United States
Environmental Protection
Agency

Office of Pesticides
and Toxic Substances
(7501C)

PESTICIDE FACT SHEET

Name of Chemical: KRESOXIM-METHYL
Reason for Issuance: New Chemical Registration
Date Issued: September 1998

DESCRIPTION OF CHEMICAL

ChemicalName: Methyl(E)-methoxyimino-2-[2-(o-tolyloxymethyl)phenyl] acetate

Common Name: Kresoxim-methyl

Trade Names: BAS 490, Cygnus

EPA Chemical Code: 129111

Chemical Abstracts Service
(CAS) Registry Number: 143390-89-0

Year of Initial Registration: 1998

Pesticide Type: Fungicide

U.S. Producer: BASF Corporation
P.O. Box 13528
Research Triangle Park, NC 27709

DESCRIPTION OF USE PATTERNS

The end-use product is a dry flowable formulation containing 50% active ingredient. The product is applied as a spray (backpack sprayers or overhead booms) to control powdery mildew on the following greenhouse-grown ornamental crops: ageratum, dahlias, dianthus, dusty miller, gazania, geraniums, marigolds, pansies, portulaca, snapdragons, spirea, spengril, verbena, vinca, zinnia, poinsettias, roses, cut flowers, oak trees, and dogwood trees. The formulating use product contains 94% active ingredient.

SUMMARY OF SCIENCE FINDINGS

The Agency has reviewed the toxicology and environmental fate and effects data submitted by BASF Corporation to support the use kresoxim-methyl for use on greenhouse ornamental crops. The data are considered to be adequate to ensure that use of the products for the registered purposes will cause no unreasonable adverse effects to man or the environment. Food Quality Protection Act considerations are not included since there are no food uses involved and surface and ground water would not be affected by this indoor use. The data used in this assessment are summarized below.

CHEMICAL CHARACTERISTICS

The physico-chemical characteristics of the kresoxim-methyl technical are as follows:

Color	Light brown
Molecular formula	$C_{18}H_{19}NO_4$
Molecular weight	313.8
Physical state	Solid
Melting point	98-100^{0}C
Vapor pressure	2.3 x 10^{-6} Pa at 20^{0}C
Solubility (water)	2 ppm

The physico-chemical characteristics of Cygnus Fungicide are as follows:

Color	Dark brown
Physical state	Solid
Odor:	Moderately sulfurous
Bulk density	541 g/L
pH	5.8

TOXICOLOGICAL CHARACTERISTICS

Acute Testing:

Both the technical and end-use products were in toxicity category IV from acute oral and acute inhalation tests and in toxicity category III from acute dermal and eye irritation studies. Neither product was a dermal irritant nor a dermal sensitizer.

Subchronic Toxicity:

1. In a subchronic oral toxicity study, kresoxim-methyl was administered in the diet to rats at dose levels of 0, 500, 2,000, 8,000, and 16,000 parts per million (ppm) (0, 36, 146, 577, and 1,170 mg/kg/day for males and 0, 43, 172, 672, and 1,374 mg/kg/day for females) for 3 months. Under the conditions of this study, the Lowest Observed Effect Level (LOEL) for male rats was 8,000 ppm (577 mg/kg/day) based on elevated serum GGT. A LOEL was not established for females. The No Observed Effect Level (NOEL) for males was 2,000 ppm (146 mg/kg/day) and for females was 16,000 ppm (1,374 mg/kg/day).

2. In a subchronic oral toxicity study on mice, kresoxim-methyl was administered in the diet at levels of 0, 250, 1,000, 4,000, and 8,000 ppm (0, 57, 230, 909, and 1,937 mg/kg/day for males and 0, 80, 326, 1,326 and 2,583 mg/kg/day for females). A LOEL was not determined for either sex. The NOEL was 8,000 ppm (1,937 mg/kg/day for males and 2,583 mg/kg/day for females).

3. In a repeated dose dermal toxicity study, rats were treated by dermal occlusion at doses of 0 and 1,000 mg/kg/day, 6 hours/day for 21 days. The NOEL was 1,000 mg/kg/day. A LOEL was not determined.

Chronic Toxicity

1. In a chronic toxicity study, kresoxim-methyl was administered to rats in the diet at dose levels of 0, 200, 800, 8,000, or 16,000 ppm (0, 9, 36, 370 and 746 mg/kg/day for males and 0, 12, 48, 503, and 985 mg/kg/day for females) for 24 months. The LOEL for both male and female rats was 8,000 ppm (370 mg/kg/day in males and 503 mg/kg/day in females) based in males on the increase in SGGT levels, liver weight and histopathological changes, and in females on roughly 10% lowered body weights and weight gains throughout most of the study. The NOEL for both sexes was 800 ppm, (36 mg/kg/day for males and 48 mg/kg/day for females.

