United States Environmental Protection Agency

Office of Prevention, Pesticides and Toxic Substances (7501C)

Pesticide Fact Sheet

Name of Chemical: Acibenzolar-S-Methyl
Reason for Issuance: Conditional Registration
Date Issued: August 11, 2000

DESCRIPTION OF CHEMICAL

Chemical Name:	benzo(1,2,3)thiadiazole-7-carbothioic acid-S-methyl ester
Common Name:	Acibenzolar-S-methyl
Trade Name:	Actigard
Chemical Class:	Benzothiadiazole
EPA Chemical Code:	061402
Chemical Abstracts Service (CAS) Number:	135158-54-2
Year of Initial Registration:	2000
Pesticide Type:	Plant Activator
U.S. Producer:	Novartis Crop Protection, Inc. P.O. Box 18300 Greensboro, NC 27419-8300

Use Pattern and Formulations

Actigard 50WG is a water-dispersible granular formulation containing 50% active ingredient. Acibenzolar is a selective, systemic compound which induces host plant resistance. This is a unique mode of action which mimics the natural systemic activated resistance (SAR) response found in most plant species. It has no direct effect on the target pests. Actigard is applied by ground or aerial equipment at the rate of 1.0 ounce of product per acre for the control of downy mildew on leafy vegetables (including Brassica (cole) leafy vegetables, bacterial spot

and bacterial speck on tomatoes, and blue mold on tobacco. Boost 500SC is a soluble concentrate formulation which will be used only on bananas for importation. Acibenzolar-S-methyl Technical is a 98.6% solid (powder) formulation and is intended for use only in the manufacturing of end-use products.

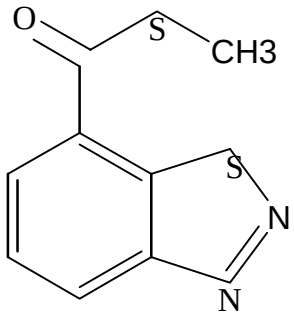
Science Findings

Summary Science Statement:

EPA has concluded from the review of the supporting data that there are no risks of concern from the use of acibenzolar-S-methyl. There was no significant acute toxicity in a battery of acute toxicity studies and no dermal sensitivity was detected with Actigard. It was calculated that the risk due to exposure to residues in food and water or in tobacco was below the Agency's level of concern for all population subgroups, including infants and children. Risk from exposure of workers (applicators and other handlers) was also below the Agency's level of concern. There are no residential uses of Actigard either registered or pending. The Agency also concluded that the use of Actigard for the labeled uses is unlikely to represent a significant threat to non-target organisms or the environment.

Physical/Chemical Properties:

Chemical Name: Benzo(1,2,3)thiadiazole-7-carbothioic acid-S-methyl ester
Molecular Formula: $C_8H_6N_2OS_2$
Molecular weight: 210.3 g/mole
Physical State: beige fine powder
Melting point: 132.9°C
Density: 1.54 X 10^3 g/cm^3 at 22°C
Vapor pressure (25 C): 3.5 x 10^{-6} mm Hg
Henry's Constant: 1.26 X 10^{-7} atm m^3 $mole^{-1}$ (calc.)
Solubility: Water (25 C, pH 7.5-7.9): 7.7 mg/L (7.7 ppm)
log P_{ow} : 3.1 @ 25°C
Water solubility of the degradate CGA-210007 (benzo[1,2,3]thiadiazole-7-carboxylic acid) is approx. 225 ppm at 25°C pH 3.6-3.8



Acibenzolar-S-methyl

Toxicological Characteristics:

Acute effects.

