INFORMATION CONCERNING PRODUCT IMPURITIES IS NOT INCLUDED

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 000244

323C

DATE: April 17, 1978

SUBJECT: BAS 352 F Fungicide. Vinclozolin. Temporary Tolerance & EUP for Use on Strawberries. Evaluation of Toxicity Data. BASF Wyandotte Corp., Parsippany, New Jersey

FROM: Roland A. Gessert, D.V.M., Toxicology Branch

TO: Special Registrations Section

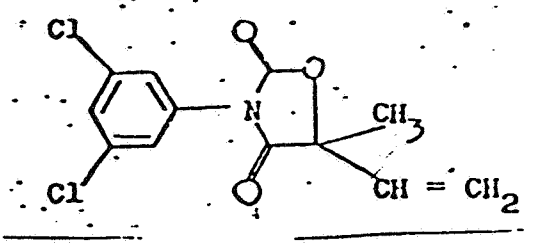
BASF Wyandotte Corporation requests an EUP and proposes establishment of a temporary tolerance for combined residues of Vinclozolin: 3-(3,5-dichlorophenyl)-5 methyl-5-vinyl-1,3-oxazolidine-2,4-dione in or on strawberries at 5 ppm.

CHEMICAL NAME: 3-(3,5-dichlorophenyl)-5-methyl-5-vinyl-1,3-oxazolidine-2,4-dione

Chemical Abstracts Usage (50471-44-8):

3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedione

CHEMICAL STRUCTURE:



EMPIRICAL FORMULA: $C_{12}H_9NO_3Cl_2$

COMMON NAME: Vinclozolin (proposed)

SYNONYMNS: BAS 352 F; 83 258

TRADE NAME: RONILAN (proposed); 50% by weight

PURITY OF TECHNICAL ACTIVE INGREDIENT: 93%, at least

IMPURITIES:

[redacted]

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EPA FORM 1320-6 (REV. 3-76)

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Studies Conducted with Technical Material:

ACUTE ORAL TOXICITY, Male & Female Rats: LD_{50} greater than 10,000 mg/kg

ACUTE INTRAPERITONEAL TOXICITY, Male & Female Guinea Pigs: LD_{50} = 3,000 mg/kg

ACUTE INTRAPERITONEAL TOXICITY, Male & Female Mice: LD_{50} = 5,000 mg/kg

TOXIC SYMPTOMS: dyspnea, tremors, spasms, lethargy

POST MORTEM: hyperemia

ACUTE DERMAL TOXICITY, Male & Female Rats: LD_{50} greater than 2,500 mg/kg
No toxicity observed

PRIMARY SKIN IRRITATION, Male & Female Rabbits: Primary Skin Irritation Value = 1.3 (moderate)

PRIMARY EYE IRRITATION, Male & Female Rabbits: Primary Eye Irritation Value = 1.89; no keratitis

Studies Conducted with Formulation:

ACUTE ORAL TOXICITY, Male & Female Rats: LD_{50} greater than 16,000 mg/kg

ACUTE DERMAL TOXICITY, Male & Female Rabbits: LD_{50} greater than 2,000 mg/kg

PRIMARY EYE IRRITATION, Female Rabbits: Mean Primary Eye Irritation Score of 19.7; some corneal opacity and conjunctivitis; no iritis

ACUTE INHALATION TOXICITY IN RAT (dust): No mortality after 4-hour exposure to a dust concentration of 1.17 mg/l, equivalent to 0.59 mg/l active ingredient. The single, 4-hour inhalation caused slight mucosa irritations in some animals.

ACUTE INHALATION TOXICITY IN RAT (aqueous spray of 1% suspension): No mortality after 4-hour exposure to a spray concentration of 0.2 mg/liter of air, corresponding to an active ingredient concentration of 0.1 mg/liter of air. The single, 4-hour inhalation of the spray caused slight irritations of the mucous membrane.

PRIMARY SKIN IRRITATION, Male & Female Rabbits: Primary Skin Irritation Value of formulation = 2.75

SUBCHRONIC (90 day) TOXICITY IN MALE & FEMALE RATS: No influence at 150 or 450 ppm in food on behavior, external appearance, food or water consumption, body weight gain, hematology, clinical biochemistry, urine composition, eyes, hearing, dentition, gross appearance of organs & tissues, organ weights, nor on histological examination of liver, adrenal, and pituitary. No rats died prematurely. The lowest toxic dose exceeds 450 ppm.

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SUBCHRONIC (90 day) TOXICITY IN MALE & FEMALE DOGS: At 100, 300, 1000, or 2000 ppm in food over a period of 3 months, all doses were tolerated well without externally recognizable symptoms of intoxication. Repeated ophthalmological examinations revealed no changes in the refractory media or in the fundus of the eye. Feed acceptance was variable in one male at 2000 ppm and in all females, including the control group, but no adverse effect was observed on weight gain. Clinical chemistry studies and urine analyses revealed no biologically relevant differences between the trial and control groups.

Hematograms revealed increased platelet counts in females receiving 1000 and 2000 ppm, and Howell-Jolly bodies were found in differential blood counts of both males and females at these pesticide levels.

