CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION

PUBLIC REPORT 2003-3

Methoxyfenozide

Tracking ID Numbers 195668 and 196546

DESCRIPTION OF ACTION

Dow AgroSciences LLC submitted an application seeking California registrations of Intrepid 2F, EPA Reg. No. 62719-442 and Intrepid 80 WSP Agricultural Insecticide, U.S. EPA Reg. No. 62719-438, to control various insects on pome fruit and cotton. These products contain the new active ingredient methoxyfenozide.

The Department of Pesticide Regulation (DPR) evaluated the product labels and scientific data supporting registration of these products and found them to be acceptable to support conditional registration. The acute health risks from exposure to methoxyfenozide are minimal due to its low mammalian toxicity. Precautionary and first aid statements on the product labels, as well as label directions requiring personal protective equipment (PPE) and other protective measures adequately mitigate potential health risks to persons who may come in contact with the pesticide during the period of conditional registration. DPR does not expect significant adverse environmental impacts to result from registration of these products.

DPR accepted Dow's applications for registration of Intrepid 2F and Intrepid 80 WSP concurrently with Dow's submission of applications to the U.S. Environmental Protection Agency (U.S. EPA) for federal registration of the products. U.S. EPA registered Intrepid 2F Agricultural Insecticide on September 18, 2000 and Intrepid 80 WSP Agricultural Insecticide on July 5, 2000.

BACKGROUND

Registrant:	Dow AgroSciences LLC
Common name:	Methoxyfenozide
Chemical name:	Benzoic acid, 3-methoxy-2-methyl-,2-(3,5-dimethylbenzoyl)-2-(1,1-dimethylethyl) hydrazide
Brand names:	Intrepid 2F and Intrepid 80 WSP
Uses:	Insect control on pome fruit and cotton
Pests controlled:	Insects including codling moth, lesser appleworm, oriental fruit moth, obliquebanded leafroller, cabbage looper, cotton bollworm, beet armyworm and eyespotted bud moth.
Type of registration:	Conditional Registration

Intrepid 2F is formulated as a flowable concentrate and Intrepid 80 WSP is formulated as a powder in a water soluble pouch. These products are intended to provide control of insects on pome fruit and cotton. Methoxyfenozide belongs to the diacylhydrazine class of insecticides and has a novel mode of action. The chemical mimics the action of the

molting hormone of Lepidopterous (moths, butterflies) larvae. Upon ingestion, moth larvae undergo an incomplete and premature molt, which ultimately results in their death. Feeding by the larvae on the leaves of pome fruit trees and cotton plants typically ceases within hours of ingestion of the chemical even though the larvae may not die for several days. Affected larvae often become lethargic and develop discolored areas or bands between their body segments. Intrepid 2F and Intrepid 80 WSP have virtually no effect on any other type of insect, spider, or crustacean, making it an ideal tool for integrated pest management programs. This selectivity allows beneficial insects (including bees) to function unimpeded in the management of secondary pests while Intrepid provides control of troublesome Lepidoptera pests. Intrepid 2F application rates are 4 to 24 fluid ounces of product per acre (0.06 – 0.38 lbs. active ingredient (a.i.)/acre) with a maximum of 64 fluid ounces of product per acre per season. Intrepid 80 WSP application rates are 1 to 8 ounces per acre (0.05 to0.4 lbs. a.i./acre) with a maximum of 20 ounces of product per acre per season. Aerial applications to pome fruit are limited to the last two applications prior to harvest for both products.

SCIENTIFIC REVIEW

A. Chemistry

1. Product Chemistry: DPR evaluated the submitted chemistry studies for Intrepid 2F and Intrepid 80 WSP and summarized the results in the following table.