Technical-grade acibenzolar-S-methyl showed no significant acute toxicity in a battery of acute toxicity tests (Toxicity Category III or IV, all tests), but considerable skin sensitizing potential was demonstrated in a dermal sensitization study in guinea pigs. The formulated end-use product (Actigard™ 50 WG) demonstrated no significant acute toxicity; additionally, the end-use product did not show dermal sensitization in guinea pigs. Test results are as follows:

Test	Test Substance	Result	Toxicity Category
Acute Oral Toxicity	Acibenzolar-S-methyl	LD_{50} >5000 mg/kg	IV
	Actigard 50WG	LD_{50} >5000 mg/kg	IV
Acute Dermal Toxicity	Acibenzolar-S-methyl	LD_{50} >2000 mg/kg	III
	Actigard 50WG	LD_{50} >2000 mg/kg	III
Acute Inhalation Tox.	Acibenzolar-S-methyl	LC_{50} >5.022 mg/L	IV
	Actigard 50WG	LC_{50} >2.79 mg/L	IV
Primary Eye Irritation	Acibenzolar-S-methyl	Minimal	III
	Actigard 50WG	Minimal	III
Primary Dermal Irritation	Acibenzolar-S-methyl	Slight	IV
	Actigard 50WG	Moderate	III
Dermal Sensitization	Acibenzolar-S-methyl	Positive	N/A
	Actigard 50WG	Negative	N/A

Subchronic and chronic effects:

The results of the subchronic and chronic studies follow:

Toxicity Profile of Acibenzolar-S-Methyl and Related Chemicals*.

Guideline No./ Study Type	Classification /Doses	Results
870.3100 90-Day oral toxicity rats	Acceptable/guideline M : 0, 2.42, 24.6, 126, 516 mg/kg/day; F: 0, 2.64, 26.3, 131, 554 mg/kg/day	NOAEL: Males:126 mg/kg/day; Females: 131 mg/kg/day LOAEL: Males = 516 mg/kg/day; Females = 554 mg/kg/day based on decreased mean body weights, decreased food consumption and efficiency, and increased liver and spleen weights with correlates of glycogen deposition and hemosiderosis for the liver and spleen, respectively.
870.3150 90-Day oral toxicity dogs	Acceptable/guideline M & F: 0, 10, 50, 200 mg/kg/day (capsules)	NOAEL = 50 mg/kg/day LOAEL = 200 mg/kg/day based on regenerative hemolytic anemia.

Toxicity Profile of Acibenzolar-S-Methyl and Related Chemicals*.		
Guideline No./ Study Type	**Classification /Doses**	**Results**
870.3200 21/28-Day dermal toxicity rats	Acceptable/guideline M & F: 0, 10, 100, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL = not identified
870.3700a Prenatal developmental rats	Acceptable/guideline F: 0,10, 50, 200, 400 mg/kg/day	**Maternal** NOAEL = 200 mg/kg/day LOAEL = 400 mg/kg/day based on hemorrhagic perineal discharge. **Developmental** NOAEL = not identified (<10 mg/kg/day) LOAEL = 10 mg/kg/day (lowest dose tested) based on umbilical hernia.
870.3700b Prenatal developmental rabbits	Acceptable/guideline F: 0, 10, 50, 300, 600 mg/kg/day	**Maternal** NOAEL = 50 mg/kg/day LOAEL = 300 mg/kg/day based on mortality, clinical signs of toxicity, decreased maternal body weight and food consumption. **Developmental** NOAEL = 300 mg/kg/day LOAEL = 600 mg/kg/day based on a marginal increase in vertebral anomalies.
870.3800 Reproduction and fertility effects rats	Acceptable/guideline M & F: 0, 1-3, 11-31, 105-288, 223-604 mg/kg/day	**Parental/Systemic** NOAEL = 11-31 mg/kg/day LOAEL = 105-288 mg/kg/day based on increased weights and hemosiderosis of the spleen. **Reproductive** NOAEL = 223-604 mg/kg/day LOAEL > 223-604 mg/kg/day based on no effects. **Offspring** NOAEL = 11-31 mg/kg/day LOAEL = 105-288 mg/kg/day based on reduced pup body weight gains and lower pup body weights during lactation.
870.4100a Chronic toxicity rats	Acceptable/guideline M: 0, 0.77, 7.77, 96.9, 312 mg/kg/day F: 0, 0.90, 9.08, 111, 388 mg/kg/day	NOAEL = Males: 96.9 mg/kg/day; Females: 111 mg/kg/day LOAEL = Males: 312 mg/kg/day; Females: 388 mg/kg/day based on decreased body weight, body weight gain and food efficiency, mild hemolytic anemia, and increased incidence of alveolar foam cells (females only).
870.4100b Chronic toxicity dogs	Acceptable/guideline M & F: 0, 5, 25, 200 mg/kg/day (capsules)	NOAEL = 25 mg/kg/day LOAEL = 200 mg/kg/day based on effects consistent with hemolytic anemia, including hematological effects, hemosiderosis of the liver and spleen, extramedullary hematopoiesis of the spleen, and increased liver weights.

