United States Environmental Protection Agency | Prevention, Pesticides And Toxic Substances (7508W) | EPA-738-F-97-010 April 1998

R.E.D. FACTS

Diphenylamine

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. To implement provisions of the Food Quality Protection Act of 1996, EPA considers the special sensitivity of infants and children to pesticides, as well as aggregate exposure of the public to pesticide residues from all sources, and the cumulative effects of pesticides and other compounds with common mechanisms of toxicity. The Agency develops any mitigation measures or regulatory controls needed to effectively reduce each pesticide's risks. EPA then reregisters pesticides that meet the safety standard of the FQPA and 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 2210, diphenylamine.

Use Profile

Diphenylamine (DPA) is a plant growth regulator used post-harvest to control storage scald on apples. This end use pattern for the current formulations has been classified as an indoor food use.

Formulations include an emulsifiable concentrate, a wettable powder, a soluble concentrate/liquid and a ready-to-use liquid.

DPA is applied by is applied by dipping, drenching or spraying.

Regulatory History

DPA was first registered as a pesticide in the U.S. in 1947. A January 1991 Data Call-In (DCI) required additional product chemistry, ecological, residue chemistry and exposure data. Currently, three products are registered. On August 3, 1996, the Food Quality Protection Act of 1996 (FQPA) was signed into law. FQPA amends both the Federal Food, Drug, and Cosmetic (FFDCA), and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The FQPA amendments were considered during this reregistration decision.

Human Health Assessment

Toxicity

In studies using laboratory animals, DPA generally has been shown to be slightly toxic by the oral, dermal, and inhalation routes and has been placed in Toxicity Category III (second lowest of four categories) for these effects.

In a chronic feeding study using beagle dogs, diphenylamine caused alterations in clinical chemistry. For chronic toxicity, a No Observed Effect Level was not achieved, however, a Lowest Observed Effect Level was based on the alterations in clinical chemistry parameters.

DPA has been evaluated for potential carcinogenic activity in mice and rats. It is classified as "Not Likely" in reference to carcinogenicity based lack of evidence. However, diphenylnitrosamine (an impurity of technical grade diphenylamine), is classified as a probable human carcinogen based on increased incidence of bladder tumors in male and female rats, reticulum cell sarcomas in mice, and for structural relationship to carcinogenic nitrosamines. The dietary intake cancer risk for diphenylnitrosamine is 2.8×10^{-11} mg/kg/day, well below the Agency's level of concern for nitrosamine.

There was no developmental toxicity observed in either the rat or rabbit developmental studies at any dose tested.

Dietary Exposure

People may be exposed to residues of DPA through the diet. Tolerances or maximum residue limits have been established for post-harvest application on apples at 10.0 ppm and in meat and milk at 0 ppm (please see 40 CFR 180.190). EPA has reassessed the DPA tolerances and found that tolerances for residues in meat and milk, both currently 0 ppm, should be increased. Separate tolerances of 0.01 ppm should be established for residues in milk and meat, fat, and meat by-products (excluding liver) of cattle, goats, horses, and sheep. Separate tolerances of 0.1 ppm should be established for residues in liver of cattle, goats, horses, and sheep. Available data also indicate that a tolerance of 30 ppm should be established for DPA residues in wet apple pomace.

The Codex Alimentarius Commission has established a maximum residue limit (MRL) for DPA residues in apples (see Guide to Codex Maximum Limits For Pesticides Residues, Part A.1-58, 1995). The Codex residue definition and the U.S. tolerance expression for DPA are currently compatible, since each includes only the parent, DPA. However, the Codex MRL (CXL) for DPA on apples is 5 mg/kg compared to the 10 ppm U.S. tolerance for apples. Since available residue data, based on the current U.S. use pattern, indicate that the 10 ppm tolerance is appropriate, harmonization of the Codex MRL and U.S. tolerance is not possible at the present time.

EPA has assessed the dietary risk posed by DPA. The Anticipated Residue Concentration (ARC) for the overall U.S. population represents 2.27 % of the Reference Dose (RfD), or amount believed not to cause adverse effects if consumed daily over a 70-year lifetime. The most sensitive subpopulation, non-nursing infants less than one year old, has an ARC which represents 20.8 % of the RfD. This low fraction of the allowable RfD is considered to be an acceptable dietary exposure risk.

Occupational and Residential Exposure

Based on current use patterns, handlers (mixers, loaders, and applicators) may be exposed to DPA during and after normal use in agricultural and other settings. Specifically, pesticide handlers may be exposed to DPA from using it as a drench on apples following harvest. Exposure data for this use pattern are not available; consequently, the Agency had to rely on surrogate data and adjust it to fit the exposure scenario. Margins of Exposure (MOEs) were calculated for minimum and maximum label rates. MOEs were adequate when applicators were assumed to wear a single layer of clothing (long sleeved shirt and long pants) and mixer/loaders were assumed to wear chemical resistant gloves and a single layer of clothing.

