Proposed Registration Decision PRD2010-19

Acibenzolar-S-Methyl

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario
K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

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Overview

Proposed Registration Decision for Acibenzolar-S-Methyl

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Acibenzolar-S-Methyl Technical and Actigard 50WG, containing the technical grade active ingredient acibenzolar-S-methyl, to control or suppress a variety of fungal diseases in tomato and tobacco.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of acibenzolar-S-methyl and Actigard 50WG.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the PMRA section of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on acibenzolar-S-methyl, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on acibenzolar-S-methyl, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Acibenzolar-S-Methyl?

Acibenzolar-S-methyl is the active ingredient in the end-product Actigard 50WG, which is formulated as a water–dispersible granule. It controls or suppresses disease by inducing the host plant's defense responses. Actigard 50WG is to be used for suppression of bacterial spot (*Xanthomonas campestris* pv. *vesicatoria*) and bacterial speck (*Pseudomonas syringae* pv. *tomato*) on tomato and for control of blue mold (*Peronospora tabacina*) on tobacco.

Health Considerations

Can Approved Uses of Acibenzolar-S-Methyl Affect Human Health?

Acibenzolar-S-methyl is unlikely to affect your health when used according to label directions.

Potential exposure to acibenzolar-S-methyl may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only uses for which the exposure is well below levels that cause no adverse effects in laboratory animals are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no adverse effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when acibenzolar-S-methyl products are used according to label directions.

[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

In laboratory animals, the acute toxicity of acibenzolar-S-methyl was low by the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes and skin, but is considered a potential skin sensitizer. Consequently, the hazard signal words "POTENTIAL SKIN SENSITIZER" are required on the label. Similarly, in laboratory animals the acute toxicity of the end-use product Actigard 50WG was low by the oral, dermal and inhalation routes of exposure. It was minimally irritating to the eyes, but moderately irritating to the skin, and is not considered a skin sensitizer. Consequently, the hazard signal words "WARNING – SKIN IRRITANT" are required on the label.

Acibenzolar-S-methyl did not cause cancer in animals and was not genotoxic. There were also no effects on reproduction. The first signs of toxicity in adult animals given daily doses of acibenzolar-S-methyl over longer periods of time were spleen effects in the mouse. At higher doses, or with longer periods of exposure, toxicity effects occurred in the blood, liver, spleen and bone marrow in mice, rats and dogs. Body weight effects also occurred in these three species, as well as in the rabbit. There was no indication that acibenzolar-S-methyl caused damage to the adult nervous system. However, acibenzolar-S-methyl given to pregnant animals resulted in changes in brain development, as well as birth defects, at doses that were not toxic to the mother. The developing foetus and early postnatal young are potentially more sensitive to acibenzolar-S-methyl than adult animals. As a consequence, extra factors were applied during the risk assessment to further reduce the allowable level of human exposure to acibenzolar-S-methyl. The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern

Aggregate dietary intake estimates (food plus water) revealed that the general population and infants (<1 year old), the subpopulation which would ingest the most acibenzolar-S-methyl relative to body weight, are expected to be exposed to less than 9% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from acibenzolar-S-methyl is not of concern for all population sub-groups. Acibenzolar-S-methyl is not carcinogenic, therefore, a chronic cancer dietary risk assessment is not required.

An aggregate (food plus water) dietary intake estimate for the highest exposed population (children 1-2 years old) was less than 94% of the acute reference dose, which is below the level of concern. Therefore, the acute dietary risk from acibenzolar-S-methyl is below the level of concern for all population sub-groups.

The *Food and Drugs Act (FDA)* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for FDA purposes through the evaluation of scientific data under the *Pest Control Products Act (PCPA).* Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout the United States using acibenzolar-S-methyl on tomatoes and tobacco were acceptable to support the domestic uses. No new MRLs are recommended at this time as MRLs for tomatoes and tomato paste were previously established to cover residues in imported commodities. The MRLs for this active ingredient can be found in the Science Evaluation section of this consultation document.

Occupational Risks From Handling Actigard 50WG

Occupational risks are not of concern when Actigard 50WG is used according to the proposed label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply Actigard 50WG as well as field workers re-entering freshly treated fields can come in direct contact with Actigard 50WG residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying Actigard 50WG must wear a long-sleeved shirt, long pants, and shoes or boots with socks, and may not treat more than 100 hectares in a day. In addition, workers mixing and loading the concentrated product must wear chemical resistant gloves and goggles. The label also requires that workers do not enter treated fields for 12 hours after application to tomatoes and for 8 days after application to tobacco. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Acibenzolar-S-Methyl Is Introduced Into the Environment?

Environmental risks are not of concern.

Acibenzolar-S-methyl is degraded by both chemical reactions and microorganisms in soil and water. Acibenzolar-S-methyl is non-persistent in soil and in aquatic systems. Transformation in water is enhanced by sunlight, but not in soil. The major transformation product of acibenzolar-S-methyl, CGA 210007, is mobile in soil. An assessment of the leaching of CGA 210007 was conducted, and is dependent on many different factors. The assessment concluded that the concerns for CGA 210007 to leach to groundwater are minimal. Acibenzolar-S-methyl and CGA 210007 do not bioconcentrate and are therefore unlikely to bioaccumulate.

Although acibenzolar-s-methyl is highly toxic to aquatic organisms, adverse effects on these organisms through spray drift deposition in aquatic habitats adjacent to the treatment areas and at the proposed application rates, are unlikely. There are no environmental risk concerns for acibenzolar-S-methyl or its transformation products affecting non-target terrestrial organisms as a result of spray drift in areas adjacent to the treatment area, at the proposed application rates.

Value Considerations

What Is the Value of Actigard 50WG

Acibenzolar-S-methyl, the active ingredient in Actigard 50WG, suppresses bacterial spot (*Xanthomonas campestris* pv. *vesicatoria*) and bacterial speck (*Pseudomonas syringae* pv. *tomato*) on tomato and controls blue mold (*Peronospora tabacina*) on tobacco.

Acibenzolar-S-methyl has been identified as an important active for Canadian growers for use on several crops including apple, artichoke, basil, broccoli, cabbage, cucumber, lettuce, pepper, beans, strawberry, tomato, potato, pumpkin, squash and spinach.

The registration of Actigard 50WG on tomatoes and tobacco will provide growers with a different mode of action that would help to manage diseases on these crops. Currently, only two actives are registered for bacterial spot and bacterial speck on tomatoes while four actives are registered for blue mold control in tobacco.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Actiguard 50WG to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

As there is a concern with users coming into direct contact with Actigard 50WG on the skin, anyone mixing, loading and applying Actigard 50WG must wear a long-sleeved shirt, long pants, and shoes or boots with socks, and may not treat more than 100 hectares in a day. In addition, workers mixing and loading the concentrated product must wear chemical resistant gloves and goggles. The label also requires that workers do not enter treated fields for 12 hours after application for tomatoes and for 8 days after application for tobacco. Standard label statements to protect against drift during application were added to the label.

Next Steps

Before making a final registration decision on acibenzolar-S-methyl, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

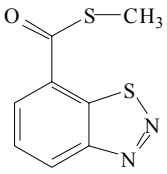
When the PMRA makes its registration decision, it will publish a Registration Decision on acibenzolar-S-methyl (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Acibenzolar-S-Methyl

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Acibenzolar-S-methyl
Function	Fungicide, plant growth regulator
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	*S*-methyl benzo[1,2,3]thiadiazole-7-carbothioate
2. Chemical Abstracts Service (CAS)	*S*-methyl 1,2,3-benzothiadiazole-7-carbothioate 1,2,3-benzothiadiazole-7-carbothioic acid *S*-methyl ester
CAS number	135158-54-2
Molecular formula	$C_8H_6N_2OS_2$
Molecular weight	210.3
Structural formula	
Purity of the active ingredient	99%

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—Acibenzolar-S-Methyl Technical

Property	Result
Colour and physical state	Beige powder
Odour	Weak burnt-like
Melting point	132.9°C
Boiling point	~267°C
Density at 20°C	1.54 g/cm^3
Vapour pressure at 20°C	0.22 mPa
Ultraviolet (UV)-visible spectrum	λ_{max} = 253, 288 and 324 nm No absorption at wavelengths above 355 nm
Solubility in water at 25°C	7.7 mg/L (pH 7.5-7.9)

Property	Result
Solubility in organic solvents at 25°C (g/L)	Solvent / Solubility n-hexane 1.3 methanol 4.2 n-octanol 5.4 ethyl acetate 25 acetone 28 toluene 36 dichloromethane 160
n-Octanol-water partition coefficient (K_{ow})	log P = 3.1± 0.1
Dissociation constant (pK_a)	No dissociation constant in an accessible pH range (pH 1-9)
Stability (temperature, metal)	Stable at 54ºC for 3 months. No significant decomposition in the presence of stainless steel, cast steel, tin shot and aluminum, and Zn (II), Al (III), Cu (II) or Fe (II) ions.

End-Use Product—Actigard 50WG

Property	Result
Colour	Light brown
Odour	Moderate, sulphurous
Physical state	Solid
Formulation type	Water dispersible granules
Guarantee	50.0% nominal
Container material and description	14-212 g plastic bottles
Bulk density	0.61 g/cm^3
pH of 1% dispersion in water	8-10
Oxidizing or reducing action	Product does not contain oxidizing or reducing agents
Storage stability	Stable at ambient temperature up to 3 years
Corrosion characteristics	Product was not corrosive to the package
Explodability	Not expected to be explosive

1.3 Directions for Use

When applied at 25 g/ha, Actigard 50WG suppresses bacterial spot (*X. campestris* pv. *vesicatoria*) and bacterial speck (*P. syringae* pv. *tomato*) on tomato. Make up to 8 weekly sequential applications.

Actigard 50WG controls blue mold (*Peronospora tabacina*) on tobacco when applied at 35 g/ha. Make up to three applications with an application interval of 10 days.

Actigard 50WG should be applied to plant foliage preventively, before disease is observed in the field.

1.4 Mode of Action

Acibenzolar-S-methyl is a Group P fungicide and is classified as a benzo-thiadiazole. Acibenzolar-S-methyl mimics the natural systemic acquired resistance response found in plant species. Actigard 50WG has no direct activity against target pathogens.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Acibenzolar-S-Methyl Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

For data generation and enforcement purposes in plant matrices, a high performance liquid chromatography (HPLC) method with UV detection was developed and proposed. The method is a common moiety method, which analyzes the parent and the metabolite CGA 210007 as CGA 210007. The method fulfilled the requirements with regards to specificity, accuracy and precision at the method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant matrices. Adequate extraction efficiencies were demonstrated using radiolabelled tomato, lettuce and tobacco samples analyzed with the enforcement method.

For data generation and enforcement purposes in environmental media, high-performance liquid chromatography methods with ultraviolet absorbance detection (HPLC-UV) were developed and proposed. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for acibenzolar-S-methyl was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. In addition, the acute and short-term toxicological effects, as well as the genotoxic potential of the primary metabolite in rodents, a carboxylic acid derivative of the parent (CGA-210007), were characterized. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific

quality of the data is generally high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical.

The acute toxicity of acibenzolar-S-methyl was low by the oral route in mice and rats and low by the dermal and inhalation routes in rats. It was minimally irritating to the eyes and skin of rabbits. Acibenzolar-S-methyl was a dermal sensitizer in guinea pigs. The acute toxicity profile of CGA-210007 differed slightly from the parent in that it was moderately irritating to the eyes of rabbits and not a skin sensitizer in guinea pigs. The acute toxicity of the end-use product, Actigard 50WG, was low by the oral, dermal and inhalation routes of exposure in rats. Actigard 50WG was moderately irritating to the skin of rabbits, but only minimally irritating to the eyes. It was not a dermal sensitizer in guinea pigs.

The toxicokinetic behaviour of orally and dermally administered acibenzolar-S-methyl was characterized in rats. When administered via the oral route, acibenzolar-S-methyl was rapidly absorbed and eliminated from the blood. Acibenzolar-S-methyl was completely absorbed at both the low and high dose levels. After repeat dosing, concentrations in the blood peaked within 1 h at the low dose and between 4 to 8 h at the high dose. There was no evidence that the absorption or elimination kinetics were saturated at the high dose of 100 mg/kg bw. However, in the rat developmental toxicity study, there was a steep increase in the maternal/developmental toxicity when animals were treated with acibenolar-S-methyl at greater than or equal to 400 mg/kg bw/day. This indicates that acibenzolar-S-methyl may exhibit zero-order elimination kinetics (i.e. saturable) at dose levels that are greater than the highest dose level that was investigated in the oral toxicokinetic study.

Acibenzolar-S-methyl was metabolized via hydrolysis and conjugation. Metabolism was rapid and extensive, and the metabolic fate was largely independent of sex, dose level, and pretreatment. Unchanged parent was detected only in the faeces and was present at no greater than 1% of the administered dose (AD). The metabolite pattern was relatively simple, consisting of only three fractions in both the faeces (including parent) and the urine. A carboxylic acid derivative, CGA-210007, was the primary metabolite in both the faeces and the urine, accounting for up to 3 and 92% of the AD, respectively. In the urine, an unidentified polar compound and the glycine derivative of CGA-210007 were detected at 4.5 and 2.2% of the AD, respectively. The only other metabolite detected occurred in the faeces at no more than 0.4% of the AD. There was no evidence of enterohepatic circulation and the expired air contained only negligible amounts of radiolabel.

Tissue residues of acibenzolar-S-methyl declined very rapidly, with typical organ-specific elimination half-life times of less than 2 h at the low dose and less than 5 h at the high dose (longest for the liver and bone). At the high dose, organ-specific half-lives for elimination in females were up to three times greater than those of males. Consistent with this, residue levels were two to three times higher in females than in males, regardless of the dose level. Nevertheless, excretion was rapid and nearly complete within the first 24 h (70 to 90% of AD), regardless of the dose level. Further, absolute residue levels were extremely low (< 1% of AD) in the carcass and tissues one week after dosing, regardless of either the sex or the dose level administered. At the low dose, residues were detected in the carcass, liver and kidneys following either single or repeated doses. At the high dose, residues were also detected in the blood

plasma, lungs, and spleen. There was no evidence that acibenzolar-S-methyl accumulated in the tissues. Elimination was predominantly via the urine. The route and rate of elimination were largely independent of sex, dose level, or whether the doses were administered singly or repeatedly.