Toxicity Profile of Acibenzolar-S-Methyl and Related Chemicals*.		
Guideline No./ Study Type	**Classification /Doses**	**Results**
870.4200a Carcinogenicity rats	Acceptable/guideline M: 0, 0.77, 7.77, 96.9, 312 mg/kg/day F: 0, 0.90, 9.08, 111, 388 mg/kg/day	NOAEL = Males: 96.9 mg/kg/day; Females: 111 mg/kg/day LOAEL = Males: 312 mg/kg/day; Females: 388 mg/kg/day based on decreased body weight, body weight gain and food efficiency, mild hemolytic anemia, and increased incidence of alveolar foam cells (females only). **No evidence of carcinogenicity**
870.4200b Carcinogenicity mice	Acceptable/guideline M: 0, 1.14, 11.1, 237, 698 mg/kg/day F: 0, 1.14, 10.8, 234, 696 mg/kg/day	NOAEL = Males:11.1 mg/kg/day; Females: 10.8 mg/kg/day LOAEL = Males: 237 mg/kg/day; Females: 234 mg/kg/day based on mild hemolytic anemia and hemosiderosis of the liver, spleen, and bone marrow, and extramedullary hematopoiesis of the spleen. **No evidence of carcinogenicity**
870.5100 Bacterial reverse mutation assay (Ames test)	Acceptable/guideline 312.5, 625, 1250, 2500, 5000 µg/plate	Negative with and without S-9 activation at 5000 µg/plate and less.
870.5100 Bacterial reverse mutation assay (Ames test) Test Material: CGA-362020 (isomer of acibenzolar-S-methyl)	Acceptable/guideline 61.73 to 5000 µg/plate (+S-9) 30-86 to 2500 µg/plate (-S-9)	Positive in *S. typhimurium* strain TA1537 at 277.8 µg/plate and higher in the absence of S-9. Negative with S-9 activation at 5000 µg/plate and less.
870.5100 Bacterial reverse mutation assay (Ames test) Test Material: NOA-419191 (by-product of acibenzolar-S-methyl)	Acceptable/guideline 312.5 to 5000 µg/plate (± S-9)	Negative with or without S-9 activation at 5000 µg/plate and less
870.5100 Bacterial reverse mutation assay (Ames test) Test Material: CGA-323060 (plant metabolite of acibenzolar-S-methyl)	Acceptable/guideline 312.5 to 5000 µg/plate (± S-9)	Negative with or without S-9 activation at 5000 µg/plate and less

