warfarin indicates that the pesticide is practically nontoxic to game birds. In subacute studies, warfarin is moderately toxic to practically nontoxic to upland game birds and waterfowl. Since use of warfarin and its sodium salt according to label directions and restrictions would not result in significant exposure of wild avian species, no additional avian testing is required.

Certain questions about the toxicity of warfarin to fish remain. However, EPA is not requiring a repeat of the aquatic toxicity studies already available because of warfarin's nonaquatic use pattern, its insolubility, and long field experience showing no potential hazards to aquatic organisms.

Studies are being required to assess the toxicity of the sodium salt of warfarin to fish, since the sodium salt is more soluble in water than warfarin. However, the sodium salt is eligible for reregistration even

while these studies are being developed, since significant exposure to fish is not expected to occur from currently registered uses.

The use of warfarin as a hand-placed bait limits the potential for any secondary exposure of nontarget animals. However, because of its high degree of mammalian toxicity and its use patterns, warfarin could adversely affect endangered or threatened species. The need for further requirements to protect endangered species will be explored in a forthcoming, formal consultation between EPA and the U.S. Fish and Wildlife Service.

Additional Data Required

The generic data base for warfarin has been reviewed and found to be substantially complete. Certain product chemistry studies must be replaced. Three acute toxicity tests on fish and aquatic invertebrates must be submitted to complete a risk assessment for the sodium salt.

Product Labeling Changes Required

The labels of end-use products containing warfarin and its sodium salt must bear the following types of use directions and precautions. Please see the RED itself for the exact language of this and other required labeling:

* The Restricted Use Pesticide classification still applies to, and must appear on, tracking powder products;

* A statement regarding teratogenicity, warning of warfarin's potential to cause birth defects, must be added to tracking powder products and concentrates used to prepare dry baits;

* To prevent contamination of food and feed, tracking powder products intended for use in food/feed handling establishments must limit placement of powder to concealed, inaccessible places.

* To protect children and nontarget animals, tracking powder products must bear a strong precautionary statement and new restrictions limiting placement of powder to locations not accessible to children, pets, domestic animals or nontarget wildlife;

* To protect children and nontarget animals, bait products must require use of tamper-resistant bait stations.

Regulatory Conclusion

* All registered rodenticides containing warfarin or its sodium salt can be used without causing unreasonable adverse effects in people or the environment. Therefore, all pesticide products containing warfarin or its sodium salt as the sole active ingredient are eligible for reregistration.

* EPA is requiring product chemistry data on warfarin to replace unacceptable studies, as well as fish and aquatic invertebrate data on the sodium salt, to complete a risk assessment. Due to its limited use

pattern, however, the sodium salt is eligible for reregistration while these studies are being developed.

* Pesticide tracking powder uses in food and feed handling establishments are now considered to be food uses. Therefore, to be eligible for reregistration, warfarin products must bear new label language limiting placement of tracking powder to inaccessible areas within such establishments.

* An endangered species consultation is being initiated to determine whether any special protective measures are needed.

* EPA will reregister individual products containing warfarin or its sodium salt once the appropriate generic data, product specific data and revised product labeling are submitted to and accepted by the Agency.

For More Information

EPA is requesting public comments on the Reregistration Eligibility Document for warfarin and its sodium salt 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 or to submit written comments, please contact the Public Response and Program Resources Branch, Field Operations Division (7506C), Office of Pesticide Programs, U.S. EPA, Washington, D.C. 20460, telephone 703-557-4436, or Fax 703-557-1884. Please note that after the comment period closes, the RED will be available from NTIS, at the address and telephone number below.

To obtain a copy of the August 1981 Registration Standard for warfarin and its sodium salt, please contact the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA. 22161, telephone 703-487-4650. Request document #PB82-140716.

For more information about warfarin and its sodium salt, or about EPA's pesticide reregistration program, please contact the Special Review and Reregistration Division (7508W), Office of Pesticide Programs, U.S. EPA, Washington, D.C. 20460, telephone 703-808-8000, or Fax 703-308-8005.

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, 24 hours a day, seven days a week, or Fax your inquiry to 806-743-3094.