



R.E.D. FACTS

Vinclozolin

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 2740, vinclozolin.

Use Profile

Vinclozolin is a fungicide used to control various diseases on raspberries, chicory grown for Belgian endive, lettuce, kiwi, canola, snap beans, dry bulb onions, ornamentals, and turf. Import tolerances have been established to permit importation of vinclozolin-treated cucumbers, sweet peppers and wine. Vinclozolin is formulated as a dry flowable and extruded granular which may be applied with aerial, chemigation, or ground equipment (broadcast, band, or soil drench); as a dip treatment on ornamental bulbs and corms, cut flowers, rose budwood, or nursery stock; and with thermal foggers in greenhouses.

**Regulatory
History**

Vinclozolin has been registered in the United States since 1981 for use as a fungicide. A Data Call-In (DCI) was issued in 1991 for vinclozolin requiring the submission of additional data on product and residue chemistry, toxicity, environmental fate, and ecological effects. Subsequent DCIs were issued in 1995 and 1996 requiring additional environmental fate and ecological toxicity studies. Also, the Agricultural Data Call-In (AGDCI) was issued in 1995, which required data to help estimate postapplication occupational exposure. The Reregistration Eligibility Decision (RED) reflects a reassessment of all data which were submitted in response to the DCIs.

In April 1997, the risks from all uses were reevaluated under the Food Quality Protection Act (FQPA) when a new use for this chemical was proposed by BASF Corporation (succulent beans). The estimated dietary cancer risks were above the level generally regarded as negligible. As a result, previously registered uses were voluntarily canceled by the registrant and the Agency has revoked the related tolerances, namely for tomatoes, plums, prunes, and grapes (except wine grapes). To reduce exposure to children, residential uses of vinclozolin were deleted and turf and ornamental applications limited to commercial and industrial sites. Following this mitigation, a three-year time-limited tolerance was established for succulent beans in 1997.

In June 1998, after EPA's decision to retain the FQPA safety factor of 10X, BASF requested voluntary cancellation of its vinclozolin uses on stone fruits and strawberries to reduce dietary exposure to vinclozolin residues. The Agency published a Federal Register notice announcing the use deletions on July 30, 1998. At that time, BASF also requested use rate reductions for turf and agreed to phase out its liquid formulations, as well as phase-in water soluble packaging for the remaining formulations. Revocation of the stone fruit and strawberry tolerances will be proposed in an upcoming Federal Register notice.

On July 18, 2000 the Agency established 3 year time-limited tolerances for vinclozolin and its metabolites containing the 3,5-DCA moiety on succulent beans, canola, eggs, milk, and the meat, fat, and meat byproducts of cattle, goats, hogs, horses and sheep. In order to mitigate risk associated with the added uses, EPA accepted a proposal submitted by the registrant which includes the following actions to occur over the next 4 years: A phase out of all domestic food uses of vinclozolin except for use on canola, and revocation of all import tolerances except for wine grapes. The Agency published the proposed use deletions in the Federal Register

for public comment on September 20, 2000 (65 FR 56894, FRL-6744-2). On September 18, 2000, EPA received objections to the newly-issued tolerances on succulent beans and canola. Once EPA finalizes its response to the objections, it will amend its reregistration and reassessment decisions, if any such amendment is necessary.

In addition to the use cancellations, BASF also initiated measures at that time to mitigate risks identified through the reregistration process including cancellation of the use on ornamental plants due to postapplication risk concerns and new restrictions on turf use based on non-dietary risks to children. Use on sod farm turf was prohibited (except for transplant onto golf courses) and application to turf was restricted to golf courses and industrial sites.

In an effort to promote transparency and public acceptance in regulatory decision making, the Agency, in cooperation with the U.S. Department of Agriculture (USDA), is working to modify the reregistration process. Until a final process is established, an interim process is being used to provide opportunities for stakeholders to ask questions and provide input on risk assessments and risk mitigation strategies, via conference calls and other formats. Consistent with this process, a conference call was conducted on June 1, 2000 with EPA, USDA, the registrant, and other stakeholders (e.g., growers, commodity groups, land grant universities) to discuss the basis of the calculated risks of vinclozolin, the Agency's risk concerns, and the registrant's voluntary cancellation and phase-out proposal. Also, a close-out conference call was conducted on September 25, 2000 with many of the same participants from the June 1st conference call, to discuss the additional risk management decisions and resultant changes to the vinclozolin labels.