Toxicity Profile of Acibenzolar-S-Methyl and Related Chemicals*.		
Guideline No./ Study Type	**Classification /Doses**	**Results**
870.5300 *In vitro* mammalian gene mutation assay	Acceptable/guideline 3.70 to 100 µg/ml (-S-9), 37.04 to 1000 µg/ml (+S-9)	Negative with S-9 activation up to 1000µg/ml. Negative without S-9 activation up to 100µg/ml. Compound tested to cytotoxic concentrations.
870.5375 *In vitro* mammalian chromosome aberration (CHO cells)	Acceptable/guideline 7.5 to 60 µg/ml (-S-9 and +S-9)	Suggestive of clastogenicity in the absence of S-9 activation at 30 and 60 µg/mL at the 18-hour cell harvest time; effect observed only in the presence of cytotoxicity. Increase in polyploid cells at 30 and 60 µg/mL at the 42 hour harvest time both with and without S-9. Evidence of cell cycle arresting activity at G_2.
870.5395 Mammalian erythrocyte micronucleus test	Acceptable/guideline 1000, 2000, 4000 mg/kg (oral gavage)	Negative at 16, 24, and 48, hour sacrifices.
870.5550 UDS in primary rat hepatocytes	Acceptable/guideline 9.77 to 500 µg/ml	Negative at 500 µg/ml and less.
870.7485 Metabolism and pharmacokinetics rats	Acceptable/guideline 0.5, 100 mg/kg	Following oral treatment of rats, acibenzolar-S-methyl was rapidly and nearly completely (>90% of administered dose) absorbed from the gastrointestinal tract into the general circulation. The majority (88-95%) of the administered dose was excreted in the urine within the first 48 hours. The major metabolite (79-92%) in the urine was the carboxylic acid derivative of the parent.
<u>Special studies</u>: 28-Day dietary rats	Acceptable/nonguideline M: 0, 45.9, 403, 1070 mg/kg/day; F: 0, 44.8, 376, 1000 mg/kg/day	NOAEL = M: 403 mg/kg/day; F: 376 mg/kg/day LOAEL = M: 1070 mg/kg/day; F: 1000 mg/kg/day based on decreased mean body weights, decreased liver weights, altered hematology parameters accompanied by increased spleen weights.
28-Day oral gavage rats	Acceptable/nonguideline 0, 10, 100, 800 mg/kg/day	NOAEL = 100 mg/kg/day LOAEL = 800 mg/kg/day based on decreased body weights, and decreased hemoglobin-related parameters accompanied by hemosiderosis of the spleen, increased liver and spleen weights, and decreased thymus weights.
28-Day oral capsule dogs	Acceptable/nonguideline 0, 50, 250, 500 mg/kg/day	NOAEL = 50 mg/kg/day LOAEL = 250 mg/kg/day based on decreased body weight, decreased hemoglobin-related parameters, hepatic and splenic hemosiderosis.

Toxicity Profile of Acibenzolar-S-Methyl and Related Chemicals*.		
Guideline No./ Study Type	**Classification /Doses**	**Results**
90-Day Dietary mice	Acceptable/nonguideline M: 0, 30.6, 152, 624 mg/kg/day; F: 0, 47.4, 220, 803 mg/kg/day	NOAEL = M: 30.6 mg/kg/day; F: 47.4 mg/kg/day LOAEL = M: 152 mg/kg/day; F: 220 mg/kg/day based on decreased mean body weights and body weight gain in males, increased spleen weights and splenic histopathology in both sexes.
Special Developmental toxicity rats	Acceptable/nonguideline 300 mg/kg/day, GD 6-15, 6-7, 8-9, 10-11, 12-13, or 14-15	Maternal and developmental NOAELS and LOAELS could not be identified by this protocol. The most pronounced maternal and developmental toxicity occurred when dams were treated on GD 6-15.
Special Developmental toxicity rats	Acceptable/nonguideline 400 mg/kg/day, GD 6-7, 8-9, 10-11, 12-13, or 14-15	Maternal and developmental NOAELS and LOAELS could not be identified by this protocol. The most pronounced maternal and developmental toxicity occurred when dams were treated on GD 6-7 and 8-9.
Dermal developmental toxicity rats	Acceptable/nonguideline 0, 10, 100, 500 mg/kg/day, GD 6-15	**Maternal** NOAEL 500 mg/kg/day LOAEL >500 mg/kg/day based on no effects. **Developmental** NOAEL 500 mg/kg/day LOAEL >500 mg/kg/day based on no effects.
Range-finding 1-generation reproduction rats	Acceptable/nonguideline 0, 199-209, 382-410, 700-728 mg/kg/day	**Parental/Systemic** NOAEL = 209 mg/kg/day LOAEL = 410 mg/kg/day based on decreased body weight gain and food consumption in females. **Reproductive** NOAEL = 410 mg/kg/day LOAEL = 728 mg/kg/day based on total resorptions in all dams. **Offspring** NOAEL = 209 mg/kg/day LOAEL = 410 mg/kg/day based on reduced pup body weight gains and lower pup body weights during lactation.

* All studies performed on technical-grade acibenzolar-S-methyl unless otherwise indicated; CGA-362020 (isomer of Acibenzolar-S-Methyl, 99%); NOA-419191 (by-product of Acibenzolar-S-Methyl, 98%); CGA-323060 (plant metabolite of Acibenzolar-S-Methyl, 98%)

Summary of Toxicology Findings.