Table I. Physical and Chemical Properties of Technical Methoxyfenozide

Properties	Values
Physical state	White solid
Density	0.634 g/cm^3
pH	7.1
Solubility (water)	3.3 ppm (20°C)
Vapor pressure	<1 X 10^{-7} mmHg (25°C)
Henry's law	<1.47 X 10^{-8} atm·m^3 /mole (20°C)
Stability	Stable at 54°C (2 weeks)

Table II. Physical and Chemical Properties of Intrepid 2F

Physical state	Light brown liquid
Specific gravity	1.060 (20°C)
pH	6.6 (1% aqueous suspension)
Viscosity	6.77 X 10^{-2} Pas
Stability	Stable at 54°C (2 weeks)

Table III. Physical and Chemical Properties of Intrepid 80 WSP

Physical state	Off-white solid
Density	0.37 g/cm^3 (packed)
pH	9.7 (5% aqueous dispersion)
Stability	Stable a 25°C (one year)

2. Residues in Food and Animal Feed: The submitted residue studies support the harvest and use limitations listed on the Intrepid 2F and Intrepid 80 WSP labels for pome fruit and cotton. The residue levels are well within the tolerances established by the U.S. EPA for pome fruit and cotton. The established tolerances are listed in the following tables. The rotational crop restrictions are adequate.

IV. Tolerances for residues of Methoxyfenozide(RH-2485)

Commodity	Parts per million (PPM)
Apple pomace, wet	7.0
Cotton gin byproducts	35
Cotton, undelinted seed	2.0
Fat of cattle, goats hog, horses and sheep	0.1
Meat of cattle, goats, hogs, horses and sheep	0.02
Milk	0.02
Pome fruits crop group	1.50

V. Combined Residues of Methoxyfenozide (RH-2485) and RH-1518

Commodity	PPM
Liver of cattle, goats, hogs, horses and sheep	0.1
Meats byproducts (except liver) of cattle, goats, hogs, horses and sheep	0.02

3. Environmental Fate: The methoxyfenozide environmental fate data reviewed included studies on soil adsorption coefficient, hydrolysis, aqueous and soil photolysis, aerobic soil metabolism, aerobic and anaerobic aquatic metabolism, and field dissipation. The studies were found to be satisfactory.

   The Kd values from the soil adsorption coefficient study were determined for five soils with the Freundlich Equation ranged from 1.1 ml/g for loamy sand to 6.2 ml/g for a sandy loam. The corresponding Koc values indicated low to medium mobility. The hydrolysis study was studied at pH 5, 7, and 9 in the dark at 25°C. Methoxyfenozide was stable at all three pH values. Radiolabeled methoxyfenozide in pH 7 buffer solution was subjected to photolysis under a xenon arc lamp at 25°C. No photolysis was observed. The soil photolysis of radiolabeled methoxyfenozide was investigated on a loamy sand using a xenon arc lamp. The half-life of methoxyfenozide was calculated as 363 days. There were no major photodegradates.

The aerobic soil metabolism studies showed that the first-order kinetic analysis along with linear regression resulted in a calculated half-life for methoxyfenozide of 573 days in loam soil, 336 days and 1,100 days in loamy sand, and 722 days for sandy clay loam. The half-life of the anaerobic aquatic metabolism study using clay hydrosoil was 654 days. Terrestrial field dissipation studies were conducted in California, Washington, Georgia and Texas. Soil core samples were taken to a depth of three feet for eighteen months after the last application. The first order kinetic analysis of the residue data resulted in calculated half-lives of 92 to 327 days. Significant residues were observed down to 30 inches.

The submitted product, environmental fate, and residue chemistry data support registration of the subject product with the following conditions: the applicant agrees to submit the temperature range and the mean temperature during the two-year storage stability study for Intrepid 2F and the chemical composition of two inert ingredients in the products.

B. Toxicology

Dow AgroSciences submitted adequate toxicology studies to conduct complete toxicological evaluations of Intrepid 2F and Intrepid 80 WSP. DPR evaluated the submitted data to ascertain the potential for adverse health effects. The acute toxicity parameters for Intrepid 2F and Intrepid 80 WSP are summarized in the following tables.