2. In a chronic toxicity study on dogs, kresoxim-methyl was administered in the diet at levels of 0, 1,000, 5,000 or 25,000 ppm (0, 27, 138, or 714 mg/kg/day for males and 0, 30, 146, or 761 mg/kg/day for females) for 12 months. The LOEL was 25,000 ppm (714 mg/kg/day) for males based on decreased mean body weight and body weight gain and decreased food efficiency. A LOEL was not identified for females. The NOEL was 5,000 ppm (138 mg/kg/day) for males and 25,000 ppm (761 mg/kg/day) for females.

Carcinogenicity

1. In a carcinogenicity feeding study, kresoxim-methyl was administered to rats in the diet for 24 months at dose levels of 0, 200, 800, 8,000, or 16,000 ppm (0, 9, 36, 375, and 770 mg/kg/day for males and 0, 12, 47, 497, and 1,046 mg/kg/day for females). The LOEL for both male and female rats was 8,000 ppm (375 mg/kg/day for males and 497 mg/kg/day for females). For males, this is based on the minor decrease in body weight and body weight gain and on the increase in gross and microscopic liver (and biliary) lesions. In females, the LOEL is based on the lowered body weights and weight gains and on the increased incidence of liver masses. The NOEL for both sexes was 800 ppm (36 mg/kg/day in males and 47 mg/kg/day in females). Liver carcinoma was the primary neoplastic finding in both sexes of rats, consistent with the histopathological findings.

2. In a carcinogenicity toxicity study on mice, kresoxim-methyl was administered the diet at dose levels of 0, 400, 2,000, and 8,000 ppm (0, 60, 304, and 1,305 mg/kg/day for males and 0, 81, 400, and 1,662 mg/kg/day) for 18 months. An additional 10 animals were treated for 12 months in a satellite study. The LOEL was 2,000 ppm (400 mg/kg/day) for females, based on decreased weight gain and 8,000 ppm (1,350 mg/kg/day for males, based on decreased weight gain and liver amyloidosis. The NOEL was 400 ppm (81 mg/kg/day) for females and 2,000 ppm (304 mg/kg/day) for males. At the doses

tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate and the high dose rate was above the limit dose of 1,000 mg/kg/day for both sexes.

Developmental toxicity

1. In a developmental toxicity study on rats, kresoxim-methyl was administered by gavage at doses of 0, 100, 400, or 1,000 mg/kg/day on gestation days 6-15. No clinical signs of toxicity were observed any treated animals during the study and no treatment-related gross abnormalities were observed at maternal necropsy. Therefore, the maternal toxicity NOEL is ≥1,000 mg/kg/day and the maternal toxicity LOEL was not identified. There were no treatment-related external, visceral, or skeletal malformations/variations observed in the fetuses. Therefore, the developmental toxicity NOEL is ≥1,000 mg/kg/day and the developmental toxicity LOEL was not identified.

2. In a developmental toxicity study on rabbits, kresoxim-methyl was administered by gavage at doses of 0, 100, 400 or 1,000 mg/kg/day on gestation days 7-19. No clinical signs of toxicity were observed in any treated animals during the study and no treatment-related gross abnormalities were observed at maternal necropsy. Therefore, the maternal toxicity NOEL is ≥1,000 mg/kg/day and the maternal toxicity LOEL was not identified. There was no statistically significant difference between control and treated groups of fetuses regarding the number of external, soft-tissue, or skeletal malformations/variations with the exception of fetal incidence of fused sternebrae in the low dose group compared to the controls. Since a dose-response relationship was not apparent, toxicological significance could not be established. Therefore, the developmental toxicity NOEL is ≥1,000 mg/kg/day and the developmental toxicity LOEL was not identified.

Reproductive Toxicity

Kresoxim-methyl was administered in the diet of male and female rats at concentrations of 0, 50, 1,000, 4,000, or 16,000 ppm for two generations. Two litters were produced in the first generation and one litter in the second generation. Premating doses for the males were 5.1, 102.6, 411.0, and 1,623.1 mg/kg and for females were 5.6, 108.7, 437.2 and 1,741.1 mg/kg. Premating doses for the first generation males were 4.4, 88.3, 362.7, and 1,481.6 mg/kg and for first generation females were 5.0, 100.8, 416.6, and 1,652.6 mg/kg. Animals were given test or control diet for at least 10 weeks then mated within the same dose group.