In chronic and subchronic oral studies with rats, dogs, and mice, signs of mild regenerative hemolytic anemia were consistently observed at or slightly above the LOAEL. Decreases in body weight, body weight gain, and/or food consumption were also observed in these studies. In rats and mice, acibenzolar-S-methyl was negative for carcinogenicity and in a battery of mutagenicity studies, technical-grade acibenzolar-S-methyl results were negative except in an *in vitro* chromosome aberration study with Chinese hamster ovary (CHO) cells. The results from this test, however, are considered only suggestive of a possible aneuploidy effect. Positive results in a *S. typhimurium* reverse gene mutation assay were observed in a study conducted with

a structural isomer (CGA-362020) of acibenzolar-S-methyl. Since this isomer is found at low levels (0.1%) in some batches of technical-grade acibenzolar-S-methyl manufactured by a new "thiazole process," full batteries of mutagenicity studies with CGA-362020 and with acibenzolar-S-methyl manufactured by the "thiazole process" are required.

Of significant toxicological concern was the finding of treatment-related developmental malformations, anomalies and variations in the developmental toxicity study in rats at dose levels equal to or below the NOAEL for maternal toxicity. At the highest dose level tested in this study (400 mg/kg/day), both maternal toxicity (hemorrhagic perineal discharge) and considerable developmental toxicity (including total litter resorptions, and fetal malformations, anomalies and variations) were observed. The fetal malformations noted at this dose level included treatment-related effects on nervous system tissues (hydrocephaly, craniorachisis and anophthalmia/ microphthalmia). At the lowest dose level tested (10 mg/kg/day), treatment-related umbilical hernias (considered to be a midline closure defect, along with omphalocele and gastroschisis which were observed at higher dose levels) were also observed. Therefore, no NOAEL for developmental toxicity was observed in this study and increased susceptibility of rat fetuses (as compared to adults) was evident. Further, in additional studies in rats, it was demonstrated that as few as two doses of test material could cause hemorrhagic perineal discharge and complete litter resorptions in dams. A similar increased susceptibility of fetuses or pups (as compared to adults) was not observed in a developmental toxicity study in rabbits or in a 2-generation or 1-generation (range-finding) study in rats.

Occupational and Residential Exposure and Risk Characterization.

Application of acibenzolar-S-methyl may be by ground or aerial equipment and may occur up to 6 times per growing season. Short- and intermediate-term exposures may occur. Chronic exposures are not expected. Potential mixer/loader and applicator exposures were estimated and assessed for both dermal and inhalation routes. The calculated margins of exposure (MOEs) for mixer/loaders and applicators range from 42,000 to 880,000 for dermal exposure and from 72,000 to 810,000 for inhalation exposure. The post application exposure was calculated based on hand harvesting of tomatoes for an exposure period of 8 hours. The post application MOE was estimated to be 5,400 on day 0 after application. The calculated MOEs for occupational exposure do no exceed the Agency's level of concern.

At present there are no registered or proposed residential uses of acibenzolar-S-methyl. Therefore, a residential risk assessment was not performed.

Since the registration of acibenzolar-S-methyl includes use on tobacco, an exposure assessment of risk from tobacco use was conducted. The short-term inhalation LOAEL is 10 mg/kg/day based on an oral rat development study. The short-term MOE for exposure through the use of tobacco is greater than 500,000 and is below the Agency's level of concern.

Aggregate Exposure and Risk Characterization.

1. General Considerations.

Based on the toxicological data base, the HED Hazard Identification Assessment Review Committee selected endpoints for acute dietary (females 13-50 only), chronic dietary (separate reference doses for females 13-50 versus all other population subgroups), dermal, and inhalation routes of exposure.

The FQPA safety factor for acibenzolar-S-methyl has been retained at 10X when assessing acute and chronic dietary exposures for the females aged 13-50 years population subgroup. When assessing chronic dietary exposure for other populations, the FQPA safety factor was reduced to 3X. The Safety Factor Committee determined that the factor is required based on the demonstrated increased susceptibility of fetuses (compared to dams) in the rat developmental study, the observed developmental malformations in rat fetuses at the lowest dose tested, and the requirement for a developmental neurotoxicity study in rats.