The toxicokinetic behaviour of dermally administered acibenzolar-S-methyl was also characterized in rats. When administered via the dermal route, much of the applied dose of acibenzolar-S-methyl remained unabsorbed for up to 8 h at the low dose of 0.53 mg/kg bw, and up to 24 h at the high dose of 4.51 mg/kg bw. This reflects both the low capacity (~ 0.78 $\mu g/cm^2/h$) of the processes that mediate dermal absorption and the saturation of these processes at both dose levels. At the low dose, absorption appeared to be saturated for approximately 6 h, whereas at the high dose saturation was clearly evident throughout the 24 h dosing period. As a consequence, at the high dose level, the proportion of the AD entering systemic circulation (i.e. internal dose, ID) was only 16% after 24 h. In contrast, the ID at the low dose was nearly equal to the AD after 24 h of exposure (i.e. ~ 81% of AD). The low dose applied (11.7 $\mu g/cm^2$) was considered to be very near the threshold dose required for maximal dermal penetration of acibenzolar-S-methyl. Regardless of the dose, blood concentrations peaked within 1 h, but at much lower levels than in the oral metabolism study. In contrast to the absorption characteristics via the dermal route, the distribution, metabolism and excretion of acibenzolar-S-methyl were highly comparable for both the oral and dermal routes of exposure.

In a special metabolism study, the tissue-specific hydrolysis of acibenzolar-S-methyl to CGA-210007 was explored *in vitro* in the liver, the skin, and blood plasma sampled from rats and humans. An unspecific carboxylesterase (ali-esterase) activity appeared to be solely responsible for acibenzolar-S-methyl hydrolysis. The rate of hydrolysis in liver tissue from humans was 6-fold greater than the rate in rats, whereas in the skin it was 4-fold greater in rats than in humans. In both species, hydrolysis in the blood plasma was several orders of magnitude lower than in either the liver or the skin. This suggests that the appearance of CGA-210007 in the blood is primarily a consequence of hydrolysis within peripheral tissues. It was not established whether the rate of hydrolysis of acibenzolar-S-methyl influences the maximal capacity for absorption via the skin in either humans or rats.

After oral dosing for 28 to 90 days in mice, rats and dogs, general toxicity was evidenced by decreases in body weight, body weight gain, food consumption and food efficiency in all three species. Over these short- to intermediate-term periods of oral dosing, the main target organs and tissues of acibenzolar-S-methyl were the blood, the liver, the spleen and bone marrow. The primary target was the blood and its constituent cells, which exhibited haematological changes characteristic of regenerative anaemia. Effects in the blood included decreased red blood cell (RBC) parameters (e.g. RBC numbers, haemoglobin, haematocrit) and increased reticulocyte numbers. At the highest dose levels tested, haematological changes also included decreases in white blood cell numbers, (i.e. basophils and large lymphocytes) in rodents and dogs. Increased haemosiderosis in the liver, the spleen and in bone marrow of all species tested was consistent with an increased destruction of RBCs and their probable removal at these sites. Increases in Kupffer cell pigmentation in the liver and hypercellularity in the bone marrow are considered adaptive, but also corroborative of the anaemia-related effects of acibenzolar-S-methyl. Increased liver weight and increases in plasma cholesterol and total bilirubin levels were

considered indicative of an adaptive xenobiotic response in the liver. In the spleen, changes also included increased organ weight, enlargement, and extramedullary haematopoeisis. Mice appeared to be somewhat more sensitive than rats and dogs to acibenzolar-S-methyl-induced haematology-related toxicity. There was no evidence of durational changes for the anaemia-related effects with chronic exposure.

A special immune system toxicity study was conducted in rats to determine whether the formation of antibodies against acibenzolar-S-methyl leads to its anaemia-related effects. After dosing for 25 days with up to 800 mg/kg bw/d, no antibodies against acibenzolar-S-methyl were detected. This suggests that immune system mediated binding of acibenzolar-S-methyl to circulating protein(s) in the blood is an unlikely explanation for its anaemia-related effects in laboratory animals.

Dermal dosing of rats for 28 days resulted in systemic effects at 1000 mg/kg bw/d, the highest dose tested. An increased incidence of splenic extramedullary haematopoiesis and splenic white pulp lymphatic follicle hyperplasia occurred in females only. There were no dermal effects at the site of treatment. A repeat-dose inhalation toxicity study was not available in the toxicity database.

The overall outcome of genotoxicity studies using acibenzolar-S-methyl indicates that it was not genotoxic. The gene mutation, *in vitro* unscheduled DNA synthesis, and the *in vivo* mammalian cytogenetics tests were all negative. The *in vitro* mammalian chromosomal aberrations test was positive, but only in the presence of cytotoxicity, so this clastogenic outcome was not considered a primary effect. A plant metabolite, isomer and by-product of acibenzolar-S-methyl resulted in either no gene mutations or resulted in gene mutations only at concentrations that were well in excess of those expected to be present in the technical active product. The primary metabolite CGA-210007 resulted in an increase in the number of mutations and chromosomal aberrations at doses that were only slightly cytotoxic. However, based on toxicokinetic considerations it is considered unlikely that the concentrations of CGA-210007 that resulted in these positive *in vitro* effects could be achieved *in vivo*. In contrast, acibenzolar-S-methyl demonstrated a clear cell cycle arresting activity in mammalian cells in the absence of cytotoxicity.

Acibenzolar-S-methyl did not cause cancer in mice and rats. The dosing was considered adequate in the combined chronic/carcinogenicity studies. With chronic exposure to doses that are greater than those which lead to anaemia-related effects, there were increased occurrences of foci of cellular change in the mouse liver, and alveolar foam cells in the lungs of both rodent species.

The reproductive toxicity potential of acibenzolar-S-methyl was assessed in a two-generation reproductive toxicity study in rats. Parental effects included decreased body weight, body weight gain and food consumption at dose levels greater than or equal to the upper mid-dose level. Splenic effects at the same dose levels included increases in weight, haemosiderosis and incidences of congestion. No reproductive effects occurred in males or females up to and including the highest dose tested. Offspring toxicity at greater than or equal to the upper mid-dose level was limited to decreased body weight during the late lactation period, when

acibenzolar-S-methyl dosing may occur via consumption of the treated diet and also via lactational transfer. At the highest dose tested there was also a slight delay in eye opening in F_{1a} pups. There was no evidence of increased susceptibility of the young in this study.

Developmental toxicity studies were conducted using rats and rabbits. In rats, there were three guideline studies, a range-finding study, and two special investigative studies. In one of the guideline studies, rats were exposed via the dermal route. Different strains of rat were used in the two oral developmental toxicity studies. In rabbits, a range-finding and guideline study were conducted. At the highest dose level tested orally in rats, maternal animals exhibited decreases in body weight and/or body weight gain, decreased food consumption, and large increases in both hemorrhagic perineal discharge and total litter losses. There were corresponding increases in early post implantation loss and decreases in the number of live foetuses per litter. At the highest dose level, surviving foetuses had decreased body weights, increased skeletal variations and malformations, and increased visceral malformations. Maternally adverse toxic effects occurred at the high dose level only. At oral dose levels lower than this, foetal survival was unaffected, but increased incidences of skeletal variations and visceral malformations occurred in both of the rat strains that were examined. The steep increase in the incidence of serious maternal and developmental toxic effects at the highest orally tested dose suggests that there is a dose response threshold at or near this dose level.

In both of the rat oral developmental toxicity studies, external and/or visceral malformations occurred in treated rats as a constellation of rare developmental malformations at and below the maternally toxic dose. It is considered unlikely that the number of singular incidences of rare developmental malformations occurred by chance alone in these studies. At the lowest dose tested, umbilical hernias occurred in one of the two guideline studies. This malformation also occurred at a higher dose level in the rat range-finding study. Other treatment-related developmental malformations (i.e. gastroschisis and/or micro-/anopthalmia) occurred at the mid dose range. Even though foetal survival was very low at the highest dose level tested, a comparatively large number and variety of developmental malformations were evident among the surviving young. Four of these were related to abnormal neurodevelopment (i.e craniorachischisis, micro-/anopthalmia, and brain internal hydrocephalus). At the highest dose, omphalocele and splenic aplasia also occurred. Umbilical hernias, gastroschisis and omphalocele all result from abnormal mid-line closure processes. Conceivably, they are different manifestations of a common underlying developmental abnormality. Broadly consistent with these effects, acibenzolar-S-methyl exhibits an *in vitro* cell cycle arresting activity in mammalian cells. All of the malformations that occurred are considered rare developmental events. Given this, and the small number of animals investigated, these observations could not be dismissed as being treatment-related.

In a special study conducted by the applicant, the visceral malformations and foetal resorptions that occurred in the first oral rat developmental toxicity study were investigated using benchmark dose (BMD) analyses. The apparent dose-response characteristics of these endpoints were explored using a maximum likelihood modeling procedure. Analyses were conduced using i) foetal resorptions alone, ii) the midline closure defects alone, and ii) these two types of effects combined into a single analysis. However, the PMRA considers it biologically and toxicologically inappropriate to combine data for midline closure defects and foetal resorptions

within a single BMD analysis. These two endpoints are considered fundamentally different, rather than alternate outcomes for a common developmental effect, as was proposed in the BMD study. Based on our assessment of these analyses, the foetal malformation data are not amenable to BMD modeling procedures. As a consequence, a BMD-derived regulatory point of departure (POD) was not established via the analyses conducted in this study.

In the dermal developmental toxicity study, there was no systemic maternal or foetal toxicity, and no evident developmental toxicity in animals receiving *applied* doses of up to 500 mg/kg bw/d, the highest dose tested. However, based on kinetic information from the dermal metabolism study, this applied dose level is nearly three orders of magnitude greater than the estimated corresponding oral equivalent dose. As a consequence of dose saturation via the dermal route, the maximal oral equivalent dose in this study is estimated to be approximately 0.65 mg/kg bw/d for all treated groups, regardless of the dose that was applied. This estimated oral equivalent dose is nearly 13-fold lower than the lowest dose administered orally to rats in the other developmental toxicity studies and the developmental neurotoxicity (DNT) study. As a consequence, the dermal developmental toxicity study provides very limited comparative insight into the developmental consequences of dermal exposure to acibenzolar-S-methyl.

In the rabbit developmental toxicity study, there was no evidence of increased foetal sensitivity. The maternal effects were limited to decreases in body weight gain and food consumption at greater than or equal to 300 mg/kg bw/d. At the highest dose tested, clinical signs of toxicity included perineal bleeding and increased mortality. Consistent with the developmental effects observed in the rat studies, effects at the high dose included increases in post-implantation loss and skeletal variations of the vertebrae in the foetuses. A similar reduction in foetal viability occurred at 400 mg/kg bw/d in the rabbit range-finding study. Overall, these results indicate that acibenzolar-S-methyl had no teratogenic effect in rabbits.

The neurotoxic effects of acibenzolar-s-methyl were assessed in a sub-chronic (90-day) study and in a DNT study. In the sub-chronic study there was no evidence of neurotoxicity. Evidence of systemic toxicity included decreased body weight and body weight gain in males at greater than or equal to the mid dose, and in females at the high dose only. Based on the occurrence of nervous system foetal malformations in the first rat developmental toxicity study, a DNT study was conducted.

In the DNT study there was no evidence of maternal systemic toxicity up to the highest dose level tested. In contrast, pup body weights were decreased at this dose level during the late lactation period, when consumption of the adult diet by the pups is likely. In the rat range-finding DNT study, an earlier occurrence of this pup body weight effect suggested that exposure to acibenzolar-S-methyl may occur via lactation. Male pups exhibited morphometric changes in the cerebellum and in the dorsal cortex at greater than or equal to the lowest dose tested. Although these morphometric effects were less evident in female pups, the corresponding historical control data suggest that these changes were likely either underestimated or masked, in both sexes, in the present DNT. Female pups exhibited an increase in their acoustic startle response at the high dose. Therefore, both sexes exhibited neurodevelopmental effects below the maternally toxic dose.

In male pups, clear and consistent morphometric changes occurred down to the lowest dose tested in two separate measurement locations within each of two different late-developing regions of the brain; the dorsal cortex and the cerebellum. Both regions are known to have populations of late-developing microneurons (i.e. short-axoned, or granular cell neurons). The thickness of the dorsal cortex and the molecular layer of the cerebellum were both decreased at all dose levels tested. The aetiology of these changes is not known, but the developmental timing and the locations affected suggest an underlying microneuronal hypoplasia, which is known to occur without any evident cellular degenerative change or neuropathology. Comparison to historical morphometric data suggests that, in the cerebellum, the thickness of the inner granular layer and the molecular layer were similarly affected. These adjacent layers form in tandem via reciprocal developmental signalling processes that are tightly regulated, both spatially and temporally. Given this and the extensive cellular structural elements that are shared across these two layers, the simultaneous occurrence of morphological effects in both layers is a probable outcome when the normal development of either layer is adversely affected.

The type and magnitude of the changes in the cerebellum are not anticipated to produce gross locomotory deficits. Microneuronal hypoplasia is known to result in hyperactivity in rats, which can be revealed through spontaneous running wheel-type assessments. This was not explicitly assessed in the DNT study. Also, it is conceivable that hippocampal granular cell hypoplasia was similarly affected by exposure to acibenzolar-S-methyl. However, it has been documented that near-complete loss of the granular cell population of the dentate gyrus of the hippocampus has virtually no detectable gross morphometric consequences in the rat. The behavioural consequences of granular cell hypoplasia in the hippocampus include hyperactivity, deficits in discriminate sensorimotor learning (visual and tactile), and decreased inhibition of learned responses following task reversals. To reveal such behavioural deficits, the task stringency must be difficult to very difficult during the behavioural assessment. Behavioural assays with an appropriate level of task difficulty were not conducted in the DNT study using acibenzolar-S-methyl.

In female pups, an increase in the amplitude of the acoustic startle response occurred at the high dose only. This response, which is mediated primarily by the cerebellum and the brain stem, was considered evidence of neurodevelopmental toxicity. Compared to a larger group of similarly conducted historical DNT studies, the sensitivity of the acoustic startle procedure in the present DNT study was among the lowest. As a consequence, the dose dependence of this effect in pups may have been underestimated in the present DNT study. Other behavioural effects of exposure to acibenzolar-S-methyl were not detected in the study. However, the Y-maze assessment of learning and memory, which was used in the present DNT, is a low sensitivity assay of behavioural change. Although this assay can have acceptable behavioural discriminatory value when an appropriate level of task stringency (i.e. difficulty) is incorporated into the basic assessment, this was not done in the present study. Without this level of stringency, it is highly unlikely that the discriminatory power of the Y-maze procedure was sufficient to detect the anticipated behavioural consequences of the brain morphometric changes. The behavioural consequences of granule cell hypoplasia are often not revealed at all by even moderately difficult learning aquisition tasks.