There were no dose- or treatment-related clinical signs of toxicity in the parental animals of either sex or generation. No dose- or treatment related gross or histological abnormalities were observed at necropsy in either parent or first generation animals of either sex. The LOEL for systemic/postnatal developmental toxicity was 4,000 ppm based on reduced body weights and body weight gains of the parent and first generation parental animals and delayed growth and maturation of the first and second generation pups. The systemic toxicity NOEL was 1,000 ppm.

No treatment-related effects were observed on the reproductive performances of either generation. There were no dose- or treatment-related clinical signs of toxicity in the offspring of either generation. Therefore, the NOEL for reproductive toxicity is ≥ 16,000 ppm and the corresponding LOEL for reproductive toxicity was not identified.

Mutagenicity

Mutagenicity studies included: Salmonella/mammalian activation gene mutation assay, mammalian cells in culture gene mutation assay in Chinese hamster ovary CHO cells, in vitro mammalian cytogenetics chromosomal aberrations assay in human lymphocytes, and in vivo mammalian cytogenetics micronucleus assay in mice. Other genotoxicity studies were: unscheduled DNA synthesis in primary rat hepatocytes/mammalian cell cultures and unscheduled DNA synthesis in rat hepatocytes/mammalian cells-in vivo/in vitro procedures. Based on available studies, there are no concerns for mutagenicity at this time.

Metabolism

In a metabolism study, kresoxim-methyl was administered to rats as single gavage doses or 50 or 500 mg/kg or 15-day repeated doses of 50 mg/kg, or as a single intravenous dose of 5 mg/kg/day. Radiolabeled test compound was included in one 500 mg/kg dose group to facilitate metabolite identification. Biliary metabolites were assessed in rats with cannulated bile ducts given an oral dose of 50 or 500 mg/kg/day.

Orally administered test compound was widely distributed and quickly eliminated. Results indicated there was no bioaccumulation. In both sexes, the major routes of excretion were feces and the urine. No radioactivity was detected in exhaled air. A total of 32 different metabolites were identified in the urine, feces, bile, plasma, liver, and kidneys of rats. There were some sex, dose, route, and label-dependent differences in the metabolite profiles. The metabolism study was classified as unacceptable but upgradable because there was an inadequate accounting of radioactivity in biliary metabolites of low-dose rats, which may be due to a typographical error.

ECOLOGICAL CHARACTERISTICS

The following ecological effects studies were submitted:

1. An avian single-dose LD_{50} test using bobwhite quail was conducted and resulted in an LD_{50} of >2,150 mg ai/kg, which is considered practically non-toxic to upland gamebird species. The NOEL was 2,150 mg ai/kg.

2. An upland game bird dietary LC_{50} test was conducted on Bobwhite quail and resulted in an 8-day LC_{50} of >5,000 ppm ai which is considered to be practically non-toxic.

3. A waterfowl dietary LC_{50} test on Mallard ducks resulted in an LC_{50} of >5,000 ppm ai which is considered to be practically non-toxic.

4. An avian reproduction study was conducted using Bobwhite quail. No treatment related effects occurred in the adult generation or in the 50 or 500 mg/kg F_1 groups. However, significant effects did occur in the 1,000 mg/kg group when compared to the control group. The LOEC was 1,000 ppm ai and the NOEC was 500 ppm ai.

5. An acute LC_{50} test with a warmwater fish was conducted with Bluegill sunfish and resulted in an LC_{50} of 499 ppb ai which is considered to be highly toxic.

6. An acute LC_{50} test with a coldwater fish was conducted with Rainbow trout and resulted in an LC_{50} of 190 ppb ai which is considered to be highly toxic. A similar test using the metabolite of kresoxim-methyl (BAS 490-1) resulted in an LC_{50} of >104 ppm ai/l which is considered to be practically non-toxic.

7. An acute LC_{50} test with a freshwater invertebrate was conducted with Daphnia and resulted in an EC_{50} of 332 ug ai/L which is considered to be highly toxic. A similar study conducted with the metabolite BAS 490-1 resulted in an EC_{50} of >100 ppm ai with an NOEC of 60 ppm ai.