The tolerance expression for acibenzolar-S-methyl is for residues convertible to benzo(1,2,3)thiadiazole-7-carboxylic acid (a.k.a. CGA-210007), expressed as acibenzolar. For purposes of risk assessment, residues of the 4- and 5-hydroxy metabolites (CGA-324041 and CGA-323060) of CGA-210007 should also be considered. For this purpose, the toxicity of CGA-324041 and CGA-323060 should be considered equivalent to that of the parent compound acibenzolar. These residues occur in significant quantities in lettuce and tomato. At this time, acibenzolar-S-methyl does not have common metabolites with other agrochemicals. The residues of concern for drinking water are the same as those listed in the tolerance expression; that is, residues convertible to CGA-210007.

2. Food.

An acute dietary exposure assessment (food only) was performed using the distribution of residues observed in the crop field trials and the projected percent market share for the crops involved. The analysis used the Dietary Exposure Evaluation Model (DEEM) to develop exposure and risk estimates for the population subgroup females 13 - 50 years of age. The refined dietary exposure estimate for this subgroup is 0.0029 mg/kg/day. This is equivalent to 87% of the acute population-adjusted dose (aPAD). This risk estimate does not exceed the Agency's level of concern.

A chronic dietary exposure assessment using residue levels at the tolerance level and 100% of crop treated was performed using DEEM coupled with the 1989-1992 CSFII. The estimated dietary (food only) risks are generally less than 10% of the chronic population-adjusted dose (cPAD). An exception to this, due to the 10X FQPA safety factor, is the female 13+ population subgroups, which have risk estimates on the order of 52% of the cPAD. Risk estimates for all population subgroups, including infants and children, are below the Agency's level of concern.

3. Water.

In drinking water, the residues of concern are acibenzolar-S-methyl and its degradate CGA-210007. These residues are non-persistent to slightly persistent in the environment under aerobic aquatic conditions in and are unlikely to reach surface or ground water. In an anaerobic aquatic environment, acibenzolar-S-methyl is considered to be slightly to moderately persistent. The Tier I estimated environmental concentrations (EECs) for acibenzolar-S-methyl from the GENEEC surface water model are 640 parts per trillion (ppt) and 20 ppt for the acute (peak) and chronic (56-day) values. The acute and chronic ground water EECs are both negligible.

Aggregate Risk Assessments and Risk Characterization.

Since there are no requested residential use sites for acibenzolar and current OPP policy does not include tobacco use when aggregating sources of exposure, only dietary exposure (food plus drinking water) will be considered when assessing aggregate risk for the requested uses of acibenzolar.

The estimated acute exposure to acibenzolar-S-methyl from food is 0.0029 mg/kg/day. This exposure estimate is rather refined, incorporating field trial distributions and projected percent market share data and reflects the 99.9th percentile of exposure for the population subgroup females 13-50 years of age (the only population subgroup of concern for acute dietary exposure). Based on the aPAD of 0.0033 mg/kg/day for this exposure scenario/population subgroup, the maximum allowable exposure to acibenzolar-S-methyl from drinking water is 0.0004 mg/kg/day (0.0033 mg/kg/day - 0.0029 mg/kg/day). Using HED default assumptions of 2 L/day adult drinking water consumption and 60 kg body weight for adult females, this results in an acute drinking water level of comparison (DWLOC) of 12 µg/L. The acute EEC from GENEEC for acibenzolar-S-methyl is 640 ppt, or 0.64 µg/L and does not include estimated concentrations of CGA-210007. This EEC is well below the acute DWLOC. The EEC is the result of a Tier-1 analysis and as such is a conservative estimate. This, coupled with the degree of difference between the acute DWLOC and the acute EEC make it extremely unlikely that actual residues of concern for acibenzolar-S-methyl (including CGA-210007) will exceed the DWLOC.