Overall, acibenzolar-S-methyl was not carcinogenic or genotoxic. The anaemia-related systemic toxicological response, including the dose sensitivity, was comparable across all species tested. Rare visceral malformations, and also brain neurodevelopmental changes, occurred down to the lowest dose tested in rat, and below the maternally toxic dose level. Rare malformations specific to the nervous system occurred at greater than historical incidence rates in both of the rat guideline developmental toxicity studies. In the DNT, affected brain regions appeared to be those which undergo maturation later in the developmental sequence, but it was not clear whether these changes reflected prenatal or postnatal exposure to acibenzolar-S-methyl.

Results of the acute and chronic tests conducted on laboratory animals with acibenzolar-S-methyl and its associated end-use products, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Tables 2, 3 and 4 of Appendix I.

3.1.1 PCPA Hazard Characterization

For assessing the risks from potential residues in food or from products used in or around homes and schools, the Pest Control Products Act requires the application of an additional 10-fold factor to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and the potential for prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for acibenzolar-S-methyl. There was a two-generation rat reproductive toxicity study, oral and dermal developmental toxicity studies in the rat, and a developmental toxicity study in rabbits. Due to the occurrence of nervous system malformations in the first rat developmental toxicity study, a DNT study was also conducted.

In the DNT, aspects of the study are of lower quality than DNT studies that were conducted more recently. This is reflected, for instance, in the very low sensitivity of the startle amplitude assay in the present study. The absence of a clear behavioural correlate to the brain developmental changes may, in part, be attributable to the lower quality of the behavioural component of the DNT study. The choice and design stringency of other behavioural assays conducted in the present DNT study are additional factors that likely also diminished its capacity to detect treatment-related behavioural change. Also, since cerebral and cerebellar morphological effects were large at the lowest dose tested, the dose response below this LOAEL may be quite steep. Without a clearly defined NOAEL, uncertainty remains regarding the dose response for these serious brain effects. A small increase in dose exposure may lead to a maximal morphological effect over a narrow low-dose range. These dose-response characteristics, in combination with the inherent variability of such data, hindered the establishment of a model-derived POD for these morphometric changes based on in-house BMD analyses.

With respect to identified concerns relevant to the assessment of risk to infants and children, the developmental toxicity studies in rabbits provided no indication of increased susceptibility of rabbit foetuses following maternal exposure to acibenzolar-S-methyl. There was also no indication of increased susceptibility in the offspring, compared to parental animals, in the multi-generational reproduction study. In contrast, the developmental toxicity studies in rats indicated

that there was an increased susceptibility of rat foetuses with in utero exposure to acibenzolar-S-methyl. There were treatment-related rare malformations (umbilical hernias) observed at the lowest dose level tested and below the maternally toxic dose. Other rare malformations, including midline closure defects (omphalocele and gastroschisis) and neurodevelopmental malformations, occurred at higher dose levels. In addition, treatment-related skeletal malformations and/or variations were observed in two developmental toxicity studies in rats at doses below the LOAEL for maternal toxicity. In the DNT study, male rats exhibited morphological changes in two separate locations within each of two different regions of the brain, the dorsal cortex and the cerebellum. These regions are known to undergo development within their microneuronal granule cell populations during the early postnatal period in rats. These affected regions exhibited treatment-related change at the lowest dose tested, which was below the LOAEL for maternal toxicity. The DNT brain developmental effects and the umbilical hernias occurred at essentially the same low dose level, which resulted in very similar LOAELs for these two studies. The definitive rat developmental toxicity studies, as well as the DNT study, provide evidence of the potential susceptibility of infants and children to in utero and/or early postnatal exposure to acibenzolar-S-methyl.

Overall, residual uncertainties with respect to the completeness of the data for acibenzolar-S-methyl included the general quality, sensitivity, and stringency of the DNT study. A full 10-fold PCPA factor was retained to address these residual concerns and the serious nature of the developmental effects, which occurred in the absence of maternal toxicity.

3.2 Determination of Acute Reference Dose

For acibenzolar-S-methyl, the recommended acute reference dose (ARfD) for the general population is 0.0027 mg/kg bw, based on the LOAEL of 8.2 mg/kg bw/d in the rat developmental neurotoxicity study. The findings in male pups occurring at the LOAEL included decreased thickness of the dorsal cortex and decreased thickness of the molecular layer of the cerebellum. Both effects occurred well below the maternally toxic dose. It could not be determined from this study whether these changes occurred as a result of prenatal or postnatal exposure to acibenzolar-S-methyl. The standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional 3-fold uncertainty factor was applied for extrapolation from a LOAEL in the absence of a NOAEL. For the reasons outlined in the PCPA Hazard Characterization Section, the PCPA factor was retained at 10-fold resulting in a composite assessment factor (CAF) of 3000-fold. The selection of this endpoint is considered protective of all populations including women of child-bearing age and nursing infants.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{LOAEL}}{\text{CAF}} = \frac{8.2 \text{ mg/kg bw}}{3000} = 0.0027 \text{ mg/kg bw of acibenzolar-S-methyl}$$

This reference value results in a margin of 3704 to malformations in the developmental toxicity studies, which occurred at a LOAEL of 10 mg/kg bw/d.

3.3 Determination of Acceptable Daily Intake

For acibenzolar-S-methyl, the recommended acceptable daily intake (ADI) is 0.0027 mg/kg bw/d, based on the LOAEL of 8.2 mg/kg bw/d in the rat developmental neurotoxicity study. The findings in male pups occurring at the LOAEL included decreased thickness of the dorsal cortex and decreased thickness of the molecular layer of the cerebellum. Both effects occurred well below the maternally toxic dose. It could not be determined from this study whether these changes occurred as a result of prenatal or postnatal exposure to acibenzolar-S-methyl. The standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional 3-fold uncertainty factor was applied for extrapolation from a LOAEL in the absence of a NOAEL. For the reasons outlined in Section 3.1.1, the PCPA factor was retained at 10-fold resulting in a CAF of 3000-fold. The selection of this endpoint is considered protective of all populations including women of child-bearing age and nursing infants.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{LOAEL}}{\text{CAF}} = \frac{8.2 \text{ mg/kg bw/d}}{3000} = 0.0027 \text{ mg/kg bw/d of acibenzolar-S-methyl}$$

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to Actigard 50WG is characterized as short- to intermediate-term and is predominantly by the dermal and inhalation routes.

Since worker populations could include pregnant females, concerns relevant to the assessment of risk to infants and children are relevant to the assessment of Occupational and Residential Risks. For this reason, the LOAEL of 8.2 mg/kg bw/d in the rat DNT study, based on decreased thickness of the dorsal cortex and the molecular layer of the cerebellum, was considered the most relevant endpoint for the short- to intermediate-term occupational dermal and inhalation risk assessments. This endpoint is the lowest relevant point of departure in the toxicology database. There were no studies that assessed acibenzolar-S-methyl toxicity via the inhalation route of exposure. There was a 28-day, and a developmental, dermal toxicity study in rat, but the developmental toxicity endpoints of concern were not assessed in these studies. The standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. An additional 3-fold uncertainty factor was applied for extrapolation from a LOAEL in the absence of a NOAEL. In light of the high degree of concern for prenatal and postnatal toxicity, as outlined in the PCPA Hazard Characterization section, an additional 10-fold factor was applied. Therefore, the target margin of exposure (MOE) for this scenario is 3000. The selection of this study and this MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

Chemical-specific dermal absorption data were not provided for acibenzolar-S-methyl. Based on a weight of evidence approach which considered the physico-chemical properties of acibenzolar-S-methyl, and the results of the oral and dermal metabolism studies in rats submitted in support of the toxicological database, it was considered appropriate to decrease the dermal absorption value for this active ingredient from the default 100% to 50%.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Individuals have potential for exposure to Actigard 50WG during mixing, loading and application. Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. Therefore, dermal and inhalation exposure estimates for workers were generated from the PHED database (Table 3.4.1). PHED version 1.1 is a compilation of generic mixer/loader and applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates. With a few exceptions, the PHED estimates meet criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides.

Table 3.4.1 Summary of PHED Unit Exposure Values

Scenario	Unit Exposure (µg/kg a.i. handled)		
	Dermal	Inhalation	Total Absorbed[1]
Dry Flowable Mixing/Loading			
Single layer + gloves	163.77	1.02	82.91
Groundboom Applicator			
Single layer + gloves	32.98	0.96	17.45

[1] Total Absorbed Unit Exposure = (Dermal Unit Exposure * 50%) + Inhalation Exposure

Exposure to farmers and custom applicators mixing, loading and applying Actigard 50WG is expected to be short- to intermediate- term in duration and to occur primarily by the dermal and inhalation routes. Exposure estimates were derived for mixer/loaders/applicators applying Actigard 50WG to tomatoes and tobacco using groundboom application equipment. The exposure estimates are based on mixers/loaders/applicators wearing long-sleeved shirts, long pants and gloves.

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day and the dermal absorption value. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoint (lowest observed adverse effects level) to obtain the margin of exposure (MOE); the target MOE is 3000.

Table 3.4.2 Exposure and Risk for Workers Handling Actigard 50WG

Scenario	Rate (kg a.i./ha)	Unit Exposure [1] (µg/kg a.i. handled)	Area Treated per Day[2] (ha)	Dermal + Inhalation Exposure (µg/kg bw/day)	Combined MOE[3]
Groundboom Application (Mixing/loading and Applying) Wearing a Single Layer + Gloves					
Tomato	0.0125	100.36	26	0.466	17 600
Tobacco	0.0175	100.36	107	2.68	3055

[1] Combined Dermal and Inhalation Unit Exposure = (Dermal Unit Exposure * 50%) + Inhalation Exposure
[2]From Area Treated per Day Table, July 2009
[3] Based on a LOAEL of 8.2 mg/kg bw/day

Exposure and risk estimates for workers mixing/loading and applying Actigard 50WG are presented in Table 3.4.2. MOEs for farmers and custom applicators wearing the proposed PPE are above the target of 3000. Since the calculated MOE is very close to the target MOE for tobacco, workers are restricted to treating no more than100 ha per day with Actigard 50WG.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Exposure to workers entering fields treated with Actigard 50W is expected to be of short- to intermediate-term in duration and to occur by the dermal route.

Dermal exposure to workers entering treated fields was calculated on the day of the last application assuming that the maximum number of applications was made at the highest application rate and the shortest application interval. Since no chemical specific dislodgeable foliar residue (DFR) data was provided, a default DFR value of 20% of the application rate on the day of application was assumed with a 10% dissipation rate per day. Dislodgeable foliar residue values were coupled with generic transfer coefficients for each proposed crop, an 8 hour workday and the dermal absorption value. Exposure was normalized to mg/kg bw/day by using 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoint (lowest observed adverse effects level) to obtain the margin of exposure (MOE); the target MOE is 3000.

The MOE for workers entering treated tomato fields is above the target of 3000 on the day of the final application (Table 3.4.3). The MOE for workers entering treated tobacco fields to perform typical post-application activities is below the target on the day of the final application; an re-entry interval (REI) of 8 days is required to reach the target.

Table 3.4.3 Summary of Post-Application Exposure and Risk to Actigard 50WG

Crop	Application Rate (µg/cm^2)	Number of Applications	Transfer Coefficient (cm^2/hr)	MOE on Day of Last Application[1]	Required REI to Meet Target (days)
Tomatoes	0.125	8	1000	3002	0
Tobacco	0.175	3	2000	1202	8

[1] Based on a LOAEL of 8.2 mg/kg bw/day

3.4.3 Residential Exposure and Risk Assessment

A residential risk assessment was not required since there are no residential uses on the Actigard 50WG label.

3.4.4 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Application is limited to agricultural crops only when there is low risk of drift to areas of human habitation or activity such as houses, cottages, schools and recreational areas, taking into consideration wind speed, wind direction, temperature inversion, application equipment and sprayer settings.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for enforcement in plant products is acibenzolar-S-methyl and the acid metabolite CGA 210007. The residue definition for risk assessment in plants is acibenzolar-S-methyl, CGA 210007 and the 4- & 5-hydroxy metabolites of CGA 210007 (CGA 323060 & CGA 324041). The data gathering/enforcement analytical methodology is valid for the quantification of acibenzolar-S-methyl and CGA 210007 residues in plant matrices. The residues of acibenzolar-S-methyl and CGA 210007 are stable when stored in a freezer at -20°C for 22 months. The tomato processing data showed that residues of acibenzolar-S-methyl did not concentrate in tomato juice, but did concentrate in tomato paste with a concentration factor of 6.4. MRLs for acibenzolar-S-methyl were previously established on several imported commodities including tomatoes and tomato paste. Supervised residue trials conducted throughout the United States using an end-use product containing acibenzolar-S-methyl at exaggerated rates are sufficient to support the Canadian use on tomatoes and tobacco. There are no livestock feed items associated with tomatoes or tobacco; therefore, livestock metabolism and feeding data are not required.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following inputs were used in the refined chronic analysis: median residue values from crop field trial data, experimental processing factors, monitoring data and percent crop treated (%CT) data, where available. The refined chronic dietary exposure from all supported acibenzolar-S-methyl food uses (alone) for the total population, including infants and children, and all representative population subgroups is 1% of the acceptable daily intake (ADI). Aggregate

exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to acibenzolar-S-methyl from food and water is 3% of the ADI (0.000084 mg/kg bw/day) for the total population. The highest exposure and risk estimate is for infants <1 year old at 8% of the ADI (0.000223 mg/kg bw/day).

3.5.2.2 Acute Dietary Exposure Results and Characterization

A refined probabilistic acute assessment was conducted using residue distribution files created from supervised crop field trials and monitoring data where available. Experimental processing factors and %CT data were incorporated where available. The refined acute dietary exposure from food only for all supported acibenzolar-S-methyl registered commodities is estimated to be 46.5% of the ARfD for the total population (99.9th percentile, probabilistic).

Aggregate exposure from food and water is 49.1% of the ARfD (0.001327 mg/kg bw/day) for the total population. The highest exposure and risk estimate is for children 1-2 years old at <94% of the ARfD (0.002521 mg/kg bw/day) (99.9th percentile, probabilistic), and is considered acceptable.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for acibenzolar-S-methyl consists of exposure from food and drinking water sources only; there are no residential uses. Aggregate risks were calculated based on acute and chronic endpoints.

3.5.4 Maximum Residue Limits

The resulting residues in/on tomato commodities from the domestic use of acibenzolar-S-methyl are expected to be covered by the MRLs of 1.0 ppm for tomatoes and 3.0 ppm for tomato paste established previously for imported commodities.

For additional information on Maximum Residue Limits (MRL) in terms of the international situation and trade implications, refer to Appendix II.

