

5. EVALUATION OF DATA FOR ACCEPTABLE DAILY INTAKE AND ACUTE REFERENCE DOSE FOR HUMANS, MAXIMUM RESIDUE LEVELS AND SUPERVISED TRIALS MEDIAN RESIDUE VALUES

5.1 ACIBENZOLAR-S-METHYL (288)

TOXICOLOGY

Acibenzolar-*S*-methyl is the ISO-approved common name for *S*-methyl 1,2,3-benzothiadiazole-7-carbothioate (IUPAC), with the CAS number 135158-54-2. It is a fungicide in the benzothiadiazole class.

Acibenzolar-*S*-methyl has not been evaluated previously by JMPR and was reviewed by the present Meeting at the request of CCPR.

All critical studies contained statements of compliance with good laboratory practice (GLP) and were conducted in accordance with relevant national or international test guidelines, unless otherwise indicated.

Biochemical aspects

Acibenzolar-*S*-methyl was rapidly absorbed after oral administration to rats. The maximum concentration in plasma was reached within 4 hours, and excretion was rapid (90% for the low dose and 70% for the high dose in the first 24 hours) and predominantly in the urine. The amount of radiolabel eliminated in the faeces was less than 5%. The route and rate of excretion were independent of the sex, dose level and treatment regimen. At low and repeated doses, quantifiable levels of radioactivity were detected only in the liver and kidney. There were no indications of a potential for acibenzolar-*S*-methyl to accumulate in tissues.

The biotransformation of acibenzolar-*S*-methyl in the rat was predominantly by 1) cleavage of the *S*-methyl ester moiety, leading to the corresponding carboxylic acid, 1,2,3-benzothiadiazole-7-carboxylic acid or acibenzolar acid (CGA210007/A2079A), and subsequent conjugation with glycine or glucuronic acid; 2) reduction of the carboxylic group of acibenzolar acid, leading to the alcohol benzo[1,2,3]thiadiazole-7-yl-methanol (CGA243093); and 3) hydroxylation of the phenyl ring of acibenzolar acid, leading to the hydroxyacids 5-hydroxy acibenzolar acid (CGA324041) and 4-hydroxy acibenzolar acid (CGA323060). The major metabolite of acibenzolar-*S*-methyl was acibenzolar acid. No unchanged parent was detected in the urine.

Toxicological data

The acute oral toxicity of acibenzolar-*S*-methyl was low. The oral median lethal dose (LD₅₀) in rats was greater than 2000 mg/kg bw. The dermal LD₅₀ in rats was greater than 2000 mg/kg bw. The single-exposure 4-hour acute inhalation median lethal concentration (LC₅₀) was greater than 5 mg/L in rats. Acibenzolar-*S*-methyl showed slight skin irritation in one study in rabbits, but not in another study using the same strain of rabbit. Acibenzolar-*S*-methyl was slightly irritating to rabbit eyes in one study, but not in another study. Acibenzolar-*S*-methyl caused dermal sensitization in the guinea-pig (maximization method).

The main toxic effects of acibenzolar-*S*-methyl in short- and long-term toxicity studies were haemolytic effects and related changes observed in spleen, liver or bone marrow of mice, rats and dogs.

In a 3-month oral toxicity study in mice fed acibenzolar-*S*-methyl at a dietary level of 0, 200, 1000 or 4000 parts per million (ppm) (equal to 0, 30.6, 152 and 624 mg/kg bw per day for males and 0, 47.4, 220 and 803 mg/kg bw per day for females, respectively), the NOAEL was 200 ppm (equal to

30.6 mg/kg bw per day), based on increased haemosiderosis in the spleen at 1000 ppm (equal to 152 mg/kg bw per day).

In a 28-day oral toxicity study in rats administered acibenzolar-*S*-methyl by oral gavage at a daily dose of 0, 10, 100 or 800 mg/kg bw per day, the NOAEL was 100 mg/kg bw per day, based on haemolytic effects and related changes in haematology, bone marrow and spleen and lower body weights at 800 mg/kg bw per day.

In a 90-day oral toxicity study in rats administered acibenzolar-*S*-methyl in the diet at a level of 0, 40, 400, 2000 or 8000 ppm (equal to 0, 2.42, 24.6, 126 and 516 mg/kg bw per day for males and 0, 2.64, 26.3, 131 and 554 mg/kg bw per day for females, respectively), the NOAEL was 2000 ppm (equal to 126 mg/kg bw per day), based on lower body weights and feed consumption, slight haemolytic effects and histopathological findings in the spleen and liver at 8000 ppm (equal to 516 mg/kg bw per day).

In a 90-day oral toxicity study in dogs treated with acibenzolar-*S*-methyl in gelatine capsules at 0, 10, 50 or 200 mg/kg bw per day, the NOAEL was 50 mg/kg bw per day, based on haemolytic effects and related histopathological changes in the spleen at 200 mg/kg bw per day.

In a 52-week oral toxicity study in dogs administered acibenzolar-*S*-methyl in gelatine capsules at a dose of 0, 5, 25 or 200 mg/kg bw per day, the NOAEL was 25 mg/kg bw per day, based on haemolytic effects and related histopathological changes in the spleen and hepatotoxicity at 200 mg/kg bw per day. The marginal decreases in haematological parameters at 25 mg/kg bw per day were not considered adverse.

In an 18-month carcinogenicity study in mice administered acibenzolar-*S*-methyl at a dietary concentration of 0, 10, 100, 2000 or 6000 ppm (equal to 0, 1.14, 11.1, 237 and 698 mg/kg bw per day for males and 0, 1.14, 10.8, 234 and 696 mg/kg bw per day for females, respectively), the NOAEL was 100 ppm (equal to 10.8 mg/kg bw per day), based on haemosiderosis in the spleen at 2000 ppm (equal to 234 mg/kg bw per day). No treatment-related increase in tumour incidence was observed.

In a 2-year toxicity and carcinogenicity study in rats administered acibenzolar-*S*-methyl at a dietary concentration of 0, 20, 200, 2500 or 7500 ppm (equal to 0, 0.77, 7.77, 96.9 and 312 mg/kg bw per day for males and 0, 0.90, 9.08, 111 and 388 mg/kg bw per day for females, respectively), the NOAEL was 200 ppm (equal to 7.77 mg/kg bw per day), based on lower body weights and haemosiderosis in the spleen at 2500 ppm (equal to 96.9 mg/kg bw per day). No treatment-related increase in tumour incidence was observed.

The Meeting concluded that acibenzolar-*S*-methyl is not carcinogenic in mice or rats.

Acibenzolar-*S*-methyl was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence of genotoxicity was found.

The Meeting concluded that acibenzolar-*S*-methyl is unlikely to be genotoxic.

On the basis of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that acibenzolar-*S*-methyl is unlikely to pose a carcinogenic risk to humans.

In a two-generation reproductive toxicity study, male and female rats were given acibenzolar-*S*-methyl in the diet at a concentration of 0, 20, 200, 2000 or 4000 ppm (equal to, respectively, 0, 1.5, 15.3, 155 and 306 mg/kg bw per day for males and 0, 1.6, 16.2, 167 and 321 mg/kg bw per day for females in the F₀ generation; and 0, 1.7, 17.2, 169 and 356 mg/kg bw per day for males and 0, 1.7, 17.5, 173 and 364 mg/kg bw per day for females in the F₁ generation at pre-mating). The NOAEL for parental toxicity was 200 ppm (equal to 15.3 mg/kg bw per day), based on increased severity of splenic haemosiderosis in both males and females in the F₀ and F₁ generations at 2000 ppm (equal to 155 mg/kg bw per day). The NOAEL for offspring toxicity was 200 ppm (equal to 16.2 mg/kg bw per day), based on reduced pup body weight and body weight gain in the F₁ and F₂ generations at 2000 ppm (equal to 167 mg/kg bw per day). The NOAEL for reproductive toxicity was 4000 ppm (equal to 306 mg/kg bw per day), the highest dose tested.

Two developmental toxicity studies were conducted in two different laboratories with related strains of rats. In the first study, pregnant rats were administered acibenzolar-*S*-methyl by gavage at a dose level of 0, 10, 50, 200 or 400 mg/kg bw per day during gestation days 6–15. The NOAEL for maternal toxicity was 50 mg/kg bw per day, based on decreased feed consumption in dams at 200 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was also 50 mg/kg bw per day, based on an equivocal increase in visceral malformations, including anophthalmia and microphthalmia in one litter, at 200 mg/kg bw per day. At 400 mg/kg bw per day, there was marked maternal toxicity, and the incidences of resorptions and of malformations and skeletal anomalies were significantly increased.

In the second developmental toxicity study in rats administered acibenzolar-*S*-methyl by gavage at a dose level of 0, 10, 75, 150 or 350 mg/kg bw per day during gestation days 6–15, the NOAEL for maternal toxicity was 350 mg/kg bw per day, the highest dose tested. The NOAEL for embryo/fetal toxicity was 150 mg/kg bw per day, based on an increased incidence of skeletal variation in lumbar ribs at 350 mg/kg bw per day. No treatment-related malformations were observed.