The acute aggregate risk from exposure to acibenzolar-S-methyl residues is unlikely to exceed the Agency's level of concern for females 13-50 years old, the population subgroup of concern for acute exposure to acibenzolar. The Agency concludes that there is reasonable certainty that no harm will result to the populations of concern from acute aggregate exposure to residues of acibenzolar.

The chronic, Tier 1 EEC for acibenzolar-S-methyl is 20 ppt. Although the EEC does not include estimated concentrations of CGA-210007, it is sufficient for purposes of this risk assessment. The EEC is the result of a Tier-1 analysis and as such is a conservative estimate. The modeled chronic dietary (food only) exposures are also conservative, Tier 1 estimates; thus, the resulting chronic aggregate risk estimates shown are highly conservative in nature. Even without further refinement, the chronic aggregate risks from exposure to acibenzolar-S-methyl residues do not exceed the Agency's level of concern for the general U.S. population or any population subgroup. It is concluded that there is reasonable certainty that no harm will result to adults, infants, or children from chronic aggregate exposure to residues of acibenzolar.

Additional Toxicology Data Requirements:

The following toxicology data needs are conditions of registration:

Developmental neurotoxicity study in rats.
Subchronic neurotoxicity study in rats.
Mutagenicity study (Ames assay with both incorporation and pre-incubation) performed on technical-grade acibenzolar-S-methyl prepared by the new "thiazole" production process.

Ecological Effects/Environmental Fate Characteristics:

1. Environmental Fate Summary:

Acibenzolar (Actigard; CGA-245704) readily degrades under environmental conditions by abiotic and biotic processes. Degradation was rapid by photolysis in water and on soil at relevant environmental photoperiods and considerably less rapid hydrolytically at relevant environmental pH's (pH 6-9). The major degradates observed were benzo[1,2,3]thiadiazole-7-carboxylic acid (CGA 210007) in the hydrolysis and soil photolysis studies (up to 100 percent) with considerably lesser amounts found in the photolysis in water study (8.4 percent). The major degradate in the photolysis in water study was CO_2 (>33 percent). Other degradates identified that may be of toxicological concern were CGA 323060 and 324041 (hydroxy-metabolites from the photolysis on soil study). These were found in amounts not exceeding 0.5 percent.

Biotically, Acibenzolar rapidly degraded on soil (5 hours) and water (<1 day) aerobically, and was somewhat slower in water anaerobically indicating a biphasic pattern of decline (4 days followed by 95 days). The major degradate was again CGA 210007 (up to 88 percent), but in the aerobic soil study, significant degradation of CGA 210007 was observed (calculated half-life of 16.5 days). Under anaerobic conditions in water, CGA 210007 showed very little degradation by the end of the study (day 360). No other degradates that may be of toxicological concern were identified.

Regarding mobility of Acibenzolar, adsorption and terrestrial field studies indicate that movement below the top 3 inches is unlikely. Although Acibenzolar would sorb to soils and sediments, degradation is the principal impediment to leaching. Additionally, Acibenzolar would not be expected to accumulate in sediments due to the rapid metabolism under aerobic conditions. The major degradate, CGA 210007, is more mobile and if it reaches depths below which aerobic metabolism is likely, may be found in groundwater due to its substantially longer half-life under anaerobic conditions.

2. Ecological Effects Summary:

The acute toxicity of Acibenzolar-S-methyl, based on the maximum application rate is summarized below.

Summary of Terrestrial Ecotoxicity Studies Using Acibenzolar (97.9% ai)

Species	Toxicity Value	Toxicity Category	MRID
Mallard Duck	Acute oral LD50 >2000 mg/kg	Practically nontoxic	44537004
	Subacute Dietary LC50 >5000 ppm	Practically nontoxic	44537008
	Avian Reproduction NOAEC = 1000 ppm; LOAEC not determined[1]	-	44537010
Bobwhite	Acute oral LD50 >2000 mg/kg	Practically nontoxic	44537005
	Subacute Dietary LC50 >5000 ppm	Practically nontoxic	44537006
	Avian Reproduction NOAEC = 600 ppm; LOAEC= 1000 ppm[2]	-	44537009
Rat	Acute oral LD50 >5000 mg/kg 90-day subchronic rat feeding NOAEC =400 ppm[3] Two-generation rat reproduction NOAEC =200 ppm[3]	Practically nontoxic	44537007
Honey Bee	LD50 > 100*u*g per bee	Practically nontoxic	44537033
Seedling Emergence			
Tomato (Dicot)	21% shoot length inhibition[4]	-	44537028
Wheat (Monocot)	11% plant dry weight inhibition[4]	-	44537028
Vegetative Vigor			
Tomato (Dicot)	10% plant dry weight inhibition[4]	-	44537029
Ryegrass (Monocot)	10% plant dry weight Inhibition[4]	-	44537029