The nature of the residues in plant matrices, analytical methodology, field trial data, and the acute and chronic dietary risk estimates are summarized in Appendix I, Tables 1, 5 and 6.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

4.1.1 Soil

Acibenzolar-S-methyl enters the soil when used as a plant growth regulator for various field crops. Biotransformation is the major route of transformation of acibenzolar-S-methyl under aerobic conditions. Acibenzolar-S-methyl is non-persistent in soil with 50% dissipation time

(DT_{50}) values of 0.22 days under laboratory conditions. DT_{50} values of 0.12-7.76 days under field conditions were available, but not from ecoregions relevant to Canada. Biotransformation is also an important route of transformation of the major transformation product CGA 210007, which is further mineralized into CO_2 under aerobic conditions. It was, however, found to be stable under anaerobic conditions in the laboratory. Under field conditions, CGA 210007 was non-persistent to moderately persistent with half-lives of 4.55-109 days.

Under alkaline conditions, acibenzolar-S-methyl hydrolyses relatively quickly (half-life of 9.22 hours at pH 9) into the major transformation product CGA 210007. Therefore, hydrolysis may be an important contributor to transformation of acibenzolar-S-methyl in alkaline soil, but it is not an important pathway under neutral (half-life of 79.5 days) or acidic conditions (stable). Soil photolysis is not an important transformation pathway of acibenzolar-S-methyl in the environment as indicated by a relatively long half-life of 29.90-33.13 days.

Acibenzolar-S-methyl has low mobility in soil, and the potential for binding to soil is not dependent on the organic carbon content. While laboratory data indicate that CGA 210007 may have the potential to leach, soil-dissipation time, the field dissipation studies, and the modeling results based on conservative assumptions indicate that leaching is expected to be minimal. Overall, acibenzolar-S-methyl and CGA 210007 are not expected to pose a leaching concern.

4.1.2 Water

Acibenzolar-s-methyl and its transformation products could reach surface water systems by spray drift or runoff. The dissipation of acibenzolar-S-methyl in water is rapid, and many transformation processes are involved.

Biotransformation is an important and rapid (half-life of less than a day) route of transformation of acibenzolar-s-methyl into the major transformation product CGA 210007, which is further mineralized into CO_2 under aerobic conditions but remains stable under anaerobic conditions.

The rate of dissipation in aquatic systems may be less dependent on the aerobic/anaerobic conditions of the system and more dependent on pH of the water, due to rapid hydrolysis of acibenzolar-S-methyl at pHs higher than pH 9. It may also be more dependent on the rapid phototransformation of both acibenzolar-S-methyl and CGA 210007 in shallow (less than 9 cm) water bodies (half-lives of 0.27 hours for acibenzolar-S-methyl and 0.073 days for CGA 210007).

4.1.3 Sediment

Acibenzolar-S-methyl dissipates rapidly in aquatic systems. As such, it is not expected to accumulate in sediments. CGA 210007 is expected to be the only transformation product that could accumulate in the sediment. It remained stable over time and reached 22.06% of the applied radioactivity accumulated in the soil/sediment of the anaerobic flooded soil system (360-day study period). CGA 210007 also remained stable in the sediment of the aerobic aquatic

systems (pond and river systems) with a slow rate of dissipation (half-lives of 344-488 days) and 22.96-23.29% of the applied radioactivity accumulated at the end of the study (350-day study period for pond system and 363 days for river system).

4.1.4 Air

Based on the vapour pressure and the Henry's law constant, acibenzolar-S-methyl is not expected to volatilize from moist soils or water surfaces. This is in agreement with the results from the submitted biotransformation studies where acibenzolar-S-methyl and CGA 210007 were never detected in the volatile traps.

4.1.5 Biota

The estimated log K_{ow} values of acibenzolar-S-methyl and CGA 210007 are 3.1 and 0.18, respectively, which indicate this substance is unlikely to bioconcentrate or bioaccumulate.

In a bioaccumulation study with the bluegill fish, acibenzolar-S-methyl and major transformation product CGA 210007 did not bioaccumulate significantly (Bioconcentration factor = 118) and showed to be rapidly excreted by the fish with a depuration half-life of less than 12 hours. These results are in agreement with the estimated *n*-octanol/water partitioning coefficients.

Data on the environmental fate and behaviour of acibenzolar-S-methyl and its major transformation product CGA 210007 are summarized in Appendix I, Table 8.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (e.g. direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then

compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

The risk of acibenzolar-S-methyl to terrestrial organisms was based upon the evaluation of toxicity data for the following (see Appendix I, Table 9 for toxicity data):

- one earthworm species (acute exposure) and one bee species (oral or contact exposure) representing invertebrates;
- two bird and two mammal species representing vertebrates (acute, short-term or long-term exposure); and
- 10 crop species representing non-target vascular plants.

Additional toxicity data were also available for the major soil transformation product on small mammals (see Appendix I, Table 9).

4.2.1.1 Invertebrates

There are no concerns regarding the use of acibenzolar-S-methyl affecting earthworms or bees. Assuming eight applications of 26.25 g acibenzolar-S-methyl/ha with 7-day intervals, all screening level risk quotient values are less than the level of concern (Appendix I, Table 14).

4.2.1.2 Birds and Small Wild Mammals

There are no concerns regarding the use of acibenzolar-S-methyl and CGA 210007 affecting birds or small wild mammals on an acute basis.

Chronic exposure of birds to acibenzolar-S -methyl resulted in a reproductive effect observed in the bobwhite quail study where the survival of the 14-day old hatchlings was significantly reduced at the highest dose treatment (NOEL of 62.7 mg a.i./kg bw/day). The environmentally relevant reproductive effects observed in the rat following chronic dietary exposure to acibenzolar-S-methyl were reduced body weights (NOEL of 15.3 mg a.i./kg bw/day).

The screening level risk assessment for birds and small wild mammals assessed dietary exposure to acibenzolar-S-methyl in potential food items within the treated field immediately after eight applications of 26.25 g acibenzolar-S-methyl/ha with 7-day intervals. All screening level risk quotient values for acute, short-term and long-term effects were less than the level of concern.

Assuming 100% transformation of acibenzolar-S-methyl into CGA 210007, the equivalent application scenario also resulted with the screening level risk quotient value being less than the level of concern (Appendix I, Table 12).

4.2.1.3 Non-target Plants

There are no concerns regarding the use of acibenzolar-S-methyl and the end-use product Actigard 50WG affecting non-target terrestrial plants. The water-dispersible granular formulation of acibenzolar-S-methyl was tested with a single nominal test concentration of 105 g a.i./ha on ten crop species: bean, cabbage, carrot, lettuce, soybean, tomato, corn, onion, ryegrass, and wheat. The results from the seed germination, seedling emergence of planted seeds, and vegetative vigour of planted seeds indicate that acibenzolar-S-methyl and the end-use product Actigard 50WG do not have herbicidal activity at the tested application rate. Assuming eight applications of 26.25 g acibenzolar-S-methyl/ha with 7-day intervals, all screening level risk quotient values are less than the level of concern (Appendix I, Table 14).

4.2.2 Risks to Aquatic Organisms

The risk of acibenzolar-S-methyl to aquatic organisms was based upon the evaluation of toxicity data for the following (see Appendix I, Table 10 for toxicity data):

- one freshwater and two estuarine/marine invertebrate species (acute or chronic exposure)
- two freshwater and one estuarine/marine fish species (acute or early life stage exposure)
- one freshwater algal species
- one vascular plant species

Additional toxicity data were also available for the major soil transformation product, CGA 210007 (see Appendix I, Table 10). Overall, acibenzolar-S-methyl was found to be moderately to highly toxic to aquatic organisms. The major transformation product CGA 210007, although more soluble in water than the parent, was less toxic than the parent compound.

4.2.2.1 Freshwater Fish and Aquatic Invertebrates

There are no concerns regarding the use of acibenzolar-S-methyl (or its transformation product, CGA 210007) affecting fish and invertebrates in freshwater habitats. Dose-response relationships were observed for acibenzolar-S-methyl and CGA 210007, and the tested freshwater invertebrates and fish. The acute toxicity of the major transformation product CGA 210007 was tested on *Daphnia magna* and rainbow trout, and found to be less toxic than acibenzolar-S-methyl. Following chronic exposure to acibenzolar-S-methyl, biologically significant reduction of body weight was observed on the two test species, *Daphnia magna* (NOEC = 0.048 mg a.i./L) and the rainbow trout (early-life stage, NOEC = 0.026 mg a.i./L).

Assuming eight direct applications (with 7-day intervals) of 26.25 g acibenzolar-S-methyl/ha to aquatic habitat, all screening level risk quotient values are less than the level of concern. And assuming 100% transformation of acibenzolar-S-methyl into CGA 210007, the equivalent application scenario resulted also with all the screening level risk quotient values being less than the level of concern (Appendix I, Table 15).

4.2.2.2 Freshwater Plants

There are no concerns regarding the use of acibenzolar-S-methyl and CGA 210007 affecting algae or aquatic vascular plants in freshwater habitats. Dose-response relationships were observed for acibenzolar-S-methyl and the green algae and duckweed. Toxicity of the green algae *Selenastrum capricornutum* to CGA 210007 showed that the transformation product is less toxic than the parent compound. Assuming eight direct applications (with 7-day intervals) of 26.25 g acibenzolar-S-methyl/ha to aquatic habitat, all screening level risk quotient values were less than the level of concern. And assuming 100% transformation of acibenzolar-S-methyl into CGA 210007, the equivalent application scenario resulted also with all the screening level risk quotient value for the green algae being also less than the level of concern (Appendix I, Table 15).

4.2.2.3 Estuarine and Marine Organisms

There are no concerns regarding the use of acibenzolar-S-methyl affecting fish or other aquatic organisms in estuarine/marine habitats. Dose-response relationships were observed for acibenzolar-S-methyl and the estuarine/marine organisms. Assuming eight direct applications (with 7-day intervals) of 26.25 g acibenzolar-S-methyl/ha to aquatic habitat, all screening level risk quotient values were less than the level of concern (Appendix I, Table 15).

4.2.2.4 Amphibians

There are no concerns regarding the use of acibenzolar-S -methyl and CGA 210007 affecting amphibians. The acute and early life stage toxicity data on the rainbow trout were used as surrogate data for toxicity to amphibians. Assuming eight direct applications (with 7-day intervals) of 26.25 g acibenzolar-S-methyl/ha to a shallow seasonal water body, the screening level risk quotient value was less than the level of concern. And assuming 100% transformation of acibenzolar-S-methyl into CGA 210007, the equivalent application scenario resulted also with all the screening level risk quotient value for the green algae being also less than the level of concern (Appendix I, Table 15).

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Control of blue mold (*Peronospora tabacina*) on tobacco

Three efficacy trials conducted in the United States of America (USA; one trial in Florida and two trials in North Carolina) were submitted for review. The proposed rate and number of applications (35 g product/ha applied three times) were tested in two of three trials. One trial was not assessed since the tested rate was higher than the proposed rate. Results from the reviewed trials showed that when applied three times under medium disease pressure at the proposed rate of 35 g product/ha Actigard 50WG provided 89-93% control of blue mold. The claim for control of blue mold (*P. tabacina*) on tobacco (burley and binder) with Actigard 50WG applied at the rate of 35 g product/ha is supported.

5.1.2 Suppression of bacterial spot (*Xanthomonas campestris* pv. *vesicatoria*) on tomato

Four efficacy trials conducted in the USA (Virginia and Georgia) were submitted for review. Results from two trials conducted in Virginia showed that when applied six to nine times at 21 g product/ha under medium disease pressure Actigard 50WG provided 33-55% control of bacterial spot. The two other trials conducted in Georgia tested Actigard 50WG at the rate of 35-70 g product/ha and showed up to 100% control of bacterial spot on tomato. The claim for suppression of bacterial spot on tomato is supported at the low rate of 25 g product/ha. The high rate of 52.5 g product/ha was not tested and is not supported.

5.1.3 Suppression of bacterial speck (*Pseudomonas syringae* pv. *tomato*) on tomato

Three efficacy trials conducted in the USA (New York) were submitted for review. Actigard 50WG was tested under low disease pressure at the high proposed rate of 52.5 g product/ha and at the rate of 23 g product/ha. Results from the trials showed that when applied five to six times at the rate of 52.5 g product/ha, Actigard 50WG provided up to 92% control of bacterial speck. It is expected that under high disease pressure Actigard 50WG will provide lower efficacy. Consequently, the claim for suppression of bacterial speck on tomato is supported at the proposed rate of 25-52.5 g product/ha. However, due to results of the occupational exposure risk assessment, only the lower rate (25 g product/ha) on tomato can be supported.

5.1.4 Control or suppression of diseases on other crops

Twenty-two trials were submitted to support claims for downy mildew (*Peronospora parasitica*) and black rot (*Xanthomonas campestris*) on brassica vegetables, downy mildew (*Peronospora effucsa*) and white rust (*Albugo occidentalis*) on spinach and downy mildew (*Bremia lactucae*) on lettuce. Although efficacy was demonstrated in the trials, these uses were not supported from a human health perspective.

5.2 Phytotoxicity

No phytotoxicity was reported in any of the trials.

5.3 Economics

No market analysis was provided.

5.4 Sustainability

5.4.1 Survey of Alternatives

A list of alternatives is available in Appendix I, Table 17.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

Not assessed.

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

No information is available on the occurrence of pathogen resistance to acibenzolar-S-methyl.

5.4.4 Contribution to Risk Reduction and Sustainability

Not assessed.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, acibenzolar-S-methyl and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Acibenzolar-S-methyl does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Appendix I, Table 16 for comparison with Track 1 criteria.

- Acibenzolar-S-methyl does not form any transformation products that meet all Track 1 criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade acibenzolar-S-methyl and the end-use product Actigard 50WG do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[9].

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5 DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

8 DIR2006-02, PMRA Formulants Policy.

9 DIR2006-02, PMRA Formulants Policy.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for acibenzolar-S-methyl is adequate to define the majority of toxic effects that may result from exposure to acibenzolar-S-methyl. In subchronic and chronic studies on laboratory animals, the primary target was the blood, highly vascularized tissues and organs, as well as tissues and organs responsible for the production and elimination of blood cells. Systemic toxicity in adult animals included anaemia-related changes. There was no evidence of carcinogenicity in rats or mice with chronic dosing. There was evidence of increased susceptibility of the young in several of the rat developmental toxicity studies, but not in rabbits or in the multigeneration rat reproductive toxicity study. Rare malformations occurred in the rat developmental toxicity studies. Acibenzolar-S-methyl is considered a neurotoxicant based on the occurrence of postnatally-detected morphological changes in the rat brain. The risk assessment protects against the toxic effects noted above by establishing that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Mixer, loader applicators handling Actigard 50WG and workers re-entering treated areas are not expected to be exposed to levels of Actigard 50WG that will result in an unacceptable risk when the Actigard 50WG is used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

The nature of the residue in plants is adequately understood. The residue definition is acibenzolar-S-methyl and the metabolite CGA 210007. The proposed use of acibenzolar-S-methyl on tomatoes and tobacco does not constitute an unacceptable chronic or acute dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed. It was determined that the domestic use of acibenzolar-S-methyl on tomatoes will not result in residues exceeding the MRLs previously established for imported tomato commodities.

