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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

5/12/00

MEMORANDUM

SUBJECT: **Vinclozolin.** Revised Human Health Risk Assessment (Chemical I.D. No. 113201, DP Barcode D265863)

FROM: William J. Hazel, Ph.D., Chemist
Reregistration Branch 1
Health Effects Division (7509C)

THROUGH: Whang Phang, Ph.D., Branch Senior Scientist
Reregistration Branch 1
Health Effects Division (7509C)

TO: Deanna Scher/Susan Lewis
Reregistration Branch 1
Special Review and Reregistration Division (7508C)

Attached is the revised human health risk assessment for **Vinclozolin** prepared by Reregistration Branch 1 of the Health Effects Division (HED) of EPA's Office of Pesticide Programs. This document supersedes the 2/14/00 Preliminary Human Health Risk Assessment by incorporating: (i) selection of a toxicity endpoint and dose that is sufficiently protective to encompass all of the antiandrogenic effects contributable to vinclozolin whether they be developmental/reproductive or antiandrogen-mediated carcinogenesis; (ii) recent selection of a more sensitive dose and endpoint to be used in a threshold (nonlinear) carcinogenic dietary risk assessment; (iii) reassessment of the FQPA Safety Factors; (iv) reconsideration of aggregate risk; (v) updated figures from the Biological and Economic Analysis Division on percent wine grapes/wine treated and imported; and (vi) dietary risk estimates for various crop combination scenarios being

considered by BASF to mitigate dietary risk. The vinclozolin team in HED is comprised of J. Dawson (occupational and residential assessment), F. Fort (dietary exposure/risk), D. Anderson and L. Mendez (toxicology), and W. Hazel (risk assessor).

Attachment: 44 pp.

cc: F. Fort (HED), J. Dawson (HED), W. Hazel (HED), L. Mendez (HED), D. Anderson (HED), D. Young (EFED), List A File, SF, RF
RDI: W. Phang: 5/12/00
7509C:CM2:722J:wjh:RRB1:W.J.Hazel:305-7677:5/11/00

INTRODUCTION

This revised human health risk assessment for vinclozolin incorporates the most recent deliberations on the hazard components of risk, use and usage information, exposure refinements, and risk assessment techniques and policies. This assessment has been conducted in accordance with current interpretations of the Food Quality Protection Act (FQPA) of August 3, 1996. Probabilistic assessment of acute dietary risks has been conducted using the DEEM™ Software and refined grape usage (percent crop imported and treated) data. Chronic dietary risks were calculated using DEEM™ and recent usage data. Overall antiandrogenic dietary risk was calculated using a toxicity endpoint and dose that is sufficiently protective to encompass all of the antiandrogenic effects attributable to vinclozolin whether they be developmental/reproductive or antiandrogen-mediated carcinogenesis. In this document, a nonlinear (MOE) approach and a linear (Q_1^*) approach to calculate carcinogenic dietary risk are also used to compare with the overall antiandrogenic effects risk which is protective of cancer in all populations. An MOE approach was used for dietary cancer risk assessment because the available toxicity data indicate that vinclozolin is an endocrine-disrupting chemical that induces a hormonally-mediated increase in Leydig cell tumors in rats in what appears to be a threshold response. A policy has not yet been established regarding an appropriate Agency level of concern for cancer risk using the MOE approach. Cancer risks were also calculated applying a Q_1^* although there was no evidence of a linear, genotoxic mode of tumor induction. Thus, a comparison of the overall antiandrogenic effects to risks calculated using the more conventional risk assessment approaches has been made to permit better informed risk management decisions. The terminal metabolite of vinclozolin, 3,5-dichloroaniline (3,5-DCA), is considered to have a genotoxic mode of tumor induction based on its similarity to p-chloroaniline, the Q_1^* of which was used in a linear cancer risk assessment; 3,5-DCA is a common metabolite of two related fungicides, iprodione and procymidone. Occupational risks were calculated to reflect the following: use of chemical-specific human exposure and residue dissipation studies, selection of the most sensitive hazard endpoint and dose for short- and intermediate-term exposure durations, and calculation of occupational cancer risk using the Q_1^* for greenhouse scenarios. It has been determined that certain turf uses may result in residential exposure thus necessitating calculation of residential postapplication risk figures. An assessment of the potential exposure to vinclozolin and its degradates through drinking water was conducted by EFED. Aggregate acute, chronic (noncancer), short-term, intermediate-term, and carcinogenic risks resulting from exposure to vinclozolin via relevant dietary (food and drinking water) and residential routes of exposure were assessed.

EXECUTIVE SUMMARY

The Health Effects Division (HED) of EPA's Office of Pesticide Programs, in this revised human health risk assessment for vinclozolin, has reevaluated certain hazard and dietary exposure components. This assessment supersedes the 2/14/00 Preliminary Human Health Risk Assessment.