Summary of Aquatic Ecotoxicity Studies Using Acibenzolar (98% ai)

Species	Toxicity Value	Toxicity Category	MRID	Classification
FRESHWATER ANIMALS				
Rainbow Trout	LC50 = 0.88 ppm	Highly toxic	44537013	Core
	Fish early life stage NOAEC = 26 ppb LOAEC = 54 ppb (most sensitive endpoint was growth; weight)	-	44537019	Core
Bluegill	LC50 = 1.6 ppm	Moderately toxic	44537011	Core
Water Flea	LC50 = 2.9 ppm	Moderately toxic	44537014	Core
	Life Cycle Test	-	44537020	Core

	NOAEC = 48 ppb LOAEC = 87 ppb (most sensitive endpoint was growth; length and weight)			
ESTUARINE ANIMALS				
Sheepshead Minnow	LC50 = 1.7 ppm	Moderately toxic	44537016	Core
Eastern Oyster	EC50 = 0.59 ppm	Highly toxic	44537017	Core
Mysid Shrimp	LC50 = 0.88 ppm	Highly toxic	44537018	Core
AQUATIC PLANTS				
Green Algae	EC50 = 3.3 ppm	-	44537030	Core
Duckweed	EC50 = 0.312 ppm	-	44537030	Core

Note: Studies were conducted under flow-through conditions for animal studies

Novartis submitted three aquatic toxicity studies using the degradate, CGA-210007 (97% ai), which demonstrate minimal toxicity to aquatic organisms. These studies are scientifically sound, but were classified supplemental (see footnotes in Table 6 below).

Summary of Aquatic Ecotoxicity Studies Using the Degradate CGA-210007 (97% ai)[3]

Rainbow Trout	Acute LC50 >92 ppm	Practically nontoxic	44537012	Supplemental[1]
Water Flea	Acute LC50 = 59.9 ppm	Practically nontoxic	44537015	Core
Green Algae *S. capricornutum*	EC50 = 80.1 ppm	-	44537031	Supplemental[2]

[1] Only seven fish were tested per group rather than the recommended 30 fish per group.
[2] The study was conducted for 3 days rather than the recommended 4 or 5 days.
[3] Studies were conducted under static conditions for animal studies

Summary of Ecotoxicity Studies. Acibenzolar-S-methyl was found to be:

a. practically non-toxic to terrestrial animals on an acute and subacute basis

b. practically nontoxic to insects

c. moderately to highly toxic to freshwater and estuarine aquatic animals on an acute basis
with a narrow range of toxicity values (*i.e.*, 0.6 ppm for eastern oyster to 2.9 ppm for daphnid)

d. toxic to aquatic plants

e. avian reproduction NOAEL of 600 ppm based on a reduction in 14-day old survivor weights and the percentage of 14-day old hatchling survivors per normal hatching, LOAEC was 1000 ppm.

f. freshwater fish early life stage NOAEC of 26 ppb based on growth reduction (wet/dry weight) effects; LOAEC was 54 ppb

g. freshwater invertebrate life cycle NOAEC of 48 ppb based on growth reduction (length/dry weight) effects; LOAEC was 87 ppb

Environmental Risk Assessment.

Based on combined environmental exposure and ecological toxicity, it is unlikely Acibenzolar will pose a risk of acute or chronic toxicity to nontarget animals.

Additional Environmental Data Requirements:

The following environmental data needs are conditions of registration:

Soil photolysis study
Aerobic soil metabolism study
Aerobic aquatic metabolism study
Batch equilibrium study

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