7.2 Environmental Risk

No concerns about the use of acibenzolar-S-methyl affecting earthworms, bees, birds, wild mammals, non-target terrestrial plants, fish, amphibians, aquatic invertebrates, algae, or aquatic vascular plants as a result of spray drift have been identified in areas adjacent to the treatment area.

7.3 Value

Actigard 50WG will provide growers with a different mode of action that would help to manage bacterial spot (*X. campestris* pv. *vesicatoria*) and bacterial speck (*P. syringae* pv. *tomato*) on tomato and for control of blue mold (*Peronospora tabacina*) on tobacco.

7.4 Unsupported Uses

The unsupported and supported claims are summarized in Table 18, Appendix I.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Acibenzolar-S-Methyl Technical and Actigard 50WG, containing the technical grade active ingredient acibenzolar-S-methyl, to control or suppress a variety of fungal diseases in tomato and tobacco.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	microgram(s)
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
Ads	adsorption
AR	applied radioactivity
ARfD	acute reference dose
atm	atmosphere
BAF	bioaccumulation factor
BCF	bioconcentration factor
BMD	benchmark dose
BMDL	the lower bound of a 95% CI on the BMD
BMR	benchmark response
bw	body weight
CAF	composite assessment factor
cm^2	centimetre(s) squared
cm^3	centimetre(s) cubed
CO_2	carbon dioxide
CT	crop treated
d	day(s)
DEEM	Dietary Exposure Evaluation Model
Des	desorption
DFOP	double first order in parallel
DFR	dislodgeable foliar residue
DNT	developmental neurotoxicity
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental concentration
ELS	early-life stage
ER_{50}	effective rate for 50% of the population
F	female(s)
F_1	first generation
FDA	*Food and Drugs Act*
g	gram(s)
GAP	good agricultural practice
ha	hectare(s)
HAFT	highest average field trial
HPLC	high performance liquid chromatography
h	hour(s)

HR_{05}	hazard rate 5%
ID	internal dose
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOQ	limit of quantitation
LR_{50}	lethal rate 50%
m	metre(s)
M	male(s)
MAS	maximum average score
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
MOE	margin of exposure
MRL	maximum residue limit
N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
nm	nanometre(s)
PBI	plantback interval
PCPA	*Pest Control Product Act*
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	post natal day
POD	point of departure
PPE	personal protective equipment
ppm	parts per million
RBC	red blood cell
REI	re-entry interval
RQ	risk quotient
SFO	single first order
STMdR	supervised trial median residue
STMR	supervised trial mean residue
SSD	species sensitivity distribution
$t_{1/2}$	half-life
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
USEPA	United States of America Environmental Protection Agency
UV	ultraviolet

WBC	white blood cells
WG	water-dispersible granules
wk	week(s)

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ		Reference
Plant	AG-671A	CGA 210007	HPLC-UV	0.02	plant matrices	1058209, 1058210, 1258217
Animal	Method for meat and eggs can be used for fish					
Soil	REM-1702.04	acibenzolar-S-methyl	HPLC-UV	0.02 ppm		1587002, 1587003, 1587004, 1666307, 1741185
	REM 172.08	CGA 210007	HPLC-UV	0.004 ppm		
	REM 172.03	acibenzolar-S-methyl	HPLC-UV	0.0037 ppm		
Sediment	Extended from soil					
Water	REM 172.09	acibenzolar-S-methyl	HPLC-UV	0.05 µg/L		1587005, 1647110
		CGA 210007				

Table 2 Acute Toxicity of Acibenzolar-S-Methyl, as well as its primary metabolite (CGA 210007), an isomer (CGA 362020), a by-product (NOA 419191), a plant metabolite (CGA 323060), and its associated end-use product (Actigard 50WG)

Study Type	Species	Result[a,b]	Comment	Reference
Acute Toxicity of Acibenzolar-S-Methyl (Technical)				
Oral	Rat	LD_{50} > 5000 mg/kg bw	Low Toxicity	1058252
Oral	Mouse	LD_{50} > 5000 mg/kg bw	Low Toxicity	1586923
Oral	Rat	LD_{50} > 2000 mg/kg bw	Low toxicity	1586925
Dermal	Rat	LD_{50} > 2000 mg/kg bw	Low Toxicity	1058256
Inhalation	Rat	LC_{50} > 5.0 mg/L	Low Toxicity	1058257
Skin irritation	Rabbit	MIS_{4h} = 0.2/8, MAS=0/8	Minimally Irritating	1058155
Skin irritation	Rabbit	MIS_{24h} = 0.7/8, MAS = 0.2/8	Minimally Irritating	1586923
Eye irritation	Rabbit	MIS_{1h} = 6.7/110 MAS = 1.8/110	Minimally Irritating	1058258
Eye irritation	Rabbit	MIS_{1h} = 3.3/110 MAS = 0.22/110	Minimally Irritating	1586930
Skin sensitization	Guinea pig	Skin sensitizer	Potential skin sensitizer "POTENTIAL SKIN SENSITIZER"	1058156
Acute Toxicity of CGA 210007, the primary metabolite of Acibenzolar-S-Methyl (Technical)				
Oral	Rat	LD_{50} > 2000 mg/kg bw	Low Toxicity	1586984
Dermal	Rat	LD_{50} > 2000 mg/kg bw	Low Toxicity	1586985
Skin irritation	Rabbit	MIS_{24h} = 0.7/8, MAS = 0.2/8	Minimally Irritating	1586983
Eye irritation	Rabbit	MIS_{1h} = 38.3/110 MAS = 22.4/110	Moderately Irritating	1586986
Skin sensitization	Guinea pig	Not a skin sensitizer	Not a Skin Sensitizer	1586982

Study Type	Species	Result[a,b]	Comment	Reference
Acute Toxicity of an isomer (CGA 362020), by-product (NOA 419191), and plant metabolite (CGA 323060) of Acibenzolar-S-Methyl				
Oral (CGA 362020)	Rat	LD_{50} > 5000 mg/kg bw	Low Toxicity	1058253
Oral (NOA 419191)	Rat	LD_{50} > 5000 mg/kg bw	Low Toxicity	1058255
Oral (CGA 323060)	Rat	LD_{50} > 2000 mg/kg bw	Low Toxicity	1058254
Acute Toxicity of the end-use product – Actigard 50WG				
Oral	Rat	LD_{50} >5000 mg/kg bw	Low toxicity	1058175
Dermal	Rabbit	LD_{50} >2000 mg/kg bw	Low Toxicity	1058176
Inhalation	Rat	LD_{50} >2.79 mg/kg bw	Low Toxicity	1058177
Skin irritation	Rabbit	MIS_{4h} =4.5/8, MAS = 2.1/8	Moderately Irritating	1058186
Eye irritation	Rabbit	MIS_{1h} = 9.8/110, MAS = 1.3/110 (unwashed)	Minimally Irritating	1058185
Skin sensitization	Guinea pig	Not a skin sensitizer	Not a Skin Sensitizer	1058187

[a]MAS = maximum average score for 24, 48 and 72 hours; [b]MIS = maximum irritation score

Table 3 Toxicity Profile of Technical Acibenzolar-S-Methyl, short-term toxicity and genotoxicity of its primary metabolite (CGA 210007), and gene mutation assessments of an isomer (CGA 362020), a by-product (NOA 419191), and a plant metabolite (CGA 323060) of Technical Acibenzolar-S-Methyl

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
Technical Acibenzolar-S-Methyl			
28-day dermal toxicity	Rat	Dermal irritation: No treatment-related effects were observed at any dose NOAEL: 1000/100 LOAEL: Not determined/1000, based on increased extramedullary haematopoiesis and white pulp in the spleen, and hyperplasia of lymphatic follicles in females.	1058162
28-day dietary	Rat	NOAEL: 385/47 LOAEL: 984/360, based on decreased body weight gain and food consumption, decreased RBC parameters, increased RBC volume distribution width and reticulocyte numbers, decreased plasma globulin and chloride levels, and increased spleen weight and spleen enlargement in males. In females, the LOAEL was based on decreases in red blood cell haematology parameters, decreased plasma chloride, and increased cholesterol.	1058159

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
28-day oral (gavage)	Rat	NOAEL: 100 LOAEL: 800, based on decreased body weight, body weight gain, food consumption and food efficiency, decreased RBC and WBC parameters (F), altered clinical chemistry parameters, decreased thymus weight, increased haemosiderosis in the absence of extramedullary haematopoiesis in the spleen, and necrotic hepatocytes.	1058160
90-day dietary	Mouse	NOAEL: Not established LOAEL: 30.6/47.4, based on changes in the spleen, which included increased weight, haemosiderosis and extramedullary haematopoiesis.	1058158
90-day dietary	Rat	NOAEL: 126/131 LOAEL: 516/554, based on decreased body weight, body weight gain, food consumption and food efficiency, increased liver weight with glycogen deposition, and increased spleen weight with haemosiderosis. The splenic haemosiderosis remained after 4 weeks of recovery.	1058157
90-day capsule	Dog	NOAEL: 50 LOAEL: 200, based on decreased body weight, body weight gain, and food consumption in females, and also decreased RBC and WBC parameters, increased reticulocytes and mean cell volume, increased spleen weight and haemosiderosis, increased liver weight and Kupffer cell pigmentation, increased bone marrow hypercellularity, and decreased plasma lipids. The body weight effect in females, and Kupffer cell pigmentation in both sexes remained after 4 weeks of recovery.	1058163
12-month capsule	Dog	NOAEL: 25 LOAEL: 200, based on decreased body weight gain in females, and also increased liver weights, intrahepatic cholestasis in bile canaliculi and inflammatory cell infiltrates, decreased plasma proteins, increased plasma lipids, decreased RBC and WBC parameters, increased reticulocytes, increased splenic extramedullary hematopoiesis and haemosiderosis, increased Kupffer cell and bone marrow haemosiderosis, increased platelets with an accelerated prothrombin time, and decreased plasma sodium and calcium levels in males.	1058154
Carcinogenicity (18-month dietary)	Mouse	NOAEL: 11.4/10.8 LOAEL: 237/234, based on decreased RBC parameters, increased haemoglobin concentration distribution width, increased spleen weight, increased liver weight, and increased atrophy of the Harderian gland in females; males exhibited increased Kupffer cell haemosiderosis, extramedullary hematopoiesis of the spleen, increased focal hyperplasia of the exocrine pancreas, and increased ceroid deposition of the adrenals; there was also enlargement of the spleen and increased haemosiderosis in the spleen and bone marrow in both sexes.	1058164

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
Chronic/ Carcinogenicity (2-year dietary)	Rat	NOAEL: 97/110 LOAEL: 312/388, based on decreased body weight, body weight gain, increased food efficiency, increased water intake, decreased RBC parameters, increased reticulocytes, decreased plasma proteins, increased plasma bilirubin levels, increased weight and haemosiderosis of the spleen, increased haemosiderosis in Kupffer cells, and increased pulmonary alveolar foam cells in the lung in females.	1057606
Two-generation reproduction	Rat	**Parental toxicity**: NOAEL: 15.3/16.2 LOAEL: 155/162, based on decreased body weight, body weight gain and food consumption, as well as increased weight, haemosiderosis, and congestion of the spleen (F) **Offspring toxicity:** NOAEL: 15.3/16.2 LOAEL: 155/162, based on decreased body weight during the lactation period **Reproductive toxicity:** NOAEL: 306/621 LOAEL: Was not determined. There were no treatment-related reproductive effects.	1057607, 1057608
Developmental toxicity (supplementary, range-finding)	Rat	Effect levels were not established for this study since it was considered supplemental. Treatment-related **maternal** effects during gestation consisted of decreased body weight, body weight gain and food consumption as well as increased haemorrhagic perineal discharge. Treatment-related **developmental** effects occurring at the same dose level consisted of increased total litter resorptions, decreased gravid uterine weight, foetal weight, number of live foetuses, increased early resorptions and post-implantation loss. In addition, umbilical hernia occurred at greater than the historical incidence rate and at less than the maternally toxic dose level.	1586953
Developmental toxicity (gavage)	Rat	**Maternal:** NOAEL: 200 LOAEL: 400, based on decreased body weight gain, food consumption, and increased haemorrhagic perineal discharge. Maternal-embryo/foetal effects included increased total litter resorptions and post-implantation loss as well as decreased live foetuses/litter and foetal body weight. **Developmental:** NOAEL: Not established. LOAEL: 10, based on an umbilical hernia incidence rate that exceeds the historical rate for the same strain of rat.	1058166

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
Developmental toxicity (gavage)	Rat	**Maternal:** NOAEL: 350 LOAEL: Was not determined. There were no maternal or embryo-foetal toxic effects. **Developmental:** NOAEL: 150 LOAEL: 350, based on increased foetal skeletal variations.	1058167 & 600543
Dermal developmental toxicity	Rat	**Maternal and Developmental:** NOAEL: 500 LOAEL: Was not determined. There were no maternal or embryo-foetal developmental effects.	1058170
Developmental toxicity (supplemental investigative, gavage)	Rat	Effect levels were not established for this special investigative study since it was considered supplemental. Exposure was limited to two consecutive days at 400 mg/kg bw/d during different periods of organogenesis. There was a treatment-related mortality associated with hemorrhagic perineal discharge. Pregnancy loss was associated with hemorrhagic perineal discharge. Premature delivery, increased post-implantation loss (early resorptions), decreased foetal weight, and decreased gravid uterine weight also occurred. There were no external malformations.	1058169
Developmental toxicity (supplemental investigative, gavage)	Rat	Effect levels were not established for this special investigative study since it was considered supplemental. Exposure was limited to two consecutive days at 300 mg/kg bw/d during different periods of organogenesis, or occurred throughout organogenesis. Hemorrhagic perineal discharge occurred during all treatment periods except days 14 and 15. With exposure throughout organogenesis, there was a single incidence of total litter resorption, increased early resorptions, reduced mean foetal weight, and reduced gravid uterine weight. There were no external malformations.	1058168
Developmental toxicity (supplementary range-finding)	Rabbit	Effect levels were not established for this study since it was considered supplemental. Treatment-related **maternal** effects during gestation consisted of decreased body weight gain. There were no treatment-related external **developmental** effects. Visceral and skeletal exams were not conducted.	1586957
Developmental toxicity	Rabbit	**Maternal:** NOAEL: 50 LOAEL: 300, based on decreased body weight gain and food consumption. **Developmental:** NOAEL: 300 LOAEL: 600, based on increased post-implantation losses and skeletal variations.	1058171
Reverse gene mutation assay	*S. typhimurium* strains, *E. coli*	Negative	1058172