Human Risk Assessment

DPA generally is of low acute toxicity and has been classified as “Not Likely “ as a human carcinogen. An impurity of DPA, diphenylnitrosamine, is classified as a “probable human carcinogen”, however the cancer risks for dietary intake and worker exposure fall below the Agency’s level of concern. Food crop use consist of post-harvest use on apples. Dietary exposure to DPA residues in foods is within acceptable limits.

Of greater potential concern is the risk posed to DPA handlers, particularly mixers/loaders/applicators, and workers who come into contact with treated applescrop following application of this pesticide. Exposure and risk to workers will be mitigated by the use of personal protective

equipment (PPE) required by the Worker Protection Standard, supplemented by engineering controls as required by this RED. Applicators must wear a single layer of clothing (long sleeved shirt and long pants) and mixer/loaders must wear chemical resistant gloves and a single layer of clothing. Persons, who during the application remain inside the truck cab with the windows and doors closed need not wear the required PPE. If, however, drivers exit the truck cab in or immediately adjacent to the treatment area during the application, they must wear the required PPE. Post-application reentry workers will not be required to observe a Restricted Entry Interval, however, persons manually handling treated apples or apple containers that are still wet with DPA drench, must wear the same PPE required for applicators/handlers.

EPA conducted additional risk analyses using available data in response to the new FQPA requirements. Nothing in the available toxicity database suggests special sensitivity of infants and children to DPA. Therefore, the Agency concludes that an additional uncertainty factor is not warranted. Based on the limited use pattern for DPA as a post-harvest drench on apples and the absence of detections in the Agency's surface water and groundwater databases, dietary exposure from drinking water is expected to be negligible. Since there are no residential or non-occupational DPA uses and dietary exposure from drinking water is expected to be negligible, the only aggregate concern is dietary. All chronic dietary exposures fall below 100 % of the RfD, and there is no aggregate chronic dietary risk concern for DPA.

EPA does not have, at this time, available data to determine whether DPA has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this reregistration decision, EPA has not assumed that DPA has a common mechanism of toxicity with other substances.

Environmental Assessment

Environmental Fate

Since this is considered an indoor food end-use chemical, only hydrolysis data are required. Available data indicate that DPA is stable towards hydrolysis at pH's 5, 7, and 9. DPA has a moderate solubility in water (39.4 ppm), a relatively high octanol/water partition coefficient (K_{ow}=3,860), and a high vapor pressure (6.39×10^{-4} torr). The high rate of aqueous photolysis and the susceptibility of the chemical in aerobic environments indicate that if DPA were to reach surface waters, it would be short lived.

Ecological Effects

DPA is moderately toxic to fish and aquatic invertebrates. It is practically non-toxic to avian species on an acute and subacute basis.

Ecological Effects Risk Assessment

This is an indoor food use chemical and the Agency does not conduct risk assessments for indoor use chemicals. However, given the the limited volume and the pattern of diphenylamine use, the likelihood of adverse effects on ecological systems is considered to be minimal. Discharge of effluent containing DPA for manufacturing use is regulated by National Pollutant Discharge Elimination System (NPDES) permits.

Risk Mitigation

To lessen the worker risks posed by diphenylamine, EPA is requiring the following risk mitigation measures.

- For mixer/loaders: chemical resistant gloves and single layer body covering (long sleeved shirt and long pants).
- For applicators/drenchers: single layer body covering (long sleeved shirt and long pants).
- Labeling changes to increase user safety (see **Product Labeling Changes Required** section below)

Additional Data Required

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

- **in vivo/in vitro** Rat Hepatocyte Unscheduled DNA Synthesis Assay Guideline 84-4.
- Subchronic Dog study Guideline 82-1
- Deposition Study
- UV/Visible Absorption Study Guideline 830.7050
- Registrant must either certify that the beginning materials and manufacturing process for the technical grade active ingredient have not changed, or must submit an updated product chemistry package.
- An independent laboratory validation study if the data collection method for meat and milk is to be used as an enforcement method.

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

Product Labeling

All diphenylamine end-use products must comply with EPA's current pesticide product labeling requirements and with the following:

Changes Required

Environmental Hazards

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

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."

User Safety Requirements

"Discard clothing or other absorbent materials that may have been drenched or heavily contaminated with this product's concentrate. Do not reuse them."

"Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions 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."

Regulatory Conclusion

The use of currently registered products containing diphenylamine 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.

Diphenylamine products will be reregistered once the required product-specific data, revised Confidential Statements of Formula, and revised labeling are received and accepted by EPA.

For More Information

EPA is requesting public comments on the Reregistration Eligibility Decision (RED) document for diphenylamine 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 Information and Records Integrity Branch, Information Resources and Services Division (7502C), Office of Pesticide Programs (OPP), US EPA, Washington, DC 20460, telephone 703-305-5805.

Electronic copies of the RED and this fact sheet are available on the Internet. See http://www.epa.gov/REDs.

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 45242-2419, telephone 1-800-490-9198; fax 513-489-8695.

Following the comment period, the diphenylamine 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 diphenylamine RED, or reregistration of individual products containing diphenylamine, 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, from 6:30 am to 4:30 pm Pacific Time, or 9:30 am to 7:30 pm Eastern Standard Time, seven days a week.