ENVIRONMENTAL CHARACTERISTICS

The studies submitted to support environmental fate data requirements for the use of kresoxim-methyl on greenhouse ornamentals were: hydrolysis, aerobic soil metabolism, anaerobic aquatic metabolism, aerobic aquatic metabolism, leaching-adsorption/desorption, and field dissipation. Based upon these studies, it is concluded that the use of kresoxim-methyl for greenhouse non-food uses is unlikely to have adverse effects on the environment.

Kresoxim-methyl has the following characteristics: (1) has a low water solubility (2 ppm); (2) is very stable to hydrolysis at pH 5, relatively stable at pH 7 (half-life=34 days), and becomes more susceptible to hydrolysis at pH 9 (half-life=7 hours); (3) degrades very rapidly in soil under aerobic conditions (half-life= less than 1 day); (4) degrades very rapidly in flooded soil under anaerobic aquatic metabolism conditions (half-life=1.1day); (5) degrades very rapidly under aerobic aquatic metabolism conditions (half-life=1.2 days); (6) was found to be very mobile in sand, loamy sand, loam, and clay soils; (7) non-volatile in water and soil; and (8) will accumulate in fish. BF 490-1, the major degradate, is expected to be more mobile than the parent compound and is expected to be more persistent. Therefore, it is believed that the impact of BF 490-1 on the environment is expected to be greater than the parent compound.

The major routes of dissipation in the environment appear to be metabolism and leaching. Low soil/water partition indicates that most of the kresoxim-methyl and BF 490-1 runoff is via dissolution in runoff water, as opposed to adsorption to eroding soil. It also indicates that most of the parent compound and BF 490-1 will be partitioned in the water column instead of in the suspended and bottom sediments. Results from the confined field dissipation study showed that kresoxim-methyl dissipated relatively rapidly with a half-life of less than 4 days in a confined bare ground plot. Major degradates were also analyzed in the study. Since <10% of the applied radioactivity was detected below the 3-inch depth at any sampling interval, soils were not analyzed for the parent and its metabolites below the 3-inch depth. Taking into account its low vapor pressure and Henry's Law constant, low water solubility, and low organic carbon adsorption coefficient, it appears that the volatilization of kresoxim-methyl from soils and water will not be an important dissipation route. The moderate octanol/water partition coefficient suggests that the chemical will have a tendency to accumulate in fish.

OCCUPATIONAL EXPOSURE

Acute Dietary Exposure: No appropriate endpoint was identified for this exposure scenario.

Short-Term Dermal Exposure (1 - 7 days): This risk assessment is not required since no dermal or systemic toxicity was seen in a test in which 15 dermal applications of kresoxim-methyl was applied to rats at 0 or

1,000 mg/kg/day.

Intermediate Term Dermal Exposure (1 week to several months): No risk assessment is required since no dermal or systemic effects were seen at the Limit Test.

Chronic Dermal Exposure (Several months to lifetime): This risk assessment is not required because no long-term exposure concerns have been identified.

Inhalation Exposure (Any time period): The acute inhalation Toxicity Category from a four-hour rat study was IV with an LC_{50} of 5.6 mg/L; therefore, a risk assessment for inhalation exposure was not required.

Reference Dose

A carcinogenicity feeding study in rats was used to establish the reference dose. The LOEL for both male and female rats was 8,000 ppm (375 mg/kg/day in males and 497 mg/kg/day in females) and the NOEL for both sexes was 800 ppm (36 mg/kg/day for males and 47 mg/kg/day for females). A dermal absorption factor was required for chronic exposure because the dose identified in this risk assessment was from an oral study. A dermal absorption factor could not be estimated due to lack of appropriate toxicity data so 100% was assumed for dermal absorption. The Reference Dose (RfD) for kresoxim-methyl was established at 0.36 mg/kg/day.

Carcinogenicity

Kresoxim-methyl has recently been reviewed by the Agency for a carcinogenicity classification that was based on a standard toxicology battery of studies and a preliminary mechanistic data set provided by BASF Corporation in a greenhouse use petition submitted to EPA in 1995. This review resulted in an "interim determination of (3.05×10^{-3})" by the Cancer Peer Review Committee that kresoxim-methyl is a class "C(q)" carcinogen using linear extrapolation for determination of risk. In 1997, prior to the review of this petition, BASF submitted for a food use registration which contained additional mechanistic data on the mode of action for tumor formation that has not been previously reviewed by the Agency. The Agency intends to review this additional mechanistic data, in conjunction with the petition for food uses, to determine a definitive carcinogenicity classification for this product.

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