



R.E.D. FACTS

Hydroxytetracycline Monohydrochloride and Oxytetracycline Calcium

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 and reviews a complete set of studies from pesticide producers, describing 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 hydroxytetracycline monohydrochloride and oxytetracycline calcium.

Use Profile

Oxytetracycline is an antibiotic drug produced by a micro-organism. Two related compounds, hydroxytetracycline monohydrochloride and oxytetracycline calcium, are registered as pesticides, for use in preventing the growth of or killing bacteria, fungi and mycoplasma-like organisms. These pesticides are used primarily to control fire blight of pears, pear decline, bacterial spot on peaches and nectarines, lethal yellowing of coconut palm, and lethal decline of pritchardia palm; and as an antifoulant added to marine paints to prevent the growth of barnacles.

Oxytetracycline calcium is formulated as a wettable powder and is applied as a foliar application using ground or aircraft equipment. Hydroxytetracycline monohydrochloride is formulated as a soluble concentrate/solid and is applied either by tree injection or as an additive to paints.

Regulatory History

Oxytetracycline has been available in the United States as a drug for therapeutic use in humans since 1950. It also is used in veterinary medicine to prevent infections in fowl, cattle and swine.

Oxytetracycline first was registered as a pesticide in 1974. EPA issued a Registration Standard for oxytetracycline, hydroxytetracycline monohydrochloride and oxytetracycline calcium in December 1988 (NTIS PB89-138556). The Agency assessed the data submitted in response to the Registration Standard in developing this RED.

At present, five end-use products are registered containing hydroxytetracycline monohydrochloride or oxytetracycline calcium as active ingredients. There are no active registrations for products containing oxytetracycline, the third active ingredient covered in the 1988 Registration Standard. For this reason, the RED does not apply to oxytetracycline per se, but only to the two derivatives.

Human Health Assessment

Toxicity

EPA has waived all toxicological data requirements for hydroxytetracycline monohydrochloride and oxytetracycline calcium. The toxicity of all three oxytetracyclines is expected to be similar, and data generated on one compound can be used to assess exposure/risks of the other two. Sufficient information is available on their effects in humans, supplemented by the laboratory animal studies summarized below.

Hydroxytetracycline monohydrochloride and oxytetracycline calcium are of low acute toxicity through the oral route of exposure, and have been placed in Toxicity Category IV indicating the lowest degree of toxicity for this effect. Subchronic feeding studies in rats showed no adverse effects. In two-year chronic toxicity studies in rats and dogs, the No Observed Effect Level was the highest dose tested.

Carcinogenicity studies show some equivocal evidence of cancer in male and female rats administered extremely high doses. However, EPA has classified oxytetracycline as a "Group D" carcinogen--one that is "not classifiable as to human carcinogenicity."

One developmental toxicity study in rats showed a high incidence of maternal deaths and fetotoxicity; however, excessive dose levels were used. No adverse effects were demonstrated in another similar study.

In humans administered oxytetracycline to treat infectious diseases caused by various microorganisms, a variety of adverse effects have been

reported including toxic and irritative effects, hypersensitivity and other biological effects.

Dietary Exposure

Tolerances or maximum residue limits are established for residues of oxytetracycline in or on pears at 0.35 ppm and peaches (including nectarines) at 0.1 ppm. Please see 40 CFR 180.337. Tolerances of 0.1 ppm in or on tomatoes and cherries are pending. The 1988 Registration Standard concluded that EPA had adequate data to support the registered pear and peach uses, but also concluded that the tolerance for peaches should be raised to 0.35 ppm.

Because oxytetracycline is used in veterinary medicine, tolerances for residues in animals have been established by FDA. Please see 21 CFR 520, 522, 524 and 558. No Codex Maximum Residue Limits (MRLs) and no Canadian or Mexican tolerances are established or proposed for oxytetracycline.