Table II. Acute Toxicity of Intrepid 2F

Type of Study	Acute Toxicity Values	Acute Toxicity Category
Acute Oral	LD_{50}>5.0 g/kg	IV
Acute Dermal	LD_{50}>2.0 g/kg	III
Acute inhalation	LC_{50}>0.9 mg/L	III
Primary eye irritation	N/A	IV
Primary dermal irritation	N/A	IV
Signal word	N/A	CAUTION

Table III. Acute Toxicity of Intrepid 80 WSP

Type of Study	Acute Toxicity Values	Acute Toxicity Category
Acute oral	LD_{50}>5.0 g/kg	IV
Acute dermal	LD_{50}>2.0 g/kg	III
Acute inhalation	LC_{50}>4.5 mg/L	IV
Primary eye irritation	N/A	III
Primary dermal irritation	N/A	IV
Signal word	N/A	CAUTION

DPR's evaluation of the acute toxicity studies indicates that the studies are acceptable and Intrepid 2F and Intrepid 80 WSP are low in mammalian toxicity. The precautionary language on the product label adequately identifies the acute toxicity hazards noted in the studies.

DPR found the submitted toxicology studies sufficient to satisfy the data requirements of the Birth Defects Prevention Act (SB 950). No adverse effects were observed. At this time, methoxyfenozide has not been prioritized by DPR for risk assessment. DPR prioritizes pesticide active ingredients for risk assessment based on the nature of the potential adverse health effects, number of potential adverse effects, number of species affected, no effect levels (NOELs), potential for human exposure, use patterns and similar factors. Based on these criteria, pesticides with the greatest potential for health problems are placed in high priority, with other chemicals being in moderate or low priority. The purpose of the risk assessment will be to appraise the potential for methoxyfenozide to cause adverse health effects in humans if exposed to the pesticide as the result of a legal use. The potential for exposure from eating food crops treated with methoxyfenozide will also be evaluated during the risk assessment. Further toxicity information is available in DPR's Summary of Toxicology Data for methoxyfenozide, available on DPR public website at: http://www.cdpr.ca.gov/docs/toxsums/pdfs/5698.pdf.

C. Health & Safety

An evaluation of the medical management information on the Intrepid 2F and Intrepid 80 WSP labels and the acute toxicity study results indicate that the product labels bear all of the required statements and warnings regarding safety to handlers and other persons who may be exposed to the pesticide. The product labels bear an adequate First Aid statement. In addition, the product labels require persons handling and applying Intrepid 2F and Intrepid 80 WSP to wear long-sleeved shirt and long pants, waterproof gloves, and shoes plus socks. Workers wearing only work clothing are not allowed to enter a treated field until 4 hours after an application. The product label requires that persons entering a treated area before the 4 hour restricted-entry interval (REI) has elapsed must wear coveralls, waterproof gloves and shoes plus socks if they are going to contact treated plants, soil or water.

D. Fish & Wildlife

The registrant submitted fish and wildlife toxicity studies, including studies on bluegill sunfish, rainbow trout, daphnia magna, sheepshead minnow, saltwater mysid, eastern oysters, water fleas, northern bobwhite, mallard ducks, and honeybees. The submitted data are adequate to characterize the toxicity to wildlife and aquatic animals from an environmental exposure. Table VI summarizes the results of these studies.

Table VI. Summary of Toxicity Studies for Wildlife

Test Animal	Type of Study	Acute Toxicity Value[a]	Relative Toxicity
Bluegill sunfish	Water exposure (96 hrs.)	>4.3 mg a.i./l (LC_{50})	Moderately toxic
Rainbow trout	Water exposure (96 hrs.)	4.2 mg a.i./l (LC_{50})	Moderately toxic
Daphnia magna	Water exposure (48 hrs.)	3.7 mg a.i./l (EC_{50})	Moderately toxic
Sheepshead minnow	Water exposure (96 hrs.)	>2.8 mg a.i./l (LC_{50})	Moderately toxic
Mysid shrimp	Water exposure (96 hrs.)	1.3 mg a.i./l (LC_{50})	Moderately toxic
Oyster	Water exposure (96 hrs.)	1.3 mg a.i./l (EC_{50})	Moderately toxic
Bobwhite quail	Feeding study (8 days)	>5620 ppm (LC_{50})	Relatively non-toxic
Mallard duck	Feeding study (8 days)	>5620 ppm (LC_{50})	Relatively non-toxic
Honeybee	Contact (48 hrs.)	>100ug/bee (LD_{50})	Relatively non-toxic

a. Values expressed as: a. LD50= lethal dose that will kill 50% of test population, and b. LC50= lethal environmental concentration that will kill 50% of test population. The test substance used for the studies was technical methoxyfenozide.