Human Health Toxicity

Assessment

Vinclozolin generally has been shown to have low acute oral/dermal/inhalation toxicity. Vinclozolin is not an irritant to the eye/skin but can act as a skin sensitizer. The principal toxic effects induced by vinclozolin and/or its metabolites are related to its antiandrogenic activity. Androgens are the principal male steroid hormones, such as testosterone, which stimulate the development and maintenance of the male reproductive system and secondary sex characteristics. Studies show that vinclozolin may have minimal antiandrogenic activity at relevant dose levels but that at least two vinclozolin metabolites occur in mammals, plants, and soil and are responsible for much of the antiandrogenic activity attributable to vinclozolin. Vinclozolin exerts its effects most dramatically during the developmental stages of

animals ultimately resulting in reproductive effects. At low dose levels in rats (>3 mg/kg/day), the most androgen sensitive effects are noted, such as decreased prostate weight, weight reduction in other sex organs, nipple/areolas development, and decreased ano-genital distance in male rats. At higher dose levels, the reduction in male sex organ weight is exacerbated, and sex organ malformations are seen, such as reduced penis size, ectopic testes, vaginal pouches, hypospadias, and additional ambiguities of the urogenital system. In some studies reduced fertility from the hypospadias, delayed puberty and kidney stones were noted. Since the androgen receptor is widely conserved across species lines, anti-androgenic effects would be expected in humans. However, the human consequence of many of the low dose effects in male rats such as reduced ano-genital distance, areola and nipple development, and reduced prostate weight is unknown. Vinclozolin and/or its metabolites cause Leydig cell (testicular) tumors in rats. There is also evidence in the published literature that vinclozolin may affect the development and function of the neuroendocrine system. The Agency has also determined that vinclozolin's terminal metabolite, 3,5-dichloroaniline (3,5-DCA), should be regulated based on potential carcinogenic concerns. 3,5-DCA is a common metabolite of two related fungicides, iprodione and procymidone.

Dietary Exposure

People may be exposed to residues of vinclozolin and its metabolites containing the 3,5-dichloroaniline moiety through the diet. Tolerances or maximum residue limits have been established in 40 CFR §180.380 for: succulent beans; Belgian endive tops; cucumbers; wine grapes; kiwifruit; leaf and head lettuce; dry bulb onions; bell peppers; raspberries; stonefruits except plums/fresh prunes; strawberries; canola; milk; cattle fat, meat, and meat byproduct; eggs; poultry fat, meat and meat byproduct; sheep fat, meat and meat byproduct; goat fat, meat and meat byproduct; hog fat, meat and meat byproduct; horses fat, meat, and meat byproduct.

The following tolerances do not need to be amended at this time: wine grapes, canola and the animal products associated with canola in feed. All other tolerances will be proposed for revocation within the next few years after use cancellation.

Risk From Food

For vinclozolin, acute, chronic and carcinogenic dietary risk from food is not of concern. Cancer dietary risk from 3,5-DCA in food is also not of concern ($<1 \times 10^{-6}$).

Risk From Food + Drinking Water

Model estimates of potential drinking water exposure from ground and surface water sources are not of concern for vinclozolin. Based on screening-level models, carcinogenic dietary risk from vinclozolin-derived 3,5-DCA in drinking water is above the Agency's level of concern. 3,5-DCA exhibits fate properties (high mobility and persistence) of pesticides which may be found in ground and surface waters.

Risk From Non-dietary Exposure

There are no vinclozolin pesticide products registered for use by homeowners. Vinclozolin can, however, be occupationally used in a manner that may lead to post-application exposures to golfers playing on treated golf courses and homeowners and their families coming into contact with or playing on sod which has been previously treated on a sod farm. No chronic exposures or exposures of sufficient duration to cause cancer were identified. The short-/intermediate-term risk to golfers of all age ranges is below the Agency's level of concern. Risks to toddlers playing on treated sod fall beneath the Agency's level of concern 24 days after application. To mitigate the unacceptable risk resulting from exposure before the 24 day period has elapsed, the registrant has submitted label amendments deleting use on sod farms (except for transplant onto golf courses), and has begun the immediate restickering of all product in the channels of trade to require a 24 day period before sod can be harvested. Although the Agency's level of concern would have been exceeded, the risk reduction measures implemented by the registrant immediately reduce risk such that it is below the Agency's level of concern.