Vinclozolin [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedione] is a dicarboximide fungicide registered in the United States for foliar use on caneberries, Belgian endive, lettuce, kiwi, and dry bulb onions. Tolerances are expressed in terms of vinclozolin and its metabolites containing the 3,5-dichloroaniline moiety (40 CFR 180.380). A tolerance for vinclozolin residues in or on succulent beans expired 10/1/99; the Agency did not renew this tolerance. Two Section 18 Emergency Exemptions have permitted use in previous years on canola in MN and ND; however, these registrations were not approved by the Agency for the 1999 growing season. A petition (PP#0F6079) has been submitted by BASF (received 11/17/99) requesting tolerances for vinclozolin residues in or on canola and snap bean as well as Section 3 registrations for use on these crops. Tolerances have been established with no U.S. registrations to permit importation of vinclozolin-treated cucumbers, sweet peppers, and wine reflecting treatment of wine grapes. Also, tolerances currently exist for vinclozolin residues in/on stone fruits and strawberries; BASF Corporation, Agricultural Products voluntarily cancelled these uses and deleted them from their vinclozolin labels on 9/4/98 in response to the cancellation notice in the Federal Register (7/30/98). However, in accordance with the existing stocks provision, use was permitted on stone fruits and strawberries through 1/30/00. Therefore, the Agency has estimated dietary risks both including and excluding these foods from the diet. An additional acute dietary risk assessment evaluated the effects of a mitigation plan proposed by BASF involving immediate cancellation of certain uses.

Vinclozolin is formulated as a 50% dry flowable (DF) or 50% extruded granule (EG) in water-soluble bags (both under EPA Reg. No. 7969-85). Vinclozolin is applied using either aerial or ground equipment. Applications may be made between 7 and 30 days of harvest of food crops. Residential exposure to vinclozolin is expected as a result of the use on turf sod and recreational exposure is expected from use on golf course greens, tees, and other areas mowed to a maximum height of 1 inch.

The principal toxic effects induced by vinclozolin are related to its antiandrogenic activity and its ability to act as a competitive antagonist at the androgen receptor. There is evidence that vinclozolin binds fairly weakly to the androgen receptor but that at least two vinclozolin metabolites occurring in mammals, plants, and soil are responsible for much of the antiandrogenic activity attributable to vinclozolin.

The FQPA Safety Factor for the protection of infants and children (as required by FQPA) has been **retained (10X)** for vinclozolin. The rationale for retention of the 10X FQPA Safety Factor is: (i) there is evidence of increased susceptibility to offspring following *in utero* exposure to vinclozolin in the prenatal developmental toxicity study in rats and (ii) 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. Note that reproductive effects (seen in testes, sperm, epididymes, and ovaries) were observed at one or more dose levels in the chronic studies used to establish the chronic RfD. Also, the developmental neurotoxicity study could provide information relevant to all population subgroups and exposure durations.

Some of the effects induced by vinclozolin and/or its metabolites are summarized below as are the doses to be used in the various types of risk assessments:

- **Acute dietary.** The No Observed Adverse Effect Level (NOAEL), adjusted for a single dose, for acute dietary risk assessment was 6 mg/kg/day from an oral developmental rat study. Decreased ventral prostate weight in male offspring occurred at the adjusted Lowest Observed Adverse Effect Level (LOAEL) of 11.5 mg/kg/day. This effect is the most sensitive indicator of acute antiandrogenic developmental toxicity. Acute dietary risk assessment has been conducted only on females of child-bearing age because this toxicity endpoint is an *in utero* effect. Adverse effects applicable to other subpopulations and resulting from a single dose were not observed. The total uncertainty factor is assessed at 1000X (10X for interspecies extrapolation, 10X for intraspecies variation, and the 10X FQPA factor). Division of the NOAEL by this total uncertainty factor results in a Population Adjusted Dose (aPAD) for females 13-50 of 0.006 mg/kg/day.

- **Overall antiandrogenic effects.** The Agency has determined that use of the most sensitive toxicity endpoint and the highest uncertainty factor (UF) would be protective of the antiandrogenic effects on all populations caused by vinclozolin including developmental/reproductive effects as well as carcinogenic effects. In the case of vinclozolin, the most sensitive toxicity endpoint/dose and UF are derived from the rat oral chronic/carcinogenicity study, i.e., the NOAEL of 1.2 mg/kg/day and an UF of 1,000. The PAD of 0.0012 mg/kg/day is to be used in assessment of risks resulting from the antiandrogenic activity of vinclozolin.

- **Chronic dietary.** Effects observed at the LOAEL of 2.3 mg/kg/day in rat oral chronic/carcinogenicity studies include histopathological lesions of the lungs, liver, ovaries, and eyes. The NOAEL was 1.2 mg/kg/day. As in the case of acute dietary, the total uncertainty factor is 1000X, resulting in a cPAD of 0.0012 mg/kg/day.

- **Carcinogenic dietary.** Vinclozolin is classified as a Group C carcinogen based on Leydig (interstitial testicular) cell tumors in a perinatal rat developmental toxicity study. A nonlinear (MOE) approach was determined to be appropriate based on a weight of the evidence conclusion that tumor induction is via an antiandrogenic mechanism. Prostate weight decreases occurred at the LOAEL of 6 mg/kg/day; the point of departure for use in the nonlinear risk assessment is 3 mg/kg/day. A policy decision regarding an appropriate MOE of concern for hormonally-mediated carcinogenic effects has not yet been determined. Therefore, a Q_1^* of 2.9×10^{-1} $(mg/kg/day)^{-1}$ was calculated. The MOE and Q_1^* approaches to carcinogenic dietary risk have both been conducted to permit comparison with the overall antiandrogenic risks for risk management purposes. Use of the PAD for overall antiandrogenic effects (0.0012 mg/kg/day) is also protective of cancer effects because it is protective of the antiandrogenic effects that are, in effect, precursors to tumor formation.