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
Gene mutations in mammalian cells *in vitro*	Chinese hamster ovary cells	Negative	1058179
In vitro unscheduled DNA synthesis	Rat primary hepatocytes	Negative	1058182
In vitro mammalian chromosomal aberration	Chinese hamster ovary cells	Positive – concurrent with and possibly secondary to cytotoxicity; suggestive evidence of a possible aneuploidy effect; cell cycle arresting activity at G2+M was demonstrated.	1058180
In vivo mammalian cytogenetics	Mice	Negative	1058181
Sub-chronic Neurotoxicity (90-day, diet)	Rat	**Systemic Toxicity:** NOAEL: 24.4/143 LOAEL: 126/628, based on decreased body weight and body weight gain. **Neurotoxicity:** No treatment-related effects observed.	1058273
Developmental Neurotoxicity (supplementary, range-finding, diet)	Rat	Effect levels were not established for this study since it was considered supplemental. Treatment-related **maternal** effects, which occurred at the highest dose during gestation days 15 to 16, consisted of decreased body weight, increased vaginal bleeding, and increased total foetal resorptions. Apart from the later outcome, the only other **developmental** effect consisted of decreased body weights during the mid to late lactation period at greater than or equal to the lowest dose tested. This effect appeared to precede adult-diet consumption.	1586974
Developmental Neurotoxicity	Rat	**Maternal:** NOAEL: 326 LOAEL: Was not determined. There were no treatment-related effects. **Developmental (systemic):** NOAEL: 82 LOAEL: 326, based on decreased body weight during late lactation period. **Developmental (systemic):** NOAEL: Not established LOAEL: 8.2, based on decreases in the thickness of the dorsal cortex of the cerebrum and the molecular layer of the cerebellum (PND 63, males).	1058274, 1058275

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
Metabolism	Rat	**Absorption:** Acibenzolar-s-methyl was rapidly absorbed and excreted. There was no evidence that absorption mechanisms were saturated at the highest dose tested. **Distribution:** The highest residue concentrations were found in the liver, remaining carcass and kidneys, at seven days after dosing. Higher residue levels also occurred in the blood and blood rich tissues (lungs and spleen). Less than 0.25% of the AD remained in the tissues and carcass at termination. **Excretion:** Elimination was primarily via the urine as 70 to 90% of the AD was eliminated via this route in 24 h, whereas, 3 to 5% of the AD was eliminated via the faeces. The route and rate of excretion were independent of the sex, dose level, and pretreatment with unlabelled technical active. **Metabolism:** The metabolite pattern is relatively simple, consisting of three major fractions. The metabolic fate of was quantitatively and qualitatively independent of sex, dose level and pretreatment with unlabelled technical active. The metabolic data do not suggest significant enterohepatic circulation. Three urinary fractions detected included the carboxylic acid derivative of the parent (78.6 - 92.0% AD), was the corresponding glycine conjugate of CGA-210007 (0.4 - 2.2% AD) and a mixture of at least three unidentified polar compounds (1.3 - 4.5% AD). Parent compound was not detected in the urine. Total radioactivity in the faeces represented <5% of the administered dose. Fractions detected in the faeces included the parent (0.1 - 1.0% AD), CGA 210007 (0.7 - 2.8% AD), and an unidentified polar compound (0.2 - 0.4% AD). There were no major differences in metabolism between dose groups.	1058183, 1058184
BMD analyses of Developmental Toxicity (Non-Guideline)	Rat	**N/LOAEL** establishment is not applicable as this is a special mechanistic study. A BMDL-based POD was not established since the data were not amenable to modeling. There was insufficient evidence that combining fetal resorptions together with rare malformation data into a single BMD analysis was acceptable either biologically or toxicologically.	1058190
Antibody Formation against CGA 245704 and/or its Putative Protein Conjugates or Adducts, *in vitro* (Non-standard, acceptable)	Rat	**N/LOAEL** establishment is not applicable as this is a special mechanistic study. No evidence that antibodies are formed against CGA 245704 and/or its serum albumin conjugate. Either a protein conjugate of CGA 245704 is not formed or, if such a conjugate is formed, its structure leads to the formation of antibodies in the rat which do not recognize the synthetic antigen used in this study.	1586975

Study Type	Species	Results[a] (mg/kg/day in M/F)	Reference
Hydrolytic Stability of CGA 245704 *in vitro* (Non-standard, acceptable)	Rat, Human	**N/LOAEL** not applicable as this is a special mechanistic study. Hydrolysis to CGA 210007 was confirmed in selected tissues from rats and humans. Relative rates of hydrolysis (%) were: human liver homogenate (100) > rat liver homogenate (16) > rat skin homogenate (10) > human skin homogenate (3) >>>> rat plasma (0.04) >> human serum (0.01).	1586979
The primary metabolite (CGA 210007) of Technical Acibenzolar-S-Methyl			
28-day oral (gavage)	Rat	NOAEL: 100 LOAEL: 400, based on clinical signs in 1 moribund animal, decreased body weight, body weight gain, and food consumption, increased water consumption, decreased RBC and WBC parameters, and decreased thymus weight.	1586976
Reverse gene mutation assay	*S. typhimurium* strains, *E. coli*	Positive - Two-fold increase in reverterants of *S. typhimurium* strain TA 98 at ≥ 1250 µg/plate without and with activation.	1586960
In vitro mammalian chromosomal aberration	Chinese hamster ovary cells	Positive at 750 µg/mL with metabolic activation in the presence of a slight increase (15%) in cytotoxicity.	1586987
An isomer (CGA 362020), by-product (NOA 419191), and plant metabolite (CGA 323060) of Acibenzolar-S-Methyl			
Reverse gene mutation assay (95.5/0.5% Technical active/Isomer CGA 362020)	*S. typhimurium* strains, *E. coli*	Negative (CGA 362020 content from 1.6 to 25 µg/plate)	1586959
Reverse gene mutation assay (Isomer CGA 362020)	*S. typhimurium* strains, *E. coli*	Positive - *S. typhimurium* strain TA1537 at 277.78 µg/plate without activation. Negative at 5000 µg/plate with S9 activation	1058173
Reverse gene mutation assay (By-product NOA 419191)	*S. typhimurium* strains, *E. coli*	Negative	1058178
Reverse gene mutation assay (Plant metabolite CGA 323060)	*S. typhimurium* strains, *E. coli*	Negative	1058174

[a]Effects observed in males as well as females unless otherwise reported.

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Acibenzolar-S-Methyl

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	CAF[1] or Target MOE[2]
Acute dietary	LOAEL = 8.2	Developmental Neurotoxicity	Decreased thickness of the dorsal cortex of the cerebrum and of the molecular layer of the cerebellum.	3000
	ARD = 0.0027 mg/kg bw/d			
Chronic Dietary	LOAEL = 8.2	Developmental Neurotoxicity	Decreased thickness of the dorsal cortex of the cerebrum and of the molecular layer of the cerebellum.	3000

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	CAF[1] or Target MOE[2]
	ADI = 0.0027 mg/kg bw/d			
Short- to intermediate-term dermal and inhalation	LOAEL = 8.2	Developmental Neurotoxicity	Decreased thickness of the dorsal cortex of the cerebrum and of the molecular layer of the cerebellum.	3000

[1]Dietary scenarios. [2]Exposure scenarios.

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN LETTUCE			**PMRA # 1058207**
Radiolabel Position	**[Phenyl-(U)-^{14}C] acibenzolar-S-methyl**		
Test Site	Greenhouse		
Treatment	Foliar treatment		
Rate	35 g a.i./ha/application, 4 applications, for a total seasonal rate of 140 g a.i./ha.		
End-use product	WG 50 formulation		
Preharvest interval	1 hour, 7 days		
Matrix	**PHI**	**[Phenyl-(U)-^{14}C] acibenzolar-S-methyl**	
		TRR (ppm)	
Lettuce, head	1-hour	1.223	
	7-day	1.104	
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**
	acibenzolar-S-methyl, CGA 210007, CGA 323060		CGA 324041
NATURE OF THE RESIDUE IN TOMATOES			**PMRA # 1058204**
Radiolabel Position	**[Phenyl-(U)-^{14}C] acibenzolar-S-methyl**		
Test Site	Greenhouse		
Treatment	Foliar treatment		
Rate	91 g a.i./ha/application, 3 applications, for a total seasonal rate of 273 g a.i./ha.		
End-use product	WG 50 formulation		
Preharvest interval	1 hour, 7 days, 28 days (68 days for leaves)		
Matrix	**PHI**	**[Phenyl-(U)-^{14}C] acibenzolar-S-methyl**	
		TRR (ppm)	
Tomato fruit	1-hour	0.759	
	7-day	0.689	
	28-day	0.312	
Tomato leaves	1-hour	3.846	
	7-day	2.987	
	68-day	0.719	
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**
Tomato fruit (28 days PHI)	CGA 210007		acibenzolar-S-methyl, CGA 324041, CGA 323060
Tomato leaves (68-day PHI)	CGA 210007		CGA 324041, CGA 323060

NATURE OF THE RESIDUE IN WHEAT			**PMRA # 1058203**
Radiolabel Position	**[Phenyl-(U)-^{14}C] acibenzolar-S-methyl**		
Test Site	Greenhouse (shoot) & field (stalk, ear, straw and grain)		
Treatment	Foliar treatment		
Rate	50 g a.i./ha/application, 1 application, for a total seasonal rate of 50 g a.i./ha.		
End-use product	WG 50 formulation		
Preharvest interval	shoot – 0, 1, 3, 7, 14 days. stalk & ear – 28 days straw & grain – 75 days		
Matrix	**PHI**	**[Phenyl-(U)-^{14}C] acibenzolar-S-methyl**	
		TRR (ppm)	
Wheat shoot	0-day	1.601	
	1-day	1.013	
	3-day	0.514	
	7-day	0.312	
	14-day	0.468	
Wheat stalk	28-day	0.227	
Wheat ear	28-day	0.183	
Wheat straw	75-day	0.328	
Wheat grain	75-day	0.014	
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**
Wheat shoot (14-day PHI)	CGA 210007		CGA 324041
Wheat stalk (28-day PHI)	CGA 210007		CGA 324041
Wheat ear (28-day PHI)	CGA 210007		CGA 324041
Wheat straw (75-day PHI)	CGA 210007		CGA 324041
Wheat grain (75-day PHI)	CGA 210007		CGA 324041

NATURE OF THE RESIDUE IN TOBACCO			**PMRA # 1058205**
Radiolabel Position	**[Phenyl-(U)-^{14}C] acibenzolar-S-methyl**		
Test Site	Greenhouse		
Treatment	Foliar treatment		
Rate	3 applications at 20, 50 and 100 g a.i./ha, for a total seasonal rate of 170 g a.i./ha.		
End-use product	WG 50 formulation		
Preharvest interval	17-52 days after the last application		
Matrix	**PHI**	**[Phenyl-(U)-^{14}C] acibenzolar-S-methyl**	
		TRR (ppm)	
Tobacco lower leaves	17-45 days	1.388	
Tobacco upper leaves	52 days	0.434	
Cured tobacco lower leaves	17-45 days	11.63	
Cured tobacco upper leaves	52 days	2.719	
Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**
Tobacco lower leaves	CGA 210007		CGA 324041, CGA 323060
Tobacco upper leaves	CGA 210007		CGA 324041, CGA 323060
Cured tobacco lower leaves	CGA 210007		CGA 324041, CGA 323060
Cured tobacco upper leaves	CGA 210007		CGA 324041, CGA 323060

CONFINED ACCUMULATION IN ROTATIONAL CROPS – mustard greens, radish, wheat			PMRA # 1058200, 1058201
Radiolabel Position		**[Phenyl-(U)-^{14}C] acibenzolar-S-methyl**	
Test site		Field test plot with a wood and plastic frame box	
Formulation used for trial		[Phenyl-(U)-^{14}C] acibenzolar-S-methyl diluted with acetonitrile	
Application rate and timing		421 g a.i./ha; 30, 60 and 210 days prior to planting.	
Metabolites Identified		**Major Metabolites (> 10% TRR)**	**Minor Metabolites (< 10% TRR)**
Matrix	**PBI (days)**		
Wheat forage	30	CGA 210007	CGA 324041/CGA 323060
Wheat forage	60	CGA 210007	CGA 324041/CGA 323060
Mustard greens	60	--	CGA 210007, CGA 324041/CGA 323060
PLANT METABOLISM SUMMARY			
Acibenzolar-S-methyl is hydrolyzed to form the carboxylic acid metabolite CGA 210007. Subsequently hydroxylation of CGA 210007 at the C-4 and C-5 position to form the minor metabolites CGA 324041 and CGA 323060. Each of these acid metabolites may also form acyl sugar conjugates. The proposed metabolic scheme in rotational crops is similar to the metabolism observed in the primary crops.			
STORAGE STABILITY			**PMRA # 1058225**
The storage stability data indicate that residues of acibenzolar-S-methyl and CGA 210007 are stable under frozen storage conditions for up to 22 months in leaf lettuce, tomato (fruit and paste), wheat (grain and straw) cabbage, squash, turnip roots and tobacco (green and flue-cured).			
CROP FIELD TRIALS – Tomatoes			**PMRA # 1058222**
12 tomato trials were conducted in Zones 1 (1 trial), 2 (1 trial), 3 (2 trials), 5 (1 trial), and 10 (7 trials) during the 1996 growing season. Tomato plants were treated 4 times with acibenzolar-S-methyl at 105 g a.i./ha/application for a total of 420 g a.i./ha/season (2X the proposed Canadian GAP rate) with a preharvest interval of 13-15 days.			