Postmortem examination revealed no macroscopic changes in the organs due to the compound, but increases in the relative liver and adrenal weights in females receiving 2000 ppm were observed.

TERATOLOGY (PRENATAL TOXICITY) IN MICE: The compound was administered in food at levels of 0, 600, 6000, and 60,000 ppm during the entire gestation period. Caesareans were performed on the 18th day post coitum. All fetuses were examined for any externally recognizable symptoms of toxicity; 2/3 of the fetuses of each litter for deformities, variations, and retardations of the skeleton; and 1/3 of the fetuses of each litter for deformities, variations, and retardations of the organs.

600 ppm were tolerated without any clinically recognizable symptoms of toxicity. No changes were observed in the average amount of food consumed or in the gain in body weight of the pregnant animals. The examination of the fetuses did not reveal any indication of a compound-induced effect.

Animals which received 6000 ppm in their diet did not exhibit any clinically recognizable symptoms of toxicity. One animal died on the 10th day post coitum. In the initial days of the test the animals consumed less food than the animals which were administered 0 or 600 ppm in their diet. There was no gain in weight corresponding to the gestation. However, the animals did not lose any weight, either.

When the animals were sacrificed on the 18th day post coitum, no implantation sites were discovered. The fertilized egg cells had died before nidation.

60,000 ppm were not consumed by the animals. From the first day of the test the animals ate practically none of the food. This caused a decrease in the average body weight. All the animals died within 9 days. No nidation sites were detected in the animals which died after the 6th day post coitum.

The pesticide is not a teratogen.

3-GENERATION REPRODUCTION STUDY IN RATS: The compound was tested in different stages of development in the rat, and the examinations covered the pre- and postnatal development. Two breeding studies each were performed with 3 successive generations with oral administration of the test compound. In all, the experimental period lasted approximately 2 years. Particular attention was paid to possible teratogenic properties of the compound.

The compound was fed at levels of 162, 486, and 1458 ppm. Treatment began for the 1st (P-) generation 7 weeks before the 1st breeding test and was continued without interruption in all following generations until the end of the study. A corresponding untreated group served as control.

Fertility and breeding capacity were not definitely influenced at any of the concentrations in the examined animals (P-, F_1-, and F_2- generation): copulation, duration of pregnancy, litter size, birth weight, and breeding rate of the pups lay within the normal range. The indices of fertility, pregnancy, lactation, and viability corresponded in experimental and control animals.

Examinations of the general tolerance indicated no intolerance phenomena. Behavior, external appearance, feces, food consumption, intake of drinking water, and body weight gain were normal at all concentrations (162, 486, and 1458 ppm in the food) in the parent animals (P-, F_1-, and F_2- generation). None of these rats died prematurely. The animals of the F_3- generation developed normally, also. Specific checks of external criteria and sensory functions revealed no impairment.

On necropsy, macroscopic inspection revealed no pathological changes in parent or young animals. The comparison of organ weights and the histological examinations in the F_3-generation after 9 weeks of life disclosed no changes attributable to the test compound.

Under the test conditions the lowest toxic concentration can be said to lie above 1458 ppm in the food. The compound did not show teratogenic properties in this study.

MUTAGENIC EFFECT ON THE MALE MOUSE, USING THE DOMINANT LETHAL TEST: 2000 mg/kg was administered on 5 successive days via stomach tube in 20 ml/kg 0.5% aqueous CMC formulation. Control animals received only the CMC formulation. There were no clinically recognizable symptoms of toxicity, and no evidence of any effect on conception rate, average number of implants, percentage of viable fetuses, or percentage of dead implants. Under conditions of the test, the compound could not be shown to have any mutagenic effect on male mice.

METABOLISM; REPEATED ORAL DOSING IN RATS:

The disposition and metabolic fate of 3-(3,5-dichlorophenyl)-5-methyl-1,3-oxazolidin-2,4-dione, vinclozolin, in rats (bodyweight ca 200g) was studied after daily oral administration of the ^{14}C-labelled pesticide for seven days. All experiments were performed at a nominal dose level of 40 mg/kg bodyweight per day.

After daily oral administration of ^{14}C-vinclozolin to rats, excretion of radioactivity was fairly rapid and was similar in both male and female rats. Approximately 43% and 50% of the daily administered dose were excreted in the urine and feces, respectively, during each day of the dosing period. Six days after the final dose (12 days after the first dose) means of 47% and 54% of ~~only~~ 52.8% the total dose had been excreted in urine and feces, respectively, and means of 0.1% and 0.04% of the total dose were retained in the gastrointestinal tract and liver, respectively. No radioactivity was detected in the remainder of the body at six days after the final dose, nor was any detectable radioactivity excreted in the expired air during 24 hours after the final dose.

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After single oral doses of ^{14}C-vinclozolin to male rats with cannulated bile ducts, a mean of 65% of the dose was excreted in the bile during two days. During the same time means of 19% and 15% were excreted in urine and feces, respectively.