Aggregate Risk

The short- and intermediate-term aggregate risk assessment includes exposure from nonoccupational settings in addition to the dietary (food and water) exposure. When aggregating food and water exposure with toddler's exposure to treated sod, the sod pre-harvest interval (PHI) of 24 days results in short- and intermediate-term aggregate risk below the Agency's level of concern. Food, water, and adult/child golfer exposure do not exceed the Agency's level of concern when aggregated.

EPA also considered the relative contribution of vinclozolin-, iprodione- and procymidone-derived 3,5-DCA. The aggregate food-only cancer risk associated

with 3,5-DCA derived from **all three** of these imide fungicides is not of concern ($<1 \times 10^{-6}$). However, the vinclozolin- and iprodione-derived 3,5-DCA EECs alone exceed the carcinogenic aggregate DWLOC indicating a potential for concern.

Occupational Risk

Workers can be exposed to vinclozolin during handler activities such as mixing, loading, applying and flagging, or by re-entering treated sites. Occupational risk estimates were not considered for onions, raspberries and ornamentals because the registrant has requested immediate cancellation. Only one handler scenario, applying with an airblast sprayer (kiwi), indicates the need for an increase in protection beyond current label requirements. Lettuce, kiwi and turf pose a postapplication risk concern, i.e., the Agency does not believe that the currently labeled REIs are of sufficient duration to protect workers from exposure to residues of concern.

FQPA Considerations

EPA has determined that the established tolerances for vinclozolin, with amendments and changes as specified in this document, meet the safety standards under the FQPA amendments to section 408(b)(2)(C) of the FFDCA, that there is a reasonable certainty of no harm for infants and children. The safety determination for infants and children takes into account the possibility of increased dietary exposure due to the specific consumption patterns of infants and children, as well as the possibility of increased susceptibility to the toxic effects of vinclozolin residues in this population subgroup.

In determining whether infants and children are particularly susceptible to toxic effects from vinclozolin residues, EPA considered the completeness of the database for developmental and reproductive effects, the nature of the effects observed, and other information. For vinclozolin, the FQPA safety factor of 10 was **retained** because: (1) there is evidence of increased susceptibility to offspring following *in utero* exposure to vinclozolin in the prenatal developmental toxicity study in rats; and (2) a developmental neurotoxicity study in rats with an expanded protocol is required for vinclozolin due to concern for the antiandrogenic properties of vinclozolin and its metabolites.

In accordance with the Food Quality Protection Act (FQPA), the Agency is examining whether, and to what extent, some or all members of the imide group of

the dicarboximide class of fungicides, which include vinclozolin, iprodione and procymidone, share a common mechanism of toxicity. Although there are data suggesting that these dicarboximide fungicides induce some of the same antiandrogenic effects, the mechanism by which they cause these toxic effects has not been adequately evaluated. As a result, the Agency has not determined if it would be appropriate to include them in a cumulative risk assessment. In addition, there may be other compounds outside of this class of fungicides that may also be considered antiandrogenic. Therefore, for the purposes of this risk assessment, the Agency has assumed that vinclozolin does not share a common mechanism of toxicity with the dicarboximide fungicides or other possible antiandrogens.

Environmental Assessment

Environmental Fate

Vinclozolin dissipates in the environment by microbial-mediated hydrolysis, soil metabolism, abiotic degradation, and transport with water. Metabolite B is a common degradate of hydrolysis, soil metabolism, and photolysis. The other principal degradation products of vinclozolin are 3,5-dichloroaniline and metabolite E, which appears to be a degradation product of parent and metabolite B. Metabolite E degrades to 3,5-dichloroaniline. Experimental evidence has shown 3,5-DCA to be resistant to degradation processes.

Vinclozolin and its principal degradates are potentially very mobile to slightly mobile in soil. Metabolites B, E and 3,5-DCA may be transported with water through the soil profile or with surface runoff. Residues are likely to be most mobile in sandy soils low in organic matter.

