Health Canada Santé Canada

Evaluation Report for Category A, Subcategory 1.3 