The data indicate that methoxyfenozide is relatively non-toxic to vertebrate animals, birds and honeybees and moderately toxic to oysters, fish and freshwater invertebrates. Methoxyfenozide steadily decreased to 74% of the applied dose at the end of 365 days. A degradation study in an orchard revealed a half-life of 38 days. Methoxyfenozide has a low water solubility (3.3 ppm), is stable to hydrolysis at pH 5, 7 and 9 and is fairly stable to photolysis with half-lives of 173 days (soil photolysis) and 77 days (aqueous photolysis). The main route of degradation appears to be binding to the soil and incorporation into soil components such as humic and fulvic components. Once adsorbed to the soil, methoxyfenozide is tightly bound.

E. Efficacy & Phytotoxicity

Submitted efficacy studies indicate that Intrepid 2F and Intrepid 80 WSP provides effective control of the insects listed on the product labels. Phytotoxicity studies indicate that Intrepid 2F and Intrepid 80 WSP are not phytotoxic to apples and cotton. There also was no negative effect on yield of cotton. The aquatic growth data do not indicate any unexpected phytotoxicity. The submitted phytotoxicity data support registration of the subject products with the following conditions: Data or observations on the phytotoxicity of Intrepid 2F and Intrepid 80 WSP on pome fruit and cotton from tests conducted in California.

ALTERNATIVES

Intrepid 2F and Intrepid 80 WSP belong to the diacylhydrazine class of insecticides and have a novel mode of action. The chemical mimics the action of the molting hormone of Lepidopterous (moths, butterflies) larvae. Upon ingestion, moth larvae undergo an incomplete and premature molt, which ultimately results in their death. Feeding by the larvae on the leaves of pome fruit trees and cotton plants typically

ceases within hours of ingestion of the chemical even though the larvae may not die for several days. Affected larvae often become lethargic and develop discolored areas or bands between their body segments. Intrepid 2F and Intrepid 80 WSP have virtually no effect on any other type of insect, spider or crustacean, making it an ideal tool for integrated pest management programs. This selectivity allows beneficial insects (including bees) to function unimpeded in the management of secondary pests while Intrepid 2F and Intrepid 80 WSP provide control of troublesome Lepidoptera pests.

Currently, the herbicide tebufenozide (Confirm®) is used to control Lepidoptera pests. Tebufenozide is also a diacylhydrazine insecticide. Both compounds mimic the naturally occurring insect growth hormone, 20-hydroxyecdysone, by selectively binding to the ecdysteroid receptor of Lepidoptera larvae. This induces premature molting, which causes death of the larvae. Methoxyfenozide has a higher binding affinity for the active site than does tebufenozide and therefore is faster acting and active at lower rates.

CONCLUSION

DPR evaluated the product label and scientific data submitted to support the registrations of Intrepid 2F and Intrepid 80 WSP and found them acceptable to support conditional registration. The acute health risks to humans from exposure to methoxyfenozide are minimal due in part to its low mammalian toxicity. The precautionary and first aid statements on the product labels, as well as the required PPE and other protective measures mitigate potential health risks to persons who may be exposed to the pesticide. If a risk assessment is conducted and DPR determines that exposure to methoxyfenozide may result in unacceptable margins of exposure, further restrictions will be placed on the use of methoxyfenozide at that time. The submitted data also indicate significant adverse environmental impacts are not expected to occur from the use of Intrepid 2F or Intrepid 80 WSP. When used in accordance with label directions, these products will be effective for their intended use. DPR is proposing a one-year conditional registration of Intrepid 2F and Intrepid 80 WSP. The registrant is required to conduct and/or submit the results of the following studies: (1) the temperature range and the mean temperature during the two-year storage stability study for Intrepid 2F; (2) the chemical composition of two inert ingredients; and (3) data or observations on the phytotoxicity on pome fruit and cotton from tests conducted in California.