In terrestrial field dissipation studies, vinclozolin dissipated with half-lives of 34 to 94 days. Half-lives for total residues (vinclozolin plus its dichloroaniline-containing metabolites) were 179 to >1000 days. Persistence of total residues appeared to be attributable to the resistance of 3,5-DCA to degradation and to the inclusion of soil-bound residues in the data. Intermittent detections of residues were reported at soil depths of 12-18, 18-24, and 24-30 inches. 3,5-DCA was detected regularly deeper than 6 inches. Residues may accumulate and be available for rotational crop uptake. Vinclozolin has a low potential to bioaccumulate in fish.

Ecological Effects

Results indicate that vinclozolin is practically nontoxic to birds, mammals, and honey bees on an acute basis. Vinclozolin is moderately toxic to freshwater/estuarine fish and freshwater/estuarine invertebrates on an acute basis.

Vinclozolin and/or its metabolites have been shown *in vitro* and *in vivo* to be potent mammalian anti-androgenic compounds, inhibiting androgen receptor binding and gene expression. In addition to the adverse effects observed in the male fetuses in the mammalian species, endocrine disruption effects in birds include reduced egg laying, reduced fertility rate, and reduced hatching successes.

Ecological Effects Risk Assessment

The risk assessment for vinclozolin indicates low levels of acute risk to wildlife. The Agency's level of concern has been exceeded for chronic effects to avian species for most use sites. The registrant has already requested the phase-out of all uses except turf and canola. For canola, all avian chronic RQs are below the level of concern assuming average use rates. For turfgrass, the highest RQ is 2.7, which is slightly above the LOC of 1.0. The registrant has undertaken several mitigation measures on turf during the last few years which reduce risk to nontarget species on turf. Chronic risk to aquatic organisms has not been assessed due to lack of data.

Risk Mitigation

BASF, the vinclozolin registrant, has already requested changes to its vinclozolin registrations, including the phase-out of most uses and new restrictions on turf use. In addition to these measures, EPA is recommending the following risk mitigation measures to lessen the risks posed by vinclozolin.

- To address drinking water concerns, the registrants of vinclozolin and iprodione should initiate a surface and ground water monitoring program. Ground water and surface water advisory language is warranted on vinclozolin product labels.
- Only the extruded granular formulation packaged in water soluble bags is eligible for reregistration.
- Labels should specify enclosed cabs for airblast applicators.
- An advisory statement should be added informing crop advisors to wear early entry PPE when entering treated sites during the REI.
- A label statement should be added to the 24(c) label for chicory informing employers of chicory root workers that they must ensure that workers in the chicory root spray area wear the PPE required for applicators. Employers must provide, clean, and maintain all PPE.
- The REI for kiwi should be increased from 24 hours to 6 days. The REI on sod farm turf should be increased from 12 hours to 5 days. The REI for lettuce should be increased from 12 hours to 7 days. An exception to the 7 day REI may be established for applications to lettuce taking place within

35 days of planting. Under this exception, workers may enter to perform some tasks after 24 hours.

- A double notification statement must be included on labels. Workers will be notified of applications orally and by posting.

Additional Data The following additional generic studies for vinclozolin are necessary to confirm its regulatory assessments and conclusions:

The Agency has determined that a developmental neurotoxicity (DNT) study is warranted; however, the kinds of perturbations likely to occur with androgen/estrogen disruptor cannot be identified by the standard guideline DNT study. Consequently, the DNT study will be due 3 years after the Agency determines the protocol necessary to assess the relevant endpoints.

In addition to the water monitoring data, environmental fate studies will be requested in order to better understand the persistence and mobility of the degradates. Some ecotoxicity studies were required in a previous DCI and are still outstanding. The registrant is in the process of submitting the studies.

Product Labeling Changes All vinclozolin end-use products should comply with EPA's current pesticide product labeling requirements and with the label changes outlined in the RED document.

Regulatory Conclusion The use of currently registered products containing vinclozolin 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. This decision takes into consideration the registrant's request to cancel most currently registered uses of vinclozolin.

Vinclozolin 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 vinclozolin 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 Service Center for Environmental Publications (EPA/NSCEP), PO Box 42419, Cincinnati, OH 45242-2419, telephone 1-800-490-9198; fax 513-489-8695. Following the comment period, the vinclozolin RED document also will be available from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161, telephone 1-800-553-6847, or 703-605-6000.

For more information about EPA's pesticide reregistration program, the vinclozolin RED, or reregistration of individual products containing vinclozolin, please contact the Special Review and Reregistration Division (7508C), 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 Pesticide 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. Their Internet address is **ace.orst.edu/info/nptn**.