Occupational and Residential Exposure

When oxytetracycline calcium is applied to pears, peaches and nectarines using foliar application methods, pesticide mixers, loaders, and applicators can be exposed; fieldworkers also can be exposed, post-application. Worker exposure from trunk injection of hydroxytetracycline monohydrochloride to agricultural and ornamental trees is expected to be negligible.

Because the toxicity data for oxytetracycline do not meet EPA criteria that would trigger requirements for these studies, no occupational or residential exposure monitoring data are required. However, oxytetracycline has produced allergic reactions in some patients, and resistance to the drug could result from human exposure. Therefore, EPA will require labeling on pesticide products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium to lessen these potential risks.

Human Risk Assessment

The risks to people from dietary and occupational exposure to pesticides containing hydroxytetracycline monohydrochloride and oxytetracycline calcium are considered negligible. Chronic dietary risks posed by all food uses of these pesticides are well below the level that would reasonably cause concern.

During use and/or post-application, workers may be exposed to relatively greater amounts of these pesticides than the general public. However, label requirements will address concerns with potential allergic responses in oxytetracycline-sensitive people, as well as the potential development of resistance to oxytetracycline.

Environmental Assessment**Environmental Fate**

EPA has waived all environmental fate data requirements for hydroxytetracycline monohydrochloride and oxytetracycline calcium because of their limited pesticidal use patterns and the availability of published literature.

Ecological Effects

Acute toxicity studies in the published literature indicate that oxytetracycline is practically non-toxic to birds, fish, aquatic invertebrates and non-target insects such as honey bees.

Ecological Effects Risk Assessment

Due to their low toxicity and the low estimated environmental concentration resulting from their use as pesticides, it is unlikely that hydroxytetracycline monohydrochloride and oxytetracycline calcium pose undue risks to avian or aquatic organisms or honey bees.

Additional Data Required

EPA is requiring product-specific acute toxicity and product chemistry studies for reregistration of these pesticides.

Product Labeling Changes Required

The labels of all registered pesticide products containing hydroxytetracycline monohydrochloride and oxytetracycline calcium must comply with EPA's current pesticide labeling requirements. The Agency soon will issue a Pesticide Registration (PR) Notice providing instruction on changing labels of agricultural products in keeping with the Worker Protection Standard. That PR Notice also will apply to these products.

End-use products must bear the following additional or revised label statements in the Human Hazards section:

- Labels of products registered for use on agricultural crops by foliar application methods must include the restricted entry statement, "Entry into treated orchards (or "areas") is prohibited for 12 hours following application."
- Labels of products registered for use on agricultural crops by foliar applications must include the protective clothing statement, "Prolonged or frequently repeated exposure may cause allergic reactions in some individuals. Do not breathe dust or spray mist. Wear a MSHA/NIOSH approved TC-21C dust/mist filtering respirator, long sleeved shirt, pants, shoes, and chemical-resistant gloves while handling or applying this product. Wash thoroughly after handling or applying."

Regulatory Conclusion

Use of the active ingredients hydroxytetracycline monohydrochloride and oxytetracycline calcium in accordance with approved labeling will not result in unreasonable adverse effects to human health or the environment, and all registered pesticide products containing these active ingredients are

eligible for reregistration. These products will be reregistered once the required product-specific data and revised labeling are received and accepted by EPA.

For More Information

EPA is requesting public comments on the Reregistration Eligibility Document (RED) for hydroxytetracycline monohydrochloride and oxytetracycline calcium 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 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.

Following the comment period, the hydroxytetracycline monohydrochloride and oxytetracycline calcium RED 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 hydroxytetracycline monohydrochloride and oxytetracycline calcium or about EPA's pesticide reregistration program, please contact the Special Review and Reregistration Division (7508W), OPP, US EPA, Washington, DC 20460, telephone 703-308-8000. For information about reregistration of individual products containing these active ingredients, please contact Ben Chambliss, Product Manager, Registration Division (7505C), OPP, US EPA, Washington, DC 20460, telephone 703-305-6900.

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 8:00 am and 6:00 pm Central Time, Monday through Friday.