Two additional studies were conducted to clarify the critical period for embryotoxicity, including malformations, observed in the first developmental toxicity study in rats. In the first additional study, pregnant rats were administered acibenzolar-*S*-methyl by gavage at 400 mg/kg bw per day for 2 consecutive days (gestation days 6–7, 8–9, 10–11, 12–13 or 14–15). Although there was no increase in malformations, treatment with acibenzolar-*S*-methyl during gestation days 6–11 caused embryotoxicity (decreased fetal weight, increased post-implantation loss) and maternal toxicity (clinical signs).

In the second additional study, acibenzolar-*S*-methyl was administered by gavage at 300 mg/kg bw per day during various periods, such as gestation days 6–15, 6–7, 8–9, 10–11, 12–13 and 14–15. Maternal toxicity (decreased body weight gain and clinical signs) was observed at all durations except gestation days 14–15. The treatment during gestation days 6–15 caused embryo/fetal toxicity (decreased fetal weight, increased post-implantation loss), but there was no indication of teratogenicity.

In a developmental toxicity study in rabbits administered acibenzolar-*S*-methyl by gavage at a dose of 0, 10, 50, 300 or 600 mg/kg bw per day during gestation days 7–19, the NOAEL for maternal toxicity was 50 mg/kg bw per day, based on increased mortality of dams at 300 mg/kg bw per day and above. The NOAEL for embryo/fetal toxicity was 300 mg/kg bw per day, based on a slight increase in skeletal anomalies at 600 mg/kg bw per day. Acibenzolar-*S*-methyl was not teratogenic in rabbits in this study.

The Meeting concluded that acibenzolar-*S*-methyl has a potential for teratogenicity in rats at dose levels causing marked maternal toxicity. The Meeting noted that the malformations observed in one study at 200 mg/kg bw per day were equivocal, as they were not reproducible in three follow-up studies at the same or higher doses. The Meeting concluded that acibenzolar-*S*-methyl was not teratogenic in rabbits.

In an acute neurotoxicity study in rats administered acibenzolar-*S*-methyl by gavage at a dose of 0 or 2000 mg/kg bw, the NOAEL for acute neurotoxicity in rats was 2000 mg/kg bw, the highest dose tested.

In a 90-day neurotoxicity study in rats fed diets containing acibenzolar-*S*-methyl at a concentration of 0, 400, 2000 or 8000 ppm (equal to 0, 24.4, 126 and 575 mg/kg bw per day for males and 0, 26, 143 and 628 mg/kg bw per day for females, respectively), the NOAEL was 2000 ppm (equal to 126 mg/kg bw per day), based on lower body weight gain and feed consumption at 8000 ppm (equal to 575 mg/kg bw per day). Acibenzolar-*S*-methyl was not neurotoxic at 8000 ppm (equal to 575 mg/kg bw per day), the highest dose tested.

In a developmental neurotoxicity study, rats were administered acibenzolar-*S*-methyl in the diet at 0, 100, 1000 or 4000 ppm (equal to 0, 8.2, 82 and 326 mg/kg bw per day during gestation and 0, 15.5, 154 and 608 mg/kg bw per day during lactation, respectively) from gestation days 7 to 22.

The NOAEL for maternal toxicity was 326 mg/kg bw per day, the highest dose tested. The NOAEL for systemic toxicity in offspring was 82 mg/kg bw per day, based on lower body weights at 326 mg/kg bw per day. The NOAEL for developmental neurotoxicity in rats was 82 mg/kg bw per day, based on a decrease in the thickness of the molecular layer in the cerebellum in males at postnatal day 63 and an increase in responses to auditory startle amplitude in females at postnatal day 23 at 326 mg/kg bw per day.

The Meeting concluded that acibenzolar-*S*-methyl was unlikely to be neurotoxic to humans at dietary exposure levels.

In an immunotoxicity study in female mice fed acibenzolar-*S*-methyl in the diet at a concentration of 0, 100, 500 or 2000 ppm (equal to 0, 15, 75 and 406 mg/kg bw per day, respectively) for 28 consecutive days, there was no evidence of toxicity or of an immunosuppressant effect. The NOAEL was 2000 ppm (equal to 406 mg/kg bw per day), the highest dose tested.

The Meeting concluded that acibenzolar-*S*-methyl is not immunotoxic.

On the basis of a number of mechanistic studies, the haemolytic effect induced by acibenzolar-*S*-methyl was not considered to be caused by antibody formation against acibenzolar-*S*-methyl or its serum albumin conjugate. The complete mode of action remains undetermined; however, a plausible mechanism leading to haemolytic anaemia was postulated through glutathione depletion in erythrocytes, altered haemoglobin and increased lipid peroxidation.

Toxicological data on metabolites and/or degradates

The main metabolite in rats is acibenzolar acid (CGA210007/CA2079A), which is also found in plants. The oral LD₅₀ of acibenzolar acid in rats was greater than 2000 mg/kg bw. Acibenzolar acid was weakly irritating to the skin and eye of rabbits. Acibenzolar acid was weakly sensitizing or non-sensitizing in guinea-pigs (maximization test). In a 28-day oral toxicity study of acibenzolar acid in rats administered by gavage at a dose of 0, 10, 100, 300 or 1000 mg/kg bw per day, the NOAEL was 100 mg/kg bw per day, based on changes in haematological and blood chemistry analysis and gastrointestinal damage at 300 mg/kg bw per day. Acibenzolar acid was not genotoxic in vitro or in vivo. The toxicological profile of acibenzolar acid was similar to that of the parent.

Other minor metabolites, 4-hydroxy acibenzolar acid (CGA323060) (rat and plants), 5-hydroxy acibenzolar acid (CGA324041) (rat and plants) and 3-methanesulfinyl-benzoic acid (CGA379019) (rice only), showed low acute toxicity (LD₅₀ > 2000 mg/kg bw), and benzo[1,2,3]thiadiazole-7-yl-methanol (CGA243093) (rat and plants) had an LD₅₀ between 300 and 2000 mg/kg bw. All of the metabolites were negative in genotoxicity tests in vitro.

No other toxicological information is available. However, owing to the structural similarities of the three minor metabolites in rats with the parent, the Meeting concluded that they are unlikely to be of greater toxicity than the parent.

Human data

Acibenzolar-*S*-methyl and its formulations have been handled in large quantities for nearly 20 years at a number of sites with the use of appropriate control strategies, and no adverse health effects associated with the material have been reported in the workforce, with the exception of isolated cases of skin irritation and one case of respiratory tract irritation.

A search of the public literature did not reveal any relevant publications.

The Meeting concluded that the existing database for acibenzolar-*S*-methyl was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.08 mg/kg bw on the basis of the NOAEL of 7.77 mg/kg bw per day in a 2-year study in rats for haemosiderosis in the spleen in males observed at 96.9 mg/kg bw per day. A safety factor of 100 was applied.

The Meeting established an ARfD of 0.5 mg/kg bw on the basis of the NOAEL of 50 mg/kg bw per day in a rat developmental toxicity study for decreased maternal feed consumption early during treatment and an equivocal increase in malformations observed at 200 mg/kg bw per day. A safety factor of 100 was applied.

Acibenzolar acid (CGA210007/CA2079A), the major metabolite, is toxicologically similar to the parent and was considered to be covered by the ADI and ARfD of acibenzolar-*S*-methyl.

A toxicological monograph was prepared.

*Levels relevant to risk assessment of acibenzolar-*S*-methyl*

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity ^a	Toxicity	100 ppm, equal to 10.8 mg/kg bw per day	2 000 ppm, equal to 234 mg/kg bw per day
		Carcinogenicity	6 000 ppm, equal to 696 mg/kg bw per day ^b	–
Rat	Two-year study of toxicity and carcinogenicity ^a	Toxicity	200 ppm, equal to 7.77 mg/kg bw per day	2 500 ppm, equal to 96.9 mg/kg bw per day
		Carcinogenicity	7 500 ppm, equal to 312 mg/kg bw per day ^b	–
	Two-generation study of reproductive toxicity ^a	Reproductive toxicity	4 000 ppm, equal to 306 mg/kg bw per day ^b	–
		Parental toxicity	200 ppm, equal to 15.3 mg/kg bw per day	2 000 ppm, equal to 155 mg/kg bw per day
		Offspring toxicity	200 ppm, equal to 16.2 mg/kg bw per day	2 000 ppm, equal to 167 mg/kg bw per day
	Developmental toxicity study ^c	Maternal toxicity	50 mg/kg bw per day	200 mg/kg bw per day
		Embryo and fetal toxicity	50 mg/kg bw per day	200 mg/kg bw per day
Developmental neurotoxicity study ^a	Neurotoxicity	82 mg/kg bw per day	326 mg/kg bw per day	
Rabbit	Developmental toxicity study ^c	Maternal toxicity	50 mg/kg bw per day	300 mg/kg bw per day
		Embryo and fetal toxicity	300 mg/kg bw per day	600 mg/kg bw per day
Dog	One-year study of toxicity ^d	Toxicity	25 mg/kg bw per day	200 mg/kg bw per day

^a Dietary administration.

^b Highest dose tested.

^c Gavage administration.

^d Capsule administration.