Commodity	Total Applic. Rate (g a.i./ha)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Tomato fruit	420	13-15	24	0.06	0.61	0.47	0.17	0.19	0.12

Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES	
RESIDUE DEFINITION FOR ENFORCEMENT **Primary crops** **Rotational crops**	Acibenzolar-S-methyl, including the metabolite CGA 210007.
RESIDUE DEFINITION FOR RISK ASSESSMENT **Primary crops** **Rotational crops**	Acibenzolar-S-methyl, CGA 210007, and 4- & 5-hydroxy metabolites of CGA 210007 (CGA 323060 & CGA 324041)
METABOLIC PROFILE IN DIVERSE CROPS	similar
ANIMAL STUDIES	
ANIMALS	**Ruminant**
RESIDUE DEFINITION FOR ENFORCEMENT	not applicable
RESIDUE DEFINITION FOR RISK ASSESSMENT	not applicable

METABOLIC PROFILE IN ANIMALS (goat, hen, rat)	not provided
FAT SOLUBLE RESIDUE	--

DIETARY RISK FROM FOOD AND WATER			
	POPULATION	**ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)**	
		Food Only	**Food and Water**
Refined chronic non-cancer dietary risk **ADI = 0.0027 mg/kg bw** **Estimated chronic drinking water concentration = 2.4 μg/L**	**Total population**	1.2	3.1
	All infants < 1 year	2.1	8.3
	Children 1–2 years	3.9	6.6
	Children 3 to 5 years	2.7	5.3
	Children 6–12 years	1.6	3.4
	Youth 13–19 years	0.9	2.3
	Adults 20–49 years	1.0	2.7
	Adults 50+ years	1.1	2.9
	Females 13-49 yrs	0.9	2.7
Refined acute dietary exposure analysis, 99.9th percentile (probabilistic) **Estimated acute drinking water concentration = 2.4 μg/L** **ARfD = 0.0027 mg/kg bw**	**POPULATION**	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
	Total population	46.5	49.1
	All infants < 1 year	38.9	55.6
	Children 1–2 years	88.2	93.4
	Children 3 to 5 years	90.6	90.4
	Children 6–12 years	52.0	51.8
	Youth 13–19 years	36.7	40.2
	Adults 20–49 years	41.5	41.9
	Adults 50+ years	50.1	54.8
	Females 13-49 yrs	42.5	43.6

Table 7 Major transformation products in environmental media

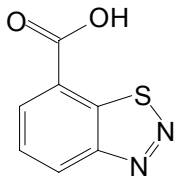
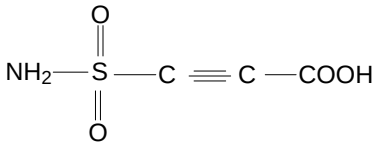
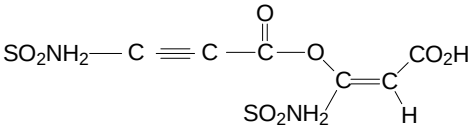
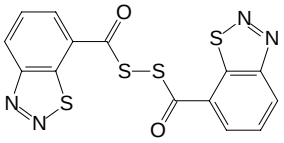
Code name	Structure Chemical name CAS number	Molecular formula Molar mass	Occurrence (max % AR)
CGA 210007	 Benzo[1,2,3] thiadiazole-7-carboxylic acid CAS# 35272-27-6	$C_7H_4N_2O_2S$ 180.2 g/mol	Hydrolysis pH 5: 4.52 Hydrolysis pH 7: 35.38 Hydrolysis pH 9: 41.27 Soil photolysis at pH 7.3, irradiated and sterile : 25.0 Aqueous photolysis at pH 5, irradiated and sterile : 2.5 Aerobic soil: 82.57 Anaerobic flooded soil: 90.89 Aerobic water/sediment: 92.87
A7		$C_3H_3NO_4S$ 149 g/mol	Aqueous photolysis at pH 5, irradiated and sterile : 38.5
A8		$C_6H_6N_2O_8S_2$ 298 g/mol	Aqueous photolysis at pH 5, irradiated and sterile : 42.2
A9	Unknown compound		Aqueous photolysis at pH 5, irradiated and sterile : 19.0
A14/A15		$C_{14}H_6N_4O_2S_4$ 390 g/mol	Aqueous photolysis at pH 5, irradiated and sterile : 27.1
A16	Unknown compound		Aqueous photolysis at pH 5, irradiated and sterile : 12.2

Table 8 Fate and behaviour in the environment

Study	Substance	Value	Remarks	Reference (PMRA#)
Hydrolysis at 24ºC	Acibenzolar-s-methyl	$T_{1/2}$ at 24º and, pH 5: 388 d (Stable) pH 7:79.5 d (SFO) pH 9: 9.22 h (SFO)	Is an important route of transformation.	1587010
Soil photolysis	Acibenzolar-s-methyl	$T_{1/2}$ at 25ºC and pH 7.3 in irradiated and sterile US sandy loam soil: Stable (29.9 d, SFO)	Is not an important route of transformation	1587012
		$T_{1/2}$ at 24ºC and pH 7.3 in irradiated dry Swiss silt loam soil (sterility not proven): 33.13 d (DFOP)	Is not an important route of transformation	1587011
Aqueous photolysis	Acibenzolar-s-methyl	$T_{1/2}$ at 25ºC and pH 5: 0.27 h (SFO)	Significant degradation process	1587016
	CGA 210007	$T_{1/2}$ at 25ºC, Natural Summer Sunlight: at pH 5: 0.055 d (SFO) at pH 7: 0.073 d (SFO) at pH 9: 0.064 d (SFO)		1587014
Bio-transformation in aerobic soil	Acibenzolar-s-methyl	DT_{50}: 0.22 d (DT_{90}: 0.73 d; SFO) CGA 210007 DT_{50}: 21 d (DT_{90}: 67.9 d; SFO)	Is an important route of transformation of the parent.	1587022
Bio-transformation in anaerobic flooded soil	Acibenzolar-s-methyl	DT_{50}: 4.06 d (DT_{90}: 13.8 d; DFOP) CGA 210007 DT_{50}: Stable	Is an important route of transformation of the parent	1587024
Bio-transformation in aerobic water/sediment systems	Acibenzolar-s-methyl	River system DT_{50}: 0.82 d (DT_{90}: 2.73 d; SFO) Pond water system DT_{50}: 0.63 d (DT_{90}: 2.10 d; SFO) CGA 210007 DT_{50}: 344-488 days		1587023
Adsorption / Desorption	Acibenzolar-s-methyl	U.S. soils Ads. K_{OC}: 492 - 3288 Des. K_{OC}: 723 - 5828	Slightly to moderately mobile	1587026
		Europe soils Ads. K_{OC}: 981 - 1885 Des. K_{OC}: 93 - 2200	Low mobility	1587025
	CGA 210007	U.S. soils Ads. K_{OC}: 40 - 312 Des. K_{OC}: 244 – 1529	Moderately to very highly mobile	1587027

Study	Substance	Value	Remarks	Reference (PMRA#)
Leaching of aged soil	Acibenzolar-s-methyl	K_{OC}: 30 – 27482 CGA 210007 was abundant in leachate	Immobile to very highly mobile.	1587029
Field dissipation (bare ground soil)	Acibenzolar-s-methyl	DT_{50}: 0.12 d (DT_{90}: 2.59 d; DFOP) CGA 210007 DT_{50}: 4.55 d (DT_{90}: 15.10 d; SFO)	Study performed in North Carolina, in an ecoregion not relevant to Canada.	1587030
	Acibenzolar-s-methyl	DT_{50}: 7.76 d (DT_{90}: 25.8 d; SFO) CGA 210007 DT_{50}: 109 d (DT_{90}: 361 d; SFO)	Study performed in California, in an ecoregion not relevant to Canada.	1587032

Table 9 Toxicity to non-target terrestrial species

Organism	Study type	Substance	Endpoint value	Degree of toxicity[a]	Reference (PMRA#)
Earthworm (*Eisenia foetida*)	Acute (14-d)	Acibenzolar-s-methyl	LC_{50} > 1000 mg a.i./kg dw soil NOEC (mortality) < 12.3 mg a.i./kg dw soil		1587043
Bee (*Apis mellifera*)	Oral (48-h)	Acibenzolar-s-methyl	LD_{50} > 128.3 µg a.i./bee NOEL = 128.3 µg a.i./bee	Relatively non-toxic	1587044
	Contact (48-h)	Acibenzolar-s-methyl	LD_{50} > 100 µg a.i./bee NOEL = 100 µg a.i./bee		
Bobwhite quail (*Colinus virginianus*)	Acute (14-d)	Acibenzolar-s-methyl	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic	1587056
	Dietary (8-d)	Acibenzolar-s-methyl	LC_{50} > 5000 mg a.i./kg diet NOEC = 5000 mg a.i./kg diet	Practically non-toxic	1587058
	Reproduction (22-wk)	Acibenzolar-s-methyl	NOEC (↓ 14-d old hatchling survivors/ normal hatchlings) = 600 mg a.i./kg diet		1587060
Mallard duck (*Anas platyrhynchos*)	Acute (14-d)	Acibenzolar-s-methyl	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic	1587057
	Dietary (8-d)	Acibenzolar-s-methyl	LC_{50} > 5000 mg a.i./kg diet NOEC (↓ body weight gain) = 2450 mg a.i./kg diet	Practically non-toxic	1587059
	Reproduction (23-wk)	Acibenzolar-s-methyl	NOEC (sub-lethal effects) = 1000 mg a.i./kg diet		1587061
Mouse	Acute	Acibenzolar-s-methyl	LD_{50} > 5000 mg a.i./kg bw	Practically non-toxic	1586923

Organism	Study type	Substance	Endpoint value	Degree of toxicity[a]	Reference (PMRA#)
Rat	Acute	Acibenzolar-s-methyl	LD_{50} > 5000 mg a.i./kg bw	Practically non-toxic	1058252
	Acute	CGA 210007	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic	1586984
	Short-term (28-day feeding)	Acibenzolar-s-methyl	NOAEL (↓ body weight gain & ↓ food consumption) = 384.8 (M) and 359.8 (F) mg a.i./kg bw/day LOAEL = 984 (M) and 922 (F) mg a.i./kg bw/day		1058159
	Reproduction (multi-generation)	Acibenzolar-s-methyl	NOAEL (↓ body weight/body weight gain & ↓ food consumption) = 15.3 (M) and 16.2 (F) mg a.i./kg bw/day LOAEL = 155 (M) and 162 (F) mg a.i./kg bw/day		1057607 1057608
Vascular plants	Seedling emergence (14-d)	CGA 245704-50WG	EC_{25} > 105 g a.i./ha		1587065
	Vegetative vigour (14-d)	CGA 245704-50WG	EC_{25} > 105 g a.i./ha		1587064

a. Atkins *et al.* (1981) for bees and US EPA classification for others, where applicable.

Table 10 Toxicity to non-target aquatic species

Organism	Study type	Substance	Endpoint value	Degree of toxicity[a]	Reference (PMRA#)
Freshwater species					
Invertebrate (*Daphnia magna*)	Acute (48-h)	Acibenzolar-s-methyl	EC_{50} (mortality) = 2.90 mg a.i./L NOEC (mortality) = 0.82 mg a.i./L	Moderately toxic	1587046
	Acute (48-h)	CGA 210007	EC_{50} (mortality) = 59.9 mg a.i./L NOEC (mortality) = 10.3 mg a.i./L	Slightly toxic	1587045
	Chronic (21-d)	Acibenzolar-s-methyl	NOEC (↓ adult body weight and length) = 0.048 mg a.i./L NOEC (↓ reproduction) = 0.087 mg a.i./L		1587047
Rainbow trout (*Oncorhynchus mykiss*)	Acute (96-h)	Acibenzolar-s-methyl	LC_{50} = 0.88 mg a.i./L NOEC (mortality & sub-lethal effects) = 0.43 mg a.i./L	Highly toxic	1587050
	Acute (96-h)	CGA 210007	LC_{50} > 92 mg a.i./L NOEC (mortality& sub-lethal effects) = 10.3 mg a.i./L	Slightly toxic	1587051

Organism	Study type	Substance	Endpoint value	Degree of toxicity[a]	Reference (PMRA#)
	Early-Life Stage (87-d)	Acibenzolar-s-methyl	NOEC (↓ body weight) = 0.026 mg a.i./L		1587054
Bluegill sunfish (*Lepomis macrochirus*)	Acute (96-h)	Acibenzolar-s-methyl	LC_{50} = 1.6 mg a.i./L NOEC (sub-lethal effects) = 0.9 mg a.i./L	Moderately toxic	1587052
	Bio-accumulation	Acibenzolar-s-methyl	BCF = 117-118 Does not bioaccumulate significantly and readily excreted		1587055
Freshwater alga (*Selenastrum capricornutum*)	Acute (96-h)	Acibenzolar-s-methyl	EC_{50} (↓ cell count) = 3.31 mg a.i./L NOEC (↓ cell count) = 1.33 mg a.i./L		1587063
	Acute (72-h)	CGA 210007	EC_{50} (↓ cell count) = 80.1 mg a.i./L NOEC (↓ cell count) = 55.7 mg a.i./L		1587062
Vascular plant (*Lemna gibba*)	Acute (7-d) dissolved	Acibenzolar-s-methyl	EC_{50} (frond count) = 0.312 mg a.i./L NOEC (frond count) = 0.0192 mg a.i./L		1587066
Marine species					
Mysid shrimp (*Mysidopsis bahia*)	Acute (96-h)	Acibenzolar-s-methyl	LC_{50} = 0.88 mg a.i./L NOEC (mortality & sub-lethal effects) = 0.37 mg a.i./L	Highly toxic	1587048
Eastern Oyster (*Crassostrea virginica*)	Acute (96-h)	Acibenzolar-s-methyl	EC_{50} (↓ shell growth) = 0.59 mg a.i./L NOEC (↓ shell growth) = 0.19 mg a.i./L	Highly toxic	1587049
Sheepshead minnow (*Cyprinodon variegatus*)	Acute (96-h)	Acibenzolar-s-methyl	LC_{50} = 1.7 mg a.i./L NOEC (sub-lethal effects) = 0.43 mg a.i./L	Moderately toxic	1587053

a. US EPA classification for others, where applicable.

Table 11 Endpoints used for the risk assessment and the uncertainty factors applied

Taxonomic group	Exposure	Endpoint	Species Uncertainty Factor
Earthworm	Acute	LC_{50}	0.5
	Chronic	NOEC	1
Bees	Acute	LD_{50}	1
Other non-target arthropods	Acute	LR_{50}	1
Birds	Acute oral	LD_{50}	0.1

Taxonomic group	Exposure	Endpoint	Species Uncertainty Factor
	Dietary	LD_{50}	0.1
	Reproduction	NOEL	1
Mammals	Acute oral	LD_{50}	0.1
	Reproduction	NOEL	1
Non-target terrestrial plants	Acute	EC_{25}, or HR_5 of SSD of ER_{50}*	1
Aquatic invertebrates	Acute	LC_{50} or EC_{50}	0.5
	Chronic	NOEC	1
Fish	Acute	LC_{50}	0.1
	Chronic	NOEC	1
Amphibians	Acute	Fish LC_{50}	0.1
	Chronic	Fish NOEC	1.0
Algae	Chronic	EC_{50}	0.5
Aquatic vascular plants	Chronic	EC_{50}	0.5

* 5^{th} percentile hazard rate of the species sensitivity distribution of ER_{50} values

Table 12 Screening level estimated daily exposure (EDE) values of Acibenzolar-s-methyl for birds and mammals

Toxicity endpoint (mg ai/kg bw/d)		Feeding Guild (food item)	On-field EDE (mg ai/kg bw)	RQ
Small Bird (0.02 kg)				
Acute	200	Insectivore (small insects)	3.3704	0.0169
	200	Granivore (grain and seeds)	0.8426	0.0042
	200	Frugivore (fruit)	1.6852	0.0084
Dietary	147.9	Insectivore (small insects)	3.3704	0.0228
	147.9	Granivore (grain and seeds)	0.8426	0.0057
	147.9	Frugivore (fruit)	1.6852	0.0114
Reproduction	62.7	Insectivore (small insects)	3.3704	0.0538
	62.7	Granivore (grain and seeds)	0.8426	0.0134
	62.7	Frugivore (fruit)	1.6852	0.0269
Medium Sized Bird (0.1 kg)				
Acute	200	Insectivore (small insects)	2.6303	0.0132
	200	Insectivore (large insects)	0.6576	0.0033
	200	Granivore (grain and seeds)	0.6576	0.0033
	200	Frugivore (fruit)	1.3151	0.0066
Dietary	147.9	Insectivore (small insects)	2.6303	0.0178
	147.9	Insectivore (large insects)	0.6576	0.0044
	147.9	Granivore (grain and seeds)	0.6576	0.0044
	147.9	Frugivore (fruit)	1.3151	0.0089

Toxicity endpoint (mg ai/kg bw/d)		Feeding Guild (food item)	On-field EDE (mg ai/kg bw)	RQ
Reproduction	62.7	Insectivore (small insects)	2.6303	0.0420
	62.7	Insectivore (large insects)	0.6576	0.0105
	62.7	Granivore (grain and seeds)	0.6576	0.0105
	62.7	Frugivore (fruit)	1.3151	0.0210
Large Sized Bird (1 kg)				
Acute	200	Insectivore (small insects)	0.7679	0.0038
	200	Insectivore (large insects)	0.1920	0.0010
	200	Granivore (grain and seeds)	0.1920	0.0010
	200	Frugivore (fruit)	0.3840	0.0019
	200	Herbivore (short grass)	2.7446	0.0137
	200	Herbivore (long grass)	1.6758	0.0084
	200	Herbivore (forage crops)	2.5393	0.0127
	200	Herbivore (leafy foliage)	5.1727	0.0259
Dietary	147.9	Insectivore (small insects)	0.7679	0.0052
	147.9	Insectivore (large insects)	0.1920	0.0013
	147.9	Granivore (grain and seeds)	0.1920	0.0013
	147.9	Frugivore (fruit)	0.3840	0.0026
	147.9	Herbivore (short grass)	2.7446	0.0186
	147.9	Herbivore (long grass)	1.6758	0.0113
	147.9	Herbivore (forage crops)	2.5393	0.0172
	147.9	Herbivore (leafy foliage)	5.1727	0.0350
Reproduction	62.7	Insectivore (small insects)	0.7679	0.0122
	62.7	Insectivore (large insects)	0.1920	0.0031
	62.7	Granivore (grain and seeds)	0.1920	0.0031
	62.7	Frugivore (fruit)	0.3840	0.0061
	62.7	Herbivore (short grass)	2.7446	0.0438
	62.7	Herbivore (long grass)	1.6758	0.0267
	62.7	Herbivore (forage crops)	2.5393	0.0405
	62.7	Herbivore (leafy foliage)	5.1727	0.0825
Small Mammal (0.015 kg)				
Acute	500	Insectivore (small insects)	1.9386	0.0039
	500	Granivore (grain and seeds)	0.4846	0.0010
	500	Frugivore (fruit)	0.9693	0.0019
Dietary	359.8	Insectivore (small insects)	1.9386	0.0054
	359.8	Granivore (grain and seeds)	0.4846	0.0013
	359.8	Frugivore (fruit)	0.9693	0.0027
Reproduction	15.3	Insectivore (small insects)	1.9386	0.1267
	15.3	Granivore (grain and seeds)	0.4846	0.0317
	15.3	Frugivore (fruit)	0.9693	0.0634
Medium Sized Mammal (0.035 kg)				
Acute	500	Insectivore (small insects)	1.6994	0.0034
	500	Insectivore (large insects)	0.4248	0.0008
	500	Granivore (grain and seeds)	0.4248	0.0008

Toxicity endpoint (mg ai/kg bw/d)		Feeding Guild (food item)	On-field EDE (mg ai/kg bw)	RQ
	500	Frugivore (fruit)	0.8497	0.0017
	500	Herbivore (short grass)	6.0735	0.0121
	500	Herbivore (long grass)	3.7084	0.0074
	500	Herbivore (forage crops)	5.6193	0.0112
	500	Herbivore (leafy foliage)	11.4468	0.0229
Dietary	359.8	Insectivore (small insects)	1.6994	0.0047
	359.8	Insectivore (large insects)	0.4248	0.0012
	359.8	Granivore (grain and seeds)	0.4248	0.0012
	359.8	Frugivore (fruit)	0.8497	0.0024
	359.8	Herbivore (short grass)	6.0735	0.0169
	359.8	Herbivore (long grass)	3.7084	0.0103
	359.8	Herbivore (forage crops)	5.6193	0.0156
	359.8	Herbivore (leafy foliage)	11.4468	0.0318
Reproduction	15.3	Insectivore (small insects)	1.6994	0.1111
	15.3	Insectivore (large insects)	0.4248	0.0278
	15.3	Granivore (grain and seeds)	0.4248	0.0278
	15.3	Frugivore (fruit)	0.8497	0.0555
	15.3	Herbivore (short grass)	6.0735	0.3970
	15.3	Herbivore (long grass)	3.7084	0.2424
	15.3	Herbivore (forage crops)	5.6193	0.3673
	15.3	Herbivore (leafy foliage)	11.4468	0.7482
Large Sized Mammal (1 kg)				
Acute	500	Insectivore (small insects)	0.9080	0.0018
	500	Insectivore (large insects)	0.2270	0.0005
	500	Granivore (grain and seeds)	0.2270	0.0005
	500	Frugivore (fruit)	0.4540	0.0009
	500	Herbivore (short grass)	3.2453	0.0065
	500	Herbivore (long grass)	1.9815	0.0040
	500	Herbivore (forage crops)	3.0026	0.0060
	500	Herbivore (leafy foliage)	6.1164	0.0122
Dietary	359.8	Insectivore (small insects)	0.9080	0.0025
	359.8	Insectivore (large insects)	0.2270	0.0006
	359.8	Granivore (grain and seeds)	0.2270	0.0006
	359.8	Frugivore (fruit)	0.4540	0.0013
	359.8	Herbivore (short grass)	3.2453	0.0090
	359.8	Herbivore (long grass)	1.9815	0.0055
	359.8	Herbivore (forage crops)	3.0026	0.0083
	359.8	Herbivore (leafy foliage)	6.1164	0.0170
Reproduction	15.3	Insectivore (small insects)	0.9080	0.0593
	15.3	Insectivore (large insects)	0.2270	0.0148
	15.3	Granivore (grain and seeds)	0.2270	0.0148
	15.3	Frugivore (fruit)	0.4540	0.0297
	15.3	Herbivore (short grass)	3.2453	0.2121
	15.3	Herbivore (long grass)	1.9815	0.1295

Toxicity endpoint (mg ai/kg bw/d)		Feeding Guild (food item)	On-field EDE (mg ai/kg bw)	RQ
	15.3	Herbivore (forage crops)	3.0026	0.1962
	15.3	Herbivore (leafy foliage)	6.1164	0.3998

Table 13 Screening level estimated daily exposure (EDE) values of CGA 210007 for mammals

Toxicity endpoint (mg ai/kg bw/d)		Feeding Guild (food item)	On-field EDE (mg ai/kg bw)	RQ
Small Mammal (0.015 kg)				
Acute	200	Insectivore (small insects)	1.6609	0.0083
	200	Granivore (grain and seeds)	0.4152	0.0021
	200	Frugivore (fruit)	0.8305	0.0042
Medium Sized Mammal (0.035 kg)				
Acute	200	Insectivore (small insects)	1.4560	0.0073
	200	Insectivore (large insects)	0.3640	0.0018
	200	Granivore (grain and seeds)	0.3640	0.0018
	200	Frugivore (fruit)	0.7280	0.0036
	200	Herbivore (short grass)	5.2037	0.0260
	200	Herbivore (long grass)	3.1773	0.0159
	200	Herbivore (forage crops)	4.8145	0.0241
	200	Herbivore (leafy foliage)	9.8074	0.0490
Large Sized Mammal (1 kg)				
Acute	200	Insectivore (small insects)	0.7780	0.0039
	200	Insectivore (large insects)	0.1945	0.0010
	200	Granivore (grain and seeds)	0.1945	0.0010
	200	Frugivore (fruit)	0.3890	0.0019
	200	Herbivore (short grass)	2.7805	0.0139
	200	Herbivore (long grass)	1.6977	0.0085
	200	Herbivore (forage crops)	2.5726	0.0129
	200	Herbivore (leafy foliage)	5.2404	0.0262

Table 14 Screening level risk assessment on non-target terrestrial species (except birds and mammals)

Organism	Exposure	Substance	Endpoint value	EEC	Units	RQ
Earthworm	Acute	Acibenzolar-s-methyl	½ LC_{50} > 500	0.012	mg /kg dw soil	0.00002
Bee	Oral	Acibenzolar-s-methyl	LD_{50} > 143.7	0.067	kg./ha	0.0005

Organism	Exposure	Substance	Endpoint value	EEC	Units	RQ
	Contact	Acibenzolar-s-methyl	LD_{50} > 112	0.067	kg /ha	0.0006
Vascular plants	Seedling emergence	CGA 245704 50WG	EC_{25} > 105	26.25	g /ha	0.2500
	Vegetative vigour	CGA 245704 50WG	EC_{25} > 105	66.89	g /ha	0.6370

Table 15 Screening level risk assessment on non-target aquatic species

Organism	Exposure	Substance	Endpoint value	EEC	Units	RQ
Freshwater organisms						
Invertebrate	Acute	Acibenzolar-s-methyl	½ EC_{50} = 1.45	0.0033	mg /L	0.0023
	Chronic	Acibenzolar-s-methyl	NOEC = 0.048	0.0033	mg /L	0.0688
	Acute	CGA 210007	½ EC_{50} = 29.95	0.0217	mg /L	0.0007
Rainbow trout	Acute	Acibenzolar-s-methyl	1/10 LC_{50} = 0.088	0.0033	mg /L	0.0375
	ELS	Acibenzolar-s-methyl	NOEC = 0.026	0.0033	mg /L	0.1269
	Acute	CGA 210007	1/10 LC_{50} > 9.2	0.0217	mg /L	0.0024
Bluegill sunfish	Acute	Acibenzolar-s-methyl	1/10 LC_{50} = 0.16	0.0033	mg/L	0.0206
Amphibians	Acute	Acibenzolar-s-methyl	1/10 LC_{50} = 0.088	0.0175	mg/L	0.198
	ELS	Acibenzolar-s-methyl	NOEC = 0.026	0.0175	mg/L	0.673
	Acute	CGA 210007	1/10 LC_{50} > 9.2	0.1159	mg/L	0.0123
Freshwater alga	Acute	Acibenzolar-s-methyl	½ EC_{50} = 1.655	0.0033	mg/L	0.0020
	Acute	CGA 210007	½ EC_{50} = 40.05	0.0217	mg/L	0.0005
Vascular plant	Acute	Acibenzolar-s-methyl	½ EC_{50} = 0.156	0.0033	mg/L	0.0212
Estuarine/marine organisms						
Mysid shrimp	Acute	Acibenzolar-s-methyl	½ LC_{50} = 0.44	0.0033	mg/L	0.0075
Eastern oyster	Acute	Acibenzolar-s-methyl	½ EC_{50} = 0.295	0.0033	mg/L	0.0112
Sheephead minnow	Acute	Acibenzolar-s-methyl	1/10 LC_{50} = 0.17	0.0033	mg/L	0.0194

Table 16 Toxic Substances Management Policy considerations

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active ingredient Endpoints (acibenzolar-s-methyl)	Transformation Product Endpoints (CGA 210007)
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes		Yes	Yes
Predominantly anthropogenic[2]	Yes		Yes	Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	DT_{50}: 0.22 days	DT_{50}: 21 days
	Water	Half-life ≥ 182 days	DT_{50}: < 1 day	Stable
	Sediment	Half-life ≥ 365 days	DT_{50}: < 1 day	Stable
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (0.46 mPa at 25ºC) and Henry's Law Constant (1.26 x 10^{-7} $atm \cdot m^3 \cdot mole^{-1}$).	N/A
Bioaccumulation[4]	Log $K_{OW} \geq 5$		Log K_{OW}: 3.1	Log K_{OW}: ≤ 0.18
	BCF ≥ 5000		118	N/A
	BAF ≥ 5000		N/A	N/A
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

[1]All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (i.e., all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]Field data (e.g., BAFs) are preferred over laboratory data (e.g., BCFs) which, in turn, are preferred over chemical properties (e.g., log K_{OW}).

Table 17 List of Active Ingredients Currently Registered on Tomato and Tobacco

Crop	Disease	Fungicide Active Ingredients
Tomato	Bacterial spot (*X. campestris* pv. *vesicatoria*)	• Copper • *Bacillus subtilis* strain QST 713
	Bacterial speck (*P. syringae* pv. *tomato*)	
Tobacco	Blue mold (*Peronospora tabacina*)	• Ferbam • Mancozeb • Fosetyl AL • Dimethomorph, mancozeb • Metalaxyl-M and S-isomer • Azoxystrobin

Table 18 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed Claims	Supported Claims
Tomato: Control of bacterial spot (*Xanthomonas campestris* pv. *vesicatoria*) and bacterial speck (*Pseudomonas syringae* pv. *tomato*) at the rate of 25-52.5 g product/ha. Make up to 8 weekly sequential applications.	**Tomato**: Suppression of bacterial spot (*X. campestris* pv. *vesicatoria*) and bacterial speck (*P. syringae* pv. *tomato*) at the rate of 25 g product/ha. Make up to 8 weekly sequential applications.
Tobacco: Control of blue mold (*Peronospora tabacina*) on tobacco at the rate of 35 g (17.5 g a.i.)/ha.	**Tobacco:** Supported as proposed.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

The residues in tomato commodities resulting from the proposed use in Canada will be covered by the established MRLs of 1.0 ppm for tomatoes and 3.0 ppm for tomato paste. These MRLs were previously established for imported commodities and are consistent with the US EPA's tolerances for the same commodities.

Currently, Codex MRLs have not been established for acibenzolar-s-methyl on any commodities.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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1302837	CGA 245704: Certification of Limits, DACO: 2.12.1 CBI
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2.0 Human and Animal Health

PMRA Document Number **Reference**

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B. Additional Information Considered

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