After the first oral dose of ^{14}C-vinclozolin to rats, mean peak concentrations of radioactivity in plasma were reached at one hour in both males (12.8 ug equivalents/ml) and females (10.1ug equivalents/ml). During the dosing period, predose concentrations of radioactivity in plasma increased gradually and were slightly higher in female rats than in males. After the final dose, mean peak plasma concentrations of radioactivity were reached at one hour in males (14.2 ug equivalents/ml) and at 7.5 hours in females (15.0 ug equivalents/ml) and declined with a half-life of about 20 hours in both cases.

After daily oral dosing of ^{14}C-vinclozolin to rats for seven days, concentrations of radioactivity were generally higher in the tissues of female rats than in those of males. Concentrations of radioactivity significantly higher than those in plasma were found at most times in liver, kidneys, gastrointestinal tract, fat, adrenals and ovaries. Radioactivity still could be detected in nearly all tissues examined at 96 hours after the final dose, but by this time concentrations were similar to those in plasma, except in liver, kidneys, gastrointestinal tract, and female fat.

Whole-body autoradiography showed an extensive distribution of radioactivity with concentrations being highest in the gastrointestinal tract, bile ducts, bladder, liver, and kidneys. Concentrations were lower in one rat sacrificed 24 hours after a single dose than in a rat killed 24 hours after the last of seven daily doses. However, at four days after the last of seven doses, radioactivity was only detectable in the gastrointestinal tract and the liver, and these concentrations were low.

A major metabolite in fecal extracts was tentatively identified by mass spectrometry as being N-(3,5-dichlorophenyl)-2-methyl-2,3,4-trihydroxybutyramide. It was also shown that the glucuronide conjugate of this metabolite was the major radioactive component excreted in urine and bile. Unchanged vinclozolin was found in fecal extracts, but not in urine.

CHRONIC TOXICITY AND ONCOGENIC STUDIES IN RATS:

Vinclozolin was given in concentrations of 162, 486, 1458, and 4374 ppm in the food for 130 weeks, when a mortality rate of approximately 70% was reached in the control group. There were 100 rats per group (50 males & 50 females).

The lowest mortality rate was found for the highest vinclozolin concentration; the highest mortality rate, in the untreated control group. Prelethal symptoms and cause of death were similar in experimental and control animals. The tumors did not disclose, in respect to their nature and extent, an influence of the test compound; at the highest treatment the tumor rate was 55% as against 63% in the control rats.

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Behavior, external appearance, feces, intake of drinking water, hematology, examination of sight, hearing, and dentition, as well as macroscopic and microscopic inspection did not indicate definite intolerance phenomena. Differing organ weights should be interpreted as a typical high deviation of aged rats, and in connection with the loss of body weight at the higher concentrations. The weights of prostate and seminal vesicles were always within the normal range.

The following effects of the test compound were seen: The body weight was significantly reduced at 1458 and 4374 ppm. The food consumption was, in relative terms, initially increased at 4374 ppm; otherwise it corresponded to body weight. At both 1458 and 4374 ppm the serum level of total bilirubin tended towards reduction. In the urine the content of 17-ketosteroid and ascorbic acid was increased, the maximum being found after 8 test weeks. After 104 test weeks at the latest these symptoms had disappeared. No further changes were revealed by clinical biochemistry or urinalysis.

Under the test conditions, the no-effect level can be said to fall between 486 and 1458 ppm in the food.

In the study, vinclozolin showed no carcinogenic properties.

CHRONIC TOXICITY AND ONCOGENIC STUDY IN MICE:

Vinclozolin was given in concentrations of 162, 486, 1458, and 4374 ppm in the food for 26 months, when a mortality rate of approximately 70% was reached in the control group. In this study special attention was paid to possible carcinogenic properties of the test compound.

None of the tested concentrations (162, 486, 1458, and 4374 ppm in the food) led to definite intolerance phenomena during the 26 months of administration. Only body weight gain of the males at 4374 ppm was slightly, but significantly inhibited, the food consumption being reduced in parallel. This finding, however, might still be incidental.

The mortality rates of experimental and control animals were nearly the same, as were the prelethal symptoms and cause of death. Neither did the tumors disclose, in respect to their nature and extent, an influence of the test compound: at the highest concentration the tumor rate amounted to 46% as against 51% in the control group. Differing organ weights should be interpreted as typical high deviation of aged mice.

Behavior, external appearance, feces, water consumption, hematology, clinical biochemistry, urinalysis, and also examination of sight, hearing, and dentition, remained unchanged even at the highest concentration (4374 ppm).

Under the test conditions the lowest toxic concentration can be expected around or slightly above 4374 ppm. Vinclozolin did not show carcinogenic properties.

These studies all meet core minimum standards.

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RECOMMENDATION: In one rat test, the no effect level appears to be between 486 and 1458 ppm. In the 3-generation rat reproduction study, the no effect level is above 1458 ppm. Other studies show vinclozolin to be exceptionally non-toxic. 1458 ppm, therefore, appears to be close to the no effect level. Using a 100-fold safety factor, a daily acceptable daily intake of 14 ppm appears to offer adequate protection. The 5 ppm tolerance requested for strawberries (which represent 0.18% of the total diet) therefore can easily be granted. Vinclozolin is a new compound for which other tolerances have not yet been requested.

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