*Acceptable daily intake (ADI; applies to acibenzolar-*S*-methyl and acibenzolar acid, expressed as acibenzolar-*S*-methyl)*

0–0.08 mg/kg bw

*Acute reference dose (ARfD; applies to acibenzolar-*S*-methyl and acibenzolar acid, expressed as acibenzolar-*S*-methyl)*

0.5 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to acibenzolar-*S*-methyl

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption	90% absorbed; T_{\max} within 0.5 h at low dose
Dermal absorption	Moderately to well absorbed
Distribution	Widely distributed; highest levels in liver and kidney
Potential for accumulation	No indication for accumulation in tissues
Rate and extent of excretion	Rapidly excreted (> 90% within 24 h at low dose)
Metabolism in animals	Cleavage of the <i>S</i> -methyl ester to carboxylic acid, and subsequent conjugation; hydrolysis, oxidation and conjugation with glycine or glucuronic acid
Toxicologically significant compounds in animals and plants	Acibenzolar- <i>S</i> -methyl, acibenzolar acid (CGA210007/CA2079A)

Acute toxicity

Rat, LD ₅₀ , oral	> 2 000 mg/kg bw
Rat, LD ₅₀ , dermal	> 2 000 mg/kg bw
Rat, LC ₅₀ , inhalation	> 5 mg/L
Rabbit, dermal irritation	Slightly irritating to skin
Rabbit, ocular irritation	Slightly irritating to eye
Guinea-pig, dermal sensitization	Sensitizing (maximization test)

Short-term studies of toxicity

Target/critical effect	Haemolytic effects (dog)
Lowest relevant oral NOAEL	25 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day, highest dose tested (rat)
Lowest relevant inhalation NOAEC	No data

<i>Long-term studies of toxicity and carcinogenicity</i>	
Target/critical effect	Red blood cells/haemolysis-related histopathological findings in the spleen (rat)
Lowest relevant NOAEL	7.77 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic in mice or rats ^a
<i>Genotoxicity</i>	
	No evidence of genotoxicity ^a
<i>Reproductive toxicity</i>	
Target/critical effect	Spleen/haemosiderosis (rat)
Lowest relevant parental NOAEL	15.3 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	16.2 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	306 mg/kg bw per day, highest dose tested (rat)
<i>Developmental toxicity</i>	
Target/critical effect	Decreased feed consumption and equivocal increase in malformations (rat)
Lowest relevant maternal NOAEL	50 mg/kg bw per day (rat)
Lowest relevant embryo/fetal NOAEL	50 mg/kg bw per day (rat)
<i>Neurotoxicity</i>	
Acute neurotoxicity NOAEL	2 000 mg/kg bw, highest dose tested (rat)
Subchronic neurotoxicity NOAEL	575 mg/kg bw per day, highest dose tested (rat)
Developmental neurotoxicity NOAEL	82 mg/kg bw per day (rat)
<i>Other toxicological studies</i>	
Immunotoxicity NOAEL	406 mg/kg bw per day, highest dose tested (mouse)
<i>Studies on toxicologically relevant metabolites</i>	
Acibenzolar acid (CGA210007/CA2079A)	Oral LD ₅₀ : > 2 000 mg/kg bw (rat) 28-day NOAEL: 100 mg/kg bw per day on the basis of haematological and blood chemistry changes (rat) Not genotoxic in vitro or in vivo
<i>Human data</i>	
	No adverse effects noted in medical surveillance reports on manufacturing plant personnel; isolated cases of skin irritation and one case of respiratory irritation reported during handling of formulations

^a Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

Summary

	Value	Study	Safety factor
ADI ^a	0–0.08 mg/kg bw	Two-year study of toxicity and carcinogenicity (rat)	100
ARfD ^a	0.5 mg/kg bw	Developmental toxicity study (rat)	100

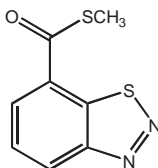
^a Applies to acibenzolar-S-methyl and acibenzolar acid, expressed as acibenzolar-S-methyl.

RESIDUE AND ANALYTICAL ASPECTS

Acibenzolar-S-methyl is a plant activator that stimulates the natural, inherent defence mechanisms of plants. Through this activation, control of *Erysiphe graminis* (powdery mildew of cereals) and *Mycosphaerella musci* (Black Sigatoka of banana) is achieved. This activation also results in partial control of *Septoria* spp. (side effect only) and *Puccinia* spp. (side effect only) in cereals. At the 47th Session of the CCPR (2015), it was scheduled for the evaluation as a new compound by the 2016 JMPR.

The Meeting received information on the metabolism of acibenzolar-S-methyl in lactating goats and laying hens, cotton, lettuce, sorghum, sunflower, rice, tomato, tobacco and wheat, as well as follow crops, methods of residue analysis, freezer storage stability, GAP information, supervised residue trials on citrus fruit (orange, grapefruit, lemon), pome fruit (apples, pears), stone fruit (apricot, peach), strawberries, bananas, kiwifruit, onions, brassica vegetables (cabbage, broccoli, mustard greens), cucurbits (cucumbers, melons, squash), tomatoes, leafy vegetables (lettuce, spinach), celery, potatoes and wheat as well as a livestock transfer study (lactating cow).

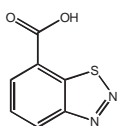
Acibenzolar-S-methyl is *S*-methyl 1,2,3-benzothiadiazole-7-carbothioate



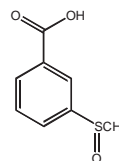
Metabolites referred to in the appraisal were addressed by their company codes:

Acibenzolar
(CGA210007)

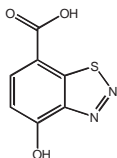
acid



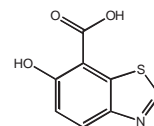
3-Methanesulfinyl-benzoic
acid
(CGA379019)



4-OH acibenzolar acid
(CGA323060)



6-OH acibenzolar acid
(SYN546642)



Studies on the metabolism in plants and livestock and environmental fate all utilised [¹⁴C-U-phenyl]-acibenzolar-S-methyl.

Plant metabolism

Acibenzolar-S-methyl is typically used for four different situations:

- as a seed treatment
- as a foliar application
- as a soil treatment for rice at transplanting
- application to the soil beneath a growing crop

The Meeting received plant metabolism studies with acibenzolar-S-methyl following seed treatment (sunflower, cotton, sorghum), foliar applications to lettuce, tobacco, tomato and wheat and soil treatment at transplanting rice.

Seed treatment

Residues in commodities at harvest of crops of cotton, sorghum and sunflower grown from seeds that were treated with [¹⁴C]-acibenzolar-S-methyl prior to planting (0.0006-0.001 mg ai/seed cotton; 0.0065 mg ai/seed sorghum; 0.048 mg ai/seed sunflower), were low at 0.002-0.006 mg equiv/kg for cotton plants, stalks, fibre and seed, < 0.001-0.002 mg equiv/kg for sorghum forage, stover and grain and 0.002 mg equiv/kg for sunflower seeds.

Foliar application

Tomato

The metabolism of [¹⁴C]-acibenzolar-S-methyl in tomato plants grown outdoors following three foliar sprays at 15 g ai/hL at 14 day intervals.

TRR found at harvest were 0.312 mg equiv/kg in tomato fruit (30 days after last application) and 0.72 mg equiv/kg in foliage (60 DALA). The ¹⁴C recovered in surface washes of fruit decreased from 35% TRR (one hour after third application) to 1.4% TRR (one month after third application).

Extractability of ¹⁴C residues with the solvent system (CH₃CN/H₂O) used was 97% of the TRR for tomato fruit at maturity, 30 DALA.

The metabolites identified in tomato fruit and foliage primarily resulted from initial hydrolysis of acibenzolar-S-methyl to give acibenzolar acid (CGA210007) followed by oxidation to give various metabolites hydroxylated at the phenyl ring. Acibenzolar-S-methyl was detected in foliage and fruit samples on the day of application and for up to a further 30 days, albeit at very low levels. At harvest, acibenzolar-S-methyl accounted for 0.8% TRR in fruit, free acibenzolar acid accounted for 8.1% TRR and conjugates of acibenzolar acid liberated by cellulase/mild base hydrolysis of the solvent extracts accounted for a further 56% TRR.

Lettuce

The metabolism of [¹⁴C]-acibenzolar-S-methyl in lettuce plants grown outdoors following three foliar sprays at 35 g ai/hL (1 ×) at 7 day intervals. An additional set of plants were treated at 105 g ai/ha (3 ×). The first applications were made at the 7-9 leaf stage (BBCH 17-19).

TRR in lettuce plants harvested one week after final application were 1.0 mg equiv/kg (1 × rate) and 3.7 mg equiv/kg (3 × rate). In these samples, parent acibenzolar-S-methyl residues were 0.17 and 0.71 mg/kg, respectively. Surface rinses contained 20% (1 ×) and 23% (3 ×) of TRR, with penetrated residue amounting to 83% (1 ×) and 74% (3 ×) of the TRR (7 DALA).

Solvent (CH₃CN/H₂O) extracted ≥ 81% of the TRR. Acibenzolar-S-methyl accounted for 17-19% TRR while free acibenzolar acid represented ≤ 5% TRR. The solvent extracts were sequentially

treated with 0.1N NaOH/cellulase to investigate the presence of conjugates. Based on the increase in acibenzolar acid on hydrolysis, conjugates of acibenzolar acid represented 12-20% TRR. The only other metabolite(s) present at levels >10% TRR were conjugates of 4-OH acibenzolar acid which represented 19-22% TRR. In contrast, free 4-OH acibenzolar acid only represented 0.9-1.1% TRR.

Tobacco

The metabolic fate of [¹⁴C]-acibenzolar-S-methyl in tobacco plants maintained outdoors was examined following three foliar sprays, starting when plants were at the seven leaf stage, of 20, 50 and 100 g ai/ha with intervals of 21 and 34 days.

Translocation of the radioactivity into new grown leaves was low. Residues found 21 days after the first application were 0.60 and 0.031 mg equiv/kg in treated and new grown leaves respectively. At maturity, TRRs in tobacco plants were 1.4 mg equiv/kg in lower leaves, 0.43 mg eq./kg in upper leaves and 0.022 mg equiv/kg in stems.

Solvent (CH₃CN/H₂O) extracted ≥ 88% of the TRR present in leaf samples collected 0 to 52 DALA.

Parent acibenzolar-S-methyl was present in low amounts in tobacco leaves 17–52 DALA (max. 6.1% TRR) with free acibenzolar acid present at 6.4–9.0% TRR. The major component of the ¹⁴C residue was conjugates of acibenzolar acid which liberate acibenzolar acid on cellulase/0.1N NaOH treatment, accounting for a further 61% TRR.

Wheat

The metabolism of [¹⁴C]-acibenzolar-S-methyl in wheat grown outdoors was studied following application to plants at the end of tillering at 50 g ai/ha. Total radioactive residues in shoots on the day of application were 1.8 mg equiv/kg, declining to 0.29 mg equiv/kg after 14 days. At harvest, 75 days after application, levels of ¹⁴C in grain, husks and straw were 0.014, 0.23 and 0.33 mg eq/kg respectively.

Solvent (CH₃CN/H₂O) extracted ≥87% of the TRR present in immature plant parts (shoots) collected 0–14 days after application. Extraction of ¹⁴C present at harvest (75 days after application) was low at 41% for grain, 39% for husks and 30% for straw.

Apart from on the day of application, acibenzolar-S-methyl was not detected in any of the samples. The metabolites identified primarily resulted from initial hydrolysis of acibenzolar-S-methyl to form acibenzolar acid followed by oxidation of the phenyl ring to give a range of hydroxy acibenzolar acid metabolites. Acibenzolar acid, and metabolites hydroxylated at the phenyl ring, can form conjugates with natural compounds such as sugars or bind to cell components such as proteins. Free acibenzolar acid accounted for 8.4, 12 and 14% TRR in grain, husks and straw respectively. Based on the increase in acibenzolar acid after mild base hydrolysis of the solvent extracts, conjugates of acibenzolar acid accounted for 15, 11 and 7.8% TRR for grain, husks and straw respectively.

The majority of the ¹⁴C present in the solids after the initial solvent extraction (PES) were associated with natural products, 21% TRR for grain, 29% for husks and 36% TRR for straw; especially starch, protein, lignin and cellulose. The severe conditions utilised for further examination of ¹⁴C residues in PES liberated additional acibenzolar acid, presumably bound to various natural components. The additional liberated acibenzolar acid accounted for a further 16, 17 and 23% TRR for grain, husks and straw respectively.

*Soil treatment at transplanting**Rice*

The metabolism of [¹⁴C]-acibenzolar-S-methyl in greenhouse grown rice plants was studied following application to soil of a granular formulation to three-week old rice plants one day prior to transplanting at a rate equivalent to 200 g ai/ha. Plants with soil were transplanted into containers and flooded with water. Mature plants were harvested 119 days after application.

Residues in paddy water reached a maximum of 25% AR at 1–2 weeks after soil application and flooding, declining to 15% AR by 40 days after application (DAA). Thereafter the ¹⁴C residues in paddy water declined rapidly to reach 0.4% AR by 60 DAA. Free acibenzolar acid was the major metabolite/degradate present in paddy water representing 32% TRR at 11 DAA and 57% TRR at 78 DAA.

One DAA, rice seedlings had taken up 1.3% AR, rising to 11.1% AR at maturity (harvest 119 DAA). At maturity, 0.2% AR was located in grain, 0.2% AR in husks and 11% AR in straw while 81% AR remained in the soil. Solvent (CH₃CN/H₂O) extracted only 6.4% TRR for grain, 33% TRR for husks and 41% TRR for straw. Parent acibenzolar-S-methyl was only detected in samples of leaves collected 1 DAA. The major metabolite identified in leaves collected 11-78 DAA was free acibenzolar acid at 6.7-11% TRR in leaves and at 1.7–10% TRR in rice commodities (grain, husks, straw) at harvest, 119 DAA.

The presence of conjugated residues in the solvent extracts was investigated. Following hydrolysis the proportion of unidentified ¹⁴C decreased and there was a concomitant increase in the proportion of acibenzolar acid and to a lesser extent 3-methanesulfinyl benzoic acid. Based on the hydrolysis results, conjugated acibenzolar acid accounted for 38, 11 and 2.0% TRR in straw, husks and grain, respectively. Conjugates of 3-methanesulfinyl benzoic acid accounted for 5.3, 3.1 and 0.7% TRR in straw, husks and grain, respectively.

As the unextracted ¹⁴C in plant samples was high, the PES were subject to harsh alkaline and acid conditions to assist further characterisation. Following hydrolysis of PES under harsh alkaline and acid conditions, the unextracted residues remaining in grain were reduced from 92% TRR to 39% TRR. While small amounts of additional acibenzolar acid were liberated (1.8–8.1% TRR), 3-methanesulfinyl benzoic acid was the major component released by the harsh treatment and accounted for 18% TRR in grain. Further investigation also revealed incorporation of ¹⁴C into natural products, 24% TRR for grain, 31% TRR for husks and 17% TRR for straw.

In summary, the metabolism of acibenzolar-S-methyl by plants is well understood. Primary metabolic pathways of acibenzolar-S-methyl in plants included: 1) hydrolysis of the S-methyl group to form acibenzolar acid; 2) oxidation at the phenyl ring to form a range of hydroxy derivatives including 4-OH acibenzolar acid; 3) opening of the thiazole ring to form 3-methanesulfinyl benzoic acid; and 4) formation of conjugates, principally with sugars.

With the exception of 3-methanesulfinyl benzoic acid (CGA379019), all plant metabolites were also identified in the rat metabolism though the conjugate partners may differ.

Crop		Tomato	Tobacco	Lettuce	Wheat			Rice		
DALA		30	17-45	7	75	75	75	119	119	119
Matrix		Fruit	Leaf	Leaf	Grain	Husks	Straw	Grain	Husks	Straw
Acibenzolar-S-methyl		0.8	6.1	16.9-19.3						
Acibenzolar acid	Free	8.1	6.4-9.0	<5	8.4	12.1	14.4	1.7	3.7	10.2
	Conj	56.2	61.4	11.5-20.1	15.1	11.4	7.8	2.0	11.3	37.9
	Bound				15.8	17.4	23.1	1.9	1.8	8.1
4-OH acibenzolar acid	Free			0.9-1.1						
	Conj			19-21.5						

Crop		Tomato	Tobacco	Lettuce	Wheat			Rice		
DALA		30	17-45	7	75	75	75	119	119	119
Matrix		Fruit	Leaf	Leaf	Grain	Husks	Straw	Grain	Husks	Straw
3-methanesulfinyl benzoic acid	Free							0.6	3.7	5.3
	Conj							0.7	3.1	5.3
	Bound							17.5	1.1	2.5

Animal metabolism

The plant metabolism studies show that livestock are unlikely to be exposed to parent acibenzolar-S-methyl. Rather, animals will be exposed to a range of metabolites that are mostly comprised of free and conjugated acibenzolar acid. Metabolism studies were made available to the Meeting that utilised dosing lactating goats and laying hens with acibenzolar-S-methyl. As acibenzolar-S-methyl is rapidly hydrolysed to acibenzolar acid, and conjugates of acibenzolar acid are readily cleaved to produce acibenzolar acid, the use of acibenzolar-S-methyl in the livestock metabolism studies is acceptable.

Lactating goats were orally dosed once daily for four consecutive days with [¹⁴C]-acibenzolar-S-methyl at a dose equivalent to 12 ppm in the feed. The majority of the ¹⁴C residues was recovered in the excreta (urine 64% AD, faeces 12% AD). For tissues, ¹⁴C residues were highest in kidney, (0.28 mg equiv/kg), followed by liver (0.041 mg equiv/kg) with muscle (0.003 mg equiv/kg) and fat (0.002–0.003 mg equiv/kg) containing very low residues. TRR in milk reached 0.12 mg equivalents/kg before the end of dosing. Solvent (CH₃CN and CH₃CN/H₂O) extracted >86% of the TRR in milk and tissues. No intact acibenzolar-S-methyl was detected in tissues or milk. The majority of the residues were present as free (33–90% TRR) and soluble conjugated forms (2.3–22% TRR) of acibenzolar acid. Significant additional acibenzolar acid was released from muscle (27% TRR) when harsh extraction conditions were used on radioactivity in solids remaining after solvent extraction.

Laying hens were orally dosed once a day for four consecutive days with [¹⁴C]-acibenzolar-S-methyl at a dose equivalent to 19 ppm in the feed. The majority of the ¹⁴C residues was recovered in the excreta (87% AD). Radioactivity in eggs reached 0.001 mg equiv/kg, with average concentrations of 0.002 mg equiv/kg for yolk and 0.001 mg equiv/kg for egg whites. Mean levels of TRR were 0.90 mg equiv/kg in kidney, 0.33 mg equiv/kg in liver, 0.013 mg equiv/kg in breast muscle, 0.013 mg equiv/kg in peritoneal fat, and 0.045 mg equiv/kg in skin plus subcutaneous fat. Solvent (CH₃CN and CH₃CN/H₂O) extracted >82% of the TRR in eggs and tissues. No intact acibenzolar-S-methyl was detected in tissues or eggs. Free acibenzolar acid accounted for the majority of the residue (50–77% TRR) with significant amounts of acibenzolar acid released from conjugates in egg white (18% TRR) when harsh extraction conditions were used.

In summary, the metabolism of acibenzolar-S-methyl in goats and laying hens is similar to metabolism in laboratory animals with acibenzolar acid (free and conjugated) the major component of the residue.

Environmental fate

The Meeting received information on soil aerobic metabolism, aqueous photolysis and aqueous hydrolysis properties of [¹⁴C]-acibenzolar-S-methyl. Studies were also received on the behaviour of [¹⁴C]-acibenzolar-S-methyl in a rotational crop situation.

The degradation of acibenzolar-S-methyl in soil maintained under aerobic conditions was rapid with acibenzolar acid and 6-OH acibenzolar acid, the major degradation products formed. While parent acibenzolar-S-methyl was degraded quickly in soils, the degradates formed are moderately to highly persistent. In the laboratory studies, soil DT₅₀ values for parent acibenzolar-S-methyl ranged from 0.031 to 2.1 days while for acibenzolar acid DT₅₀ values ranged from 4.1 to 91 days and for 6-OH acibenzolar acid 130 to >1000 days.

Acibenzolar-S-methyl was stable to hydrolysis in aqueous solutions at pH 5 and 7 but undergoes rapid hydrolysis at pH 9 and above suggesting hydrolysis plays a negligible role in its degradation under environmental conditions. The main hydrolysis degradate was acibenzolar acid which was stable at all pH values.

The soil photolysis of acibenzolar-S-methyl in dry and wet soils was investigated. Light enhanced the degradation of acibenzolar-S-methyl on both wet and dry soils. Acibenzolar acid was essentially stable on dry soils but moderately degraded in the irradiated wet soils. No other metabolites were reported to reach levels above 5% AR. Hydrolysis of acibenzolar-S-methyl to form acibenzolar acid was more rapid on wet compared to dry soils.

In a confined rotational crops study with lettuce, radish, maize and wheat, a plot of clay soil was treated with [¹⁴C]-acibenzolar-S-methyl at the equivalent of 50 g ai/ha and crops sown 30, 113, 141 and 337 days after the soil application. Lettuce was sampled at 50% maturity and at full maturity (61 and 82 DAA), radish was sampled at 180 DAA, wheat samples were taken at 180, 370 and 414 DAA and maize was sampled at 50% and full maturity (404 and 498 DAA). The uptake of radioactivity in rotational crops was very low for lettuce, winter wheat, maize and radish: all residue levels in the crops were ≤ 0.001 mg equiv/kg.

In a separate confined rotational crop study a sandy loam soil was treated with [¹⁴C]-acibenzolar-S-methyl at the equivalent of 421 g ai/ha and radish, wheat and mustard sown at 30, 60 and 210 days after application. The metabolism of acibenzolar-S-methyl in rotated crops was similar for all crop types and proceeded by hydrolysis of the S-methyl ester leading to formation of the major metabolite, acibenzolar acid which existed as polar conjugates that could be cleaved by treatment with cellulase plus NaOH. Subsequent hydroxylation of the phenyl ring gave metabolites 5-OH acibenzolar acid and 4-OH acibenzolar acid. Comparison with primary metabolism studies shows that the pathway in rotational crops is consistent with that in primary crops.

The major degradates in soil were acibenzolar acid and 6-OH acibenzolar acid, however, no 6-OH acibenzolar acid was detected in crops.

In summary, acibenzolar-S-methyl related residues in soil are unlikely to be observed at significant levels in rotational crops following application at maximum permitted seasonal rates of up to 332 g ai/ha for non-permanent crops.

Methods of Analysis

Methods have been reported in the scientific literature for the analysis of acibenzolar-S-methyl in food, including multi-residue methods. These literature methods do not involve a hydrolysis step and the residue measured is therefore parent compound (acibenzolar-S-methyl).

The metabolism of acibenzolar-S-methyl in crops results in a complex mixture of metabolites, most of which produce acibenzolar acid on base hydrolysis. Any non-metabolised parent acibenzolar-S-methyl that might be present would be converted to acibenzolar acid upon base hydrolysis. Consequently most of the methods developed to quantify acibenzolar-S-methyl residues in supervised trials on animal and plant commodities involve hydrolytic conversion of parent compound and metabolites to acibenzolar acid. This analyte is quantified and expressed in acibenzolar-S-methyl equivalents. LOQs are typically 0.01 mg/kg.

The common moiety methods all involve homogenisation and base hydrolysis (1N NaOH, typically 60–65 °C) followed by extraction of the hydrolysed samples with an organic/aqueous solvent mixture, typically CH₃OH. The main differences between methods involve clean-up conditions, instrumentation for quantification (HPLC-UV, HPLC-ECD, LC-MS/MS), and scale. Acibenzolar-S-methyl and acibenzolar acid are used as reference materials for fortification and method validation. In addition, radiovalidation studies demonstrated the acceptability of the extraction and hydrolysis used in the common moiety method as measured residues accounted for

75–110% of the residues of acibenzolar-S-methyl and acibenzolar acid (free and conjugated) identified in metabolism studies.

The methods involving hydrolysis are suitable for analysis of acibenzolar-S-methyl and acibenzolar acid (free and conjugated) in plant and animal matrices.

Multi-residue methods are currently not validated for the sum of acibenzolar-S-methyl and acibenzolar acid (free and conjugated).

A method was also made available for the analysis of 4-OH acibenzolar acid in lettuce and spinach. Following extraction with acidified acetonitrile:water, soluble conjugates were cleaved using cellulase and residues quantified using HPLC-UV (252 nm). The LOQ was 0.02 mg/kg.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of acibenzolar-S-methyl and acibenzolar acid in various matrices on freezer storage (-18 °C).

The periods of demonstrated stability cover the frozen storage intervals used in the residue studies on crops.

Residues of acibenzolar-S-methyl when measured by the common moiety method were stable in dry commodities (wheat grain) for 24 months and in high water commodities (cabbage, squash, lettuce, tomatoes, and turnip roots) and tobacco for 21 months. Residues were stable in banana for 24 months. Residues were stable in dry commodities (wheat grain) for 24 months and in high water commodities (cabbage, squash, lettuce, tomatoes, and turnip roots) and tobacco for 21 months.

The stability of acibenzolar-S-methyl in animal commodities was studied in the lactating cow residue transfer study with fortified samples stored for the same intervals as experimental samples. Acibenzolar-S-methyl, measured using the common moiety method, was stable in muscle for 87 days, kidney for 131 days, fat for 129 days and milk for 115 days. In liver, the amount remaining after 124 days was 51% of the spike concentration.

Definition of the residue

Following application of acibenzolar-S-methyl to crops the parent compound was generally only detected at short intervals after application and other than on the day of application, only as a relatively minor component of the ¹⁴C residue in the case of lettuce (17–19% TRR); tomato (0.8% TRR) and tobacco (6.1% TRR). For the other crops investigated where the interval between application and sampling was longer, parent compound was not detected (cotton, rice, sorghum, sunflower and wheat).

In crops where levels of ¹⁴C were sufficiently high to allow identification of metabolites, the major component of the ¹⁴C could generally be attributed to acibenzolar acid free+conjugated+bound: wheat grain 8.4+15+16% TRR; wheat husks 12+11+17% TRR; wheat straw 14+7.8+23% TRR; tomato fruit 8.1+56.2+0% TRR; tobacco leaf 9.0+61+0; lettuce <5+20+0% TRR; rice grain 1.7+2.0+1.9% TRR; rice husks 3.7+11+1.8% TRR and rice straw 10+38+8.1% TRR. The other components that exceeded 10% TRR were 4-OH acibenzolar acid free+conjugated in lettuce leaf (1.1+22% TRR) and 3-methanesulfinyl-benzoic acid free+conjugated+bound in rice grain (0.6+0.7+18% TRR) and rice straw (5.3+5.3+2.5% TRR).

Residues of acibenzolar-S-methyl and acibenzolar acid (free and conjugated) are unlikely to occur at significant levels in rotational (follow) crops.

There is no obvious single compound for use as a suitable marker for compliance. It is noted that the majority of the residue in crops is present as conjugates of acibenzolar acid that can easily be converted to acibenzolar acid on base hydrolysis. Acibenzolar-S-methyl is also converted to acibenzolar acid on base hydrolysis. As such a common moiety residue definition would allow

residues to be monitored in all crops and derived commodities. Validated analytical methods are available for the determination of acibenzolar-S-methyl together with free and conjugated acibenzolar acid in crop matrices.

The Meeting decided the residue definition for compliance with MRLs in plants should be the sum of acibenzolar-S-methyl and acibenzolar acid, free and conjugated, expressed as acibenzolar-S-methyl.

In deciding which additional compounds should be included in the residue definition for risk assessment the Meeting considered the toxicological properties and likely occurrence of the candidates: acibenzolar acid (free and conjugated), 4-OH acibenzolar acid (free and conjugated) and 3-methylsulfinyl benzoic acid (free and conjugated). The toxicological properties of the various metabolites were considered. Acibenzolar acid has similar potency to the parent compound, while 4-OH acibenzolar acid is considered to be of no greater lower toxicity than the parent compound. Acibenzolar acid (free and conjugated) is the major residue in most plant commodities and should be included in the residue definition for risk assessment. The 4-OH acibenzolar acid metabolite (free and conjugated) was only significant in leafy vegetables (lettuce) where it occurred at half the level of the sum of parent compound and acibenzolar acid (free and conjugated). The Meeting agreed an adjustment factor of 1.5 could be applied to residues in leafy vegetables measured according to the residue definition for compliance to convert residues to the equivalent sum of acibenzolar-S-methyl, acibenzolar acid (free and conjugated) and 4-OH acibenzolar acid (free and conjugated). The Meeting agreed residues of 4-OH acibenzolar acid (free and conjugated) should be included in the residue definition for dietary risk assessment.

The metabolite 3-methanesulfinyl benzoic acid was only detected in rice and then only at low levels. No information was available on the toxicity of 3-methanesulfinyl benzoic acid. The Meeting agreed that as rice is not among the uses currently under consideration, residues of 3-methanesulfinyl benzoic acid are not expected and the compound does not need to be considered further. If uses on rice are considered in the future, a dietary risk assessment comparing exposures against the Cramer class TTC values should be conducted.

The Meeting decided the residue definition for dietary risk assessment in plants should be: *the sum of acibenzolar-S-methyl and acibenzolar acid, (free and conjugated) and 4-OH acibenzolar acid (free and conjugated), expressed as acibenzolar-S-methyl*

The plant metabolism studies show that livestock are unlikely to be exposed to parent acibenzolar-S-methyl. Livestock will be exposed to a range of metabolites that are mostly comprised of free and conjugated acibenzolar acid. As acibenzolar-S-methyl is rapidly hydrolysed to acibenzolar acid, and conjugates of acibenzolar acid are readily cleaved to produce acibenzolar acid, the use of acibenzolar-S-methyl in the livestock metabolism studies is acceptable.

In lactating goats no intact acibenzolar-S-methyl was detected in tissues or milk. The majority of the residues were present as free (33–90% TRR) and conjugated forms (2.3–22% TRR) of acibenzolar acid. In laying hens no intact acibenzolar-S-methyl was detected in tissues or eggs. Free acibenzolar acid accounted for the majority of the residue (50–77% TRR) with conjugates of acibenzolar acid only present at significant proportion of ¹⁴C in egg white (18% TRR).

Analytical methods are available that determine residues of acibenzolar-S-methyl and acibenzolar acid, free and conjugated.

Based on the above, the Meeting decided the residue definition for animal commodities for compliance with MRLs and dietary risk assessment should be as follows:

sum of acibenzolar-S-methyl and acibenzolar acid, free and conjugated, expressed as acibenzolar-S-methyl

There is insufficient data to characterise whether the sum of residues in the residue definition (sum of acibenzolar-S-methyl and free and conjugated acibenzolar acid) is fat soluble. Total radioactive residues in muscle compared to fat and egg white compared to egg yolk suggest the

residues, measured according to the residue definition might be higher in fat however, the data are inconclusive. The log K_{ow} for acibenzolar-S-methyl is 3.1 and the log K_{ow} values of acibenzolar acid and its conjugates are expected to be lower, suggesting the residue does not preferentially partition into fatty matrices.

On the weight of evidence, the Meeting decided the residue is not *fat soluble*.

Results of supervised residue trials on crops

Supervised residue trial data were available for acibenzolar-S-methyl on citrus (oranges, grapefruit, lemons), pome fruit (apples, pears), stone fruit (peaches, apricots), strawberries, bananas, kiwifruit, brassica vegetables (cabbage, broccoli, mustard greens), leafy vegetables (head lettuce, leaf lettuce, spinach, celery), cucurbits (cucumber, melon, squash), tomatoes, potatoes, and wheat.

The residue definition for exposure assessment includes 4-OH acibenzolar acid (free and conjugated). As residues of 4-OH acibenzolar acid (free and conjugated) are only expected in leafy crops and these residues were not measured in field trials, an adjustment factor of 1.5 (see above) was used to convert residues measured using the compliance definition to that for dietary risk assessment. The Meeting considered the factor would only be applied to the highest residues of leafy vegetables to estimate the relevant STMR and HR values required for dietary risk assessment.

Citrus fruits

The Meeting received supervised residue trial data for acibenzolar-S-methyl on citrus fruit from the USA. The critical GAP for citrus in the USA is applications to soil under trees at 112 g ai/ha with a PHI of 0 days. The maximum rate per year is 448 g ai/ha. In trials approximating critical GAP in the USA residues in citrus fruit were:

Oranges: (n = 10) < 0.01 (9), 0.01 mg/kg

Lemons: (n = 5) < 0.01 (5) mg/kg

Grapefruit: (n = 6): < 0.01 (6) mg/kg.

The Meeting noted that residues following soil application to citrus are generally \leq LOQ and decided to combine the data for oranges, lemons and grapefruit to estimate a group maximum residue level. The Meeting recommended a maximum residue level, STMR and HR of 0.015, 0.01 and 0.01 mg/kg respectively for citrus fruit.

Pome fruits – apples and pears

In Italy acibenzolar-S-methyl is approved for use on apples and pears. cGAP in Italy for apples is applications at 100 g ai/ha at 5–14 day intervals and a PHI of 7 days. In trials conducted in EU member states approximating critical GAP in Italy residues in apples were: (n = 16) < 0.01 (11), 0.01 (2), 0.03, 0.16, 0.17 mg/kg. The Meeting recommended maximum residue level, STMR and HR of 0.3, 0.01 and 0.17 mg/kg respectively for apples.

cGAP in Italy for pears is applications at 100 g ai/ha at intervals of 5–7 days (pre-flowering) and 14–28 days (fruiting) with a PHI of 14 days. In trials conducted in EU member states approximating critical GAP in Italy residues in pears were: (n = 4) < 0.02 (4) mg/kg. The Meeting considered four trials insufficient to estimate a maximum residue level for pears and as the GAPs for apples and pears were different, and did not consider extrapolation of the data on apples to pears.

Peaches

Supervised residue trial data for acibenzolar-S-methyl on peaches and apricots were made available. cGAP in Italy is applications at 75 g ai/ha at intervals of 7–14 days with a PHI of 7 days.

In trials conducted in the EU approximating critical GAP in Italy residues in peaches were (n = 7): 0.02, 0.02, 0.02, 0.05, 0.05, 0.05 and 0.09 mg/kg.

In trials conducted in the EU approximating critical GAP in Italy residues in apricots were (n = 4): 0.05, 0.07, 0.08, 0.13 mg/kg.

A Mann-Whitney U-test suggest the residues in apricots and peaches are from similar populations and the Meeting decided to combine the data to estimate a maximum residue level for the Codex sub-group peaches.

Residues in eleven trials on apricots and peaches were (n = 11): 0.02, 0.02, 0.02, 0.05, 0.05, 0.05, 0.05, 0.07, 0.08, 0.09, 0.13 mg/kg.

The Meeting recommended a maximum residue level, STMR and HR of 0.2, 0.05 and 0.13 mg/kg respectively for the sub-group peaches (includes apricots and nectarines).

Low growing berries, including strawberries

The Meeting received supervised residue trial data for acibenzolar-S-methyl on strawberries. Critical GAP in the USA on low growing berries including strawberries (USA subgroup 13-07G) is applications at 26 g ai/ha with a PHI of 0 days. The maximum rate per year is 210 g ai/ha. In trials approximating critical GAP in the USA residues in strawberries were: (n = 10) 0.02, 0.02, 0.03, 0.03, 0.04, 0.05, 0.06, 0.06, 0.07, 0.08 mg/kg.

The Meeting noted residues for strawberries can be extrapolated to Codex Subgroup 004E, low growing berries and recommended a maximum residue level, STMR and HR of 0.15, 0.045 and 0.08 mg/kg respectively.

Banana

The Meeting received supervised residue trial data for acibenzolar-S-methyl on banana from Colombia, Costa Rica, Ecuador, Guatemala, France (Martinique), Malaysia and Mexico. GAP in Guatemala is applications at up to 40 g ai/ha at 30-40 day intervals with a PHI of 0 days. In trials approximating critical GAP in Guatemala residues in unbagged bananas were: (n = 15): < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, 0.03, 0.04, 0.05 mg/kg. The Meeting recommended a maximum residue level of 0.06 mg/kg.

Residues in the edible portion (pulp) were: < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, 0.02, 0.03 mg/kg. The Meeting recommended a STMR and HR of 0.02 and 0.03 mg/kg respectively for banana (pulp).

The Meeting noted that residues in bagged bananas from 15 trials were all < 0.02 mg/kg for both whole fruit and pulp.

Kiwifruit

Acibenzolar-S-methyl is approved in Italy and NZ for use on kiwifruit.

cGAP in Italy is a foliar application at 6 × 75 g ai/ha with a 14 day interval or 6 × 100 g ai/ha with a 21 day interval and a PHI of 90 days. No trials matched cGAP of Italy.

cGAP in NZ is foliar or soil applications to actively growing plants at 4 × 100 g ai/ha (10 g ai/hL). Foliar sprays are not to be applied between flowering and harvest while the PHI for soil application is 14 days. The foliar application at flowering does not lead to residues in fruit at harvest. In fourteen trials conducted in NZ that matched the GAP for soil application, residues were: (n = 14) < 0.01 (11) 0.01, 0.02, 0.02 mg/kg. The Meeting recommended a maximum residue level, STMR and HR of 0.03, 0.01 and 0.02 mg/kg respectively for kiwifruit.

Bulb onions

The Meeting received supervised residue trial data for acibenzolar-S-methyl on onions. cGAP in the USA for the US onion crop group 3-07A is applications at 35 g ai/ha at 7 – 10 day intervals with a PHI of 7 days. The maximum rate per year is 140 g ai/ha. In twelve trials that approximated critical GAP, residues were (n = 12): < 0.01, < 0.01, 0.01, 0.02, ≤ 0.05 (7), 0.06 mg/kg. The Meeting recommended a maximum residue level, STMR and HR of 0.15, 0.05 and 0.06 mg/kg respectively for onions, bulb.

The Meeting noted residues on bulb onions can be extrapolated to garlic and shallots and also recommended a maximum residue level, STMR and HR of 0.15, 0.05 and 0.06 mg/kg respectively for garlic and shallots.

Brassica vegetables

Supervised residue trial data for acibenzolar-S-methyl on Brassica vegetables were available. cGAP in the USA for Brassica (cole) crops (USA group 5) is applications at 35 g ai/ha at intervals of 7 days with a PHI of 7 days. The maximum rate per year is 140 g ai/ha.

In trials conducted in the USA on cabbages the application rate (53 g ai/ha) was higher than the current GAP (35 g ai/ha) and the Meeting agreed to utilise the proportionality approach to estimate residues matching cGAP. Unscaled residues for cabbage heads with wrapper leaves were (n = 9): 0.08, 0.13, 0.19, 0.21, 0.31, 0.32, 0.39, 0.51, 0.58 mg/kg.

After scaling using a scaling factor of 0.66 (35/53), the following residues in cabbages were obtained: 0.05, 0.09, 0.13, 0.14, 0.20, 0.21, 0.26, 0.34, 0.38 mg/kg.

In trials conducted in the USA on broccoli the application rate was higher (53 g ai/ha) than the current GAP in the USA (35 g ai/ha) and the Meeting agreed to apply proportionality in assessing the data. Unscaled residues were (n = 6): 0.20, 0.31, 0.46, 0.47, 0.55, 0.62 mg/kg.

The scaling of residues (scaling factor 53/35 = 0.66) in broccoli to match cGAP results in the following: 0.13, 0.20, 0.30, 0.31, 0.36, 0.41 mg/kg.

GAP in the USA for Brassica vegetables and a group maximum residue level recommendation may be possible based on the data for cabbages and broccoli. The medians for the two datasets differed by less than a factor of five and the Meeting decided to recommend a group maximum residue level. In deciding which datasets to use for the recommendation, as a Mann-Whitney U-test indicated the populations were not different, it was decided to combine the datasets. The combined dataset is (n = 15): 0.05, 0.09, 0.13, 0.13, 0.14, 0.20, 0.20, 0.21, 0.26, 0.30, 0.31, 0.34, 0.36, 0.38, 0.41 mg/kg.

The Meeting recommended a maximum residue level, STMR and HR of 0.7, 0.315 (= 1.5 × 0.21) and 0.62 (= 1.5 × 0.41) mg/kg respectively for Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead brassicas.

Fruiting vegetables, Cucurbits

Supervised residue trial data for acibenzolar-S-methyl on cucurbit vegetables were available. cGAP in the USA for cucurbits (crop group 9) is applications at 35 g ai/ha at intervals of 7 days with a PHI of 0 days. The maximum rate per year is 280 g ai/ha.

In trials conducted in the USA on field grown cucumbers, melons and summer squash the application rate (68 to 71 g ai/ha) was higher than the current GAP (35 g ai/ha) and the Meeting agreed to utilise the proportionality approach (scaling factor 0.48 to 0.51) to estimate residues matching cGAP. Unscaled residues for cucumbers were (n = 11): 0.07, 0.12, 0.13, 0.14, 0.15, 0.17, 0.18, 0.28, 0.46, 0.48, 0.77 mg/kg.

After scaling the following residues in cucumbers were obtained: 0.04, 0.06, 0.07, 0.07, 0.08, 0.09, 0.09, 0.14, 0.23, 0.24, 0.39 mg/kg.

For melons, unscaled residues were (n = 12): 0.15, 0.25, 0.26, 0.31, 0.31, 0.33, 0.35, 0.60, 0.63, 0.83, 0.87, 0.98 mg/kg.

Scaled residues were: 0.08, 0.13, 0.13, 0.15, 0.16, 0.17, 0.18, 0.31, 0.32, 0.42, 0.44, 0.47 mg/kg.

For summer squash, unscaled residues were (n = 4): 0.04, 0.13, 0.14, 0.18 mg/kg.

Scaled residues in summer squash were: 0.02, 0.07, 0.07, 0.09 mg/kg.

GAP in the USA is for cucurbit vegetables and a group maximum residue level recommendation may be possible based on the data for cucumber, melons and summer squash. The medians for the three datasets differed by less than a factor of five and the Meeting decided to recommend a group maximum residue level. In deciding which datasets to use for the recommendation, as a Kruskal-Wallis H-test indicated the data were not from the same population it was decided to use the dataset with the highest residues, melons, to estimate a maximum residue level for the group.

Using the melon dataset (0.08, 0.13, 0.13, 0.15, 0.16, 0.17, 0.18, 0.31, 0.32, 0.42, 0.44, 0.47 mg/kg), the Meeting recommended a maximum residue level, STMR and HR of 0.8, 0.175 and 0.47 mg/kg respectively for fruiting vegetables cucurbits.

Tomato

Supervised residue trial data for acibenzolar-S-methyl on field grown tomato were available. GAP in the USA is applications at 26 g ai/ha at intervals of 7 days with a PHI of 14 days. No trials matched USA cGAP.

GAP in France is applications at 6 ×25 g ai/ha at intervals of 7days with a PHI of 3 days. In trials conducted in the EU approximating critical GAP in France residues in tomatoes were (n = 13): 0.04, 0.05, 0.05, 0.06, 0.06, 0.07, 0.09, 0.10, 0.10, 0.12, 0.13, 0.14, 0.15 mg/kg.

The Meeting recommended a maximum residue level, STMR and HR of 0.3, 0.09 and 0.15 mg/kg respectively for tomatoes.

Lettuce

Supervised residue trial data for acibenzolar-S-methyl on lettuce were available. GAP in the USA is applications at 4 ×35 g ai/ha at intervals of 7-10 days with a PHI of 7 days. The maximum rate per year is 332 g ai/ha. In trials conducted in the US approximating critical GAP residues in lettuce were:

Head lettuce (n = 6): 0.04, 0.04, 0.05, 0.06, 0.08, 0.10 mg/kg.

Leaf lettuce (n = 6): 0.04, 0.06, 0.10, 0.14, 0.14, 0.18 mg/kg.

The Meeting recommended a maximum residue level, STMR and HR of 0.2, 0.0825 (= 1.5 ×0.055) and 0.15 (= 1.5 ×0.10) mg/kg respectively for head lettuce.

The Meeting recommended a maximum residue level, STMR and HR of 0.4, 0.18 (= 1.5 ×0.12) and 0.27 (= 1.5 ×0.18) mg/kg respectively for leaf lettuce.

Spinach

Supervised residue trial data for acibenzolar-S-methyl on spinach were available.

GAP in France is applications at 3 ×12.5 g ai/ha with a PHI of 10 days. In trials conducted in the EU approximating critical GAP in France residues in spinach were (n = 7): 0.04, 0.06, 0.06, 0.11, 0.12, 0.16, 0.18 mg/kg.

Critical GAP in the USA is applications at 4×26 g ai/ha at intervals of 7-10 days with a PHI of 7 days. The maximum rate per year is 332 g ai/ha.

In trials conducted in the USA on spinach the application rate was higher (35 g ai/ha) than the current GAP and the Meeting agreed to utilise the proportionality approach (scaling factor $26/35 = 0.74$) to estimate residues matching cGAP. The following scaled residues in spinach matched cGAP

Unscaled residues for spinach were: 0.12, 0.18, 0.21, 0.24, 0.26, 0.29, 0.29, 0.33, 0.48 mg/kg.

After scaling the following residues in spinach were obtained (n = 9): 0.09, 0.13, 0.16, 0.18, 0.19, 0.22, 0.22, 0.25, 0.36 mg/kg.

The Meeting noted residues matching cGAP were higher in the dataset from the US than France and decided to use these residue data to estimate a maximum residue level for spinach.

The Meeting recommended a maximum residue level, STMR and HR of 0.6, 0.285 (= 1.5×0.19) and 0.54 (= 1.5×0.36) mg/kg respectively for spinach.

Brassica leafy vegetables

Supervised residue trial data for acibenzolar-S-methyl on mustard greens were available. GAP in the USA for Brassica (cole) crops (USA group 5) is applications at 35 g ai/ha at intervals of 7 days with a PHI of 7 days. The maximum rate per year is 140 g ai/ha.

In trials conducted in the USA on mustard greens the application rate (53 g ai/ha) was higher than the current GAP and the Meeting agreed to utilise the proportionality approach (scaling factor $35/53 = 0.66$) to estimate residues matching cGAP. Unscaled residues were: 0.16, 0.29, 0.59, 0.67, 0.76 mg/kg. The following scaled residues in mustard greens matched cGAP (n = 5): 0.11, 0.19, 0.39, 0.44, 0.50 mg/kg

The Meeting recommended a maximum residue level, STMR and HR of 1, 0.585 (= 1.5×0.39) and 0.795 (= 1.5×0.53) (highest individual sample) mg/kg respectively for mustard greens. As the use pattern includes all Brassica leafy vegetables, the meeting agreed to extrapolate the recommendations to all Brassica leafy vegetables (VL 0054).

Potato

Supervised residue trial data for acibenzolar-S-methyl on potato were available. GAP in Brazil is 6×12.5 g ai/ha at intervals of 7 days with a PHI of 14 days. None of the trials matched cGAP (number of sprays, application rate) for Brazil.

Wheat

Supervised residue trial data for acibenzolar-S-methyl on wheat were available. Critical GAP in Brazil is 3×12.5 g ai/ha at intervals of 14 days with a PHI of 21 days. In trials conducted in the Argentina and Brazil approximating critical GAP in Brazil residues in wheat grain were (n = 4): < 0.01 , < 0.01 , 0.03 and 0.04 mg/kg. The Meeting considered the number of trials insufficient for the estimation of a maximum residue limit.

Fate of residues during processing

The Meeting received information on the fate of incurred residues of acibenzolar-S-methyl during the processing of oranges, pears and tomatoes. A study of the nature of the residue of acibenzolar-S-methyl under simulated processing conditions (pasteurization 20 minutes at 90 °C, pH 4, baking/brewing/boiling 60 minutes at 100 °C, pH 5, sterilization 20 minutes at 120 °C, pH 6) showed acibenzolar-S-methyl, if present, is hydrolytically stable under processing conditions representative of pasteurisation and baking/boiling/brewing; a significant degradation of the parent compound into

acibenzolar acid (CGA210007) occurred under sterilisation conditions. A hydrolysis study demonstrated that acibenzolar acid (CGA210007), once formed, is stable to hydrolysis.

Summary of relevant processing factors calculated for the sum of acibenzolar-S-methyl and free and conjugated acibenzolar acid is provided below.

	Processed Fraction	Processing Factor	Best estimate PF	RAC STMR or median	STMR×PF = STMR-P
Oranges	Dried pulp	4.5	4.5	< 0.01	< 0.045
	Juice	< 0.625	< 0.625		< 0.0062
	Oil	< 0.625	< 0.625		< 0.0062
Pome fruit ^A	Dried pomace	2.0 3.0 3.2 3.4	3.1	< 0.01	< 0.031
Tomato	Peeled fruit	0.83 0.50	0.67	0.09	0.060
	Juice	0.67 0.75 0.80 1.0	0.78		0.070
	Preserved fruit	0.5 0.5 0.8 0.83	0.66		0.059
	Purée	1.17 1.75 2.0 3.33	1.88		0.169
	Ketchup	1.75 2.0	1.89		0.170

^A Pfs are based on results for pear and are indicative only as the residue in the RAC used to calculate the PF was between LOD and LOQ.

The HR-P for peeled tomato fruit is $0.15 \text{ mg/kg} \times 0.67 = 0.10 \text{ mg/kg}$ and for preserved (canned) tomato fruit is $0.15 \text{ mg/kg} \times 0.66 = 0.099 \text{ mg/kg}$.

Residues in animal commodities

Farm animal feeding studies

The Meeting received information on the residue levels in tissues and milk of dairy cows dosed with acibenzolar-S-methyl at the equivalent of 0.25, 1.27 and 2.48 ppm in the feed for 28 consecutive days.

Residues in milk were < 0.005 mg/kg and tissues < 0.02 mg/kg for the 2.48 ppm dose group for all samples.

A laying hens transfer study was not available.

Estimation of livestock dietary burdens

Dietary burden calculations for beef cattle and dairy cattle and poultry are provided below. The dietary burdens were estimated using the OECD diets listed in Appendix IX of the 2016 edition of the FAO Manual.

Potential cattle feed items include: cabbage wrapper leaves, kale, apple pomace and citrus pulp.

Summary of livestock dietary burden (ppm acibenzolar-S-methyl equivalents of dry matter diet)

	US-Canada		EU		Australia		Japan	
	Max	Mean	Max	mean	max	Mean	max	Mean
Beef cattle	0.005	0.005	0.71	0.53	0.01	0.01	-	-
Dairy cattle	0.005	0.005	0.72	0.53	1.4 ^{AB}	1.0 ^{CD}	-	-
Broilers	-	-	-	-	-	-	-	-
Layers	-	-	0.18 ^E	0.13 ^F	-	-	-	-

^A Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian meat

^B Highest maximum dairy cattle dietary burden suitable for MRL estimates for mammalian milk

^C Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat.

^D Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.

^E Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs

^F Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs

Animal commodity maximum residue levels

No residues were detected in milk and tissues of lactating dairy cows dosed at 2.5 ppm in the diet, 1.8 times the maximum livestock dietary burden. The storage stability of residues in liver was poor with 51% remaining after the freezer storage period of 124 days. However, the Meeting noted that as residues were not present in liver in animals dosed at 1.8 times the maximum livestock dietary burden, even if residues had declined by 50% on storage, no residues are expected to have been present in liver.

The Meeting estimated the following maximum residue levels: milk 0.01* mg/kg; meat (mammalian except marine mammals) 0.02* mg/kg, mammalian fat (except milk fat) 0.02* mg/kg and edible offal 0.02* mg/kg. The Meeting estimated the following STMR and HR values: mammalian meat 0 mg/kg; mammalian fat 0 mg/kg; mammalian edible offal 0 mg/kg and milk 0 mg/kg.

Although a laying hens transfer study was not available, in a metabolism study where hens were dosed at the equivalent of 19.1 ppm in the diet for four days residues of acibenzolar-S-methyl and free and conjugated acibenzolar acid were < 0.01 mg/kg in eggs, 0.29 mg/kg in liver, 0.01 mg/kg in muscle and 0.03 mg/kg in skin/fat.

At the maximum dietary burden for poultry (0.18 ppm), no residues above the LOQ for analytical methods are expected in eggs ($< 0.01 \times 0.14/19.1 = < 0.00007$ mg/kg), liver (0.002 mg/kg), muscle (0.00007 mg/kg) and skin/fat (0.0002 mg/kg). The Meeting estimated the following maximum residue levels for poultry commodities: poultry meat 0.02* mg/kg; poultry edible offal 0.02* mg/kg, poultry fat 0.02* mg/kg and eggs 0.02* mg/kg. The Meeting estimated the following STMR and HR values: poultry meat 0 mg/kg; poultry fat 0 mg/kg; poultry edible offal 0 mg/kg and eggs 0 mg/kg.

RECOMMENDATIONS FURTHER WORK OR INFORMATION

On the basis of the data obtained from supervised residue trials the Meeting concluded that the residue levels listed in Annex 1 are suitable for establishing maximum residue limits and for IEDI and IESTI assessment.

Definition of the residue for compliance with MRL for animal and plant commodities and for dietary risk assessment for animal commodities: *Sum of acibenzolar-S-methyl and 1,2,3-benzothiadiazole-7-carboxylic acid (acibenzolar acid) (free and conjugates), expressed as acibenzolar-S-methyl*

Definition of residue (for dietary risk assessment for plants): *Sum of acibenzolar-S-methyl and 1,2,3-benzothiadiazole-7-carboxylic acid (acibenzolar acid), (free and conjugated) and 1,2,3-benzothiadiazole-4-hydroxy-7-carboxylic acid (4-OH acibenzolar acid) (free and conjugated), expressed as acibenzolar-S-methyl*

The residue is not fat soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The 2016 JMPR established an Acceptable Daily Intake (ADI) of 0–0.08 mg/kg bw for acibenzolar-S-methyl.

The evaluation of acibenzolar-S-methyl resulted in recommendations for MRLs and STMR values for raw and processed commodities. Where data on consumption were available for the listed food commodities, dietary intakes were calculated for the 17 GEMS/Food Consumption Cluster Diets. The results are shown in Annex 3.

The IEDIs in the seventeen Cluster Diets, based on the estimated STMRs were 0–1% of the maximum ADI (0.08 mg/kg bw). The Meeting concluded that the long-term dietary exposure to residues of acibenzolar-S-methyl from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term dietary exposure

The 2016 JMPR established an Acute Reference Dose (ARfD) of 0.5 mg/kg bw for acibenzolar-S-methyl. The IESTI of acibenzolar-S-methyl for the commodities for which STMR, HR and maximum residue levels were estimated by the current Meeting are shown in Annex 4. The IESTI represented 0–10% of the ARfD (0–9% general population, 0–10% children 8 months–6 years old).

The Meeting concluded that the short-term dietary exposure to residues of acibenzolar-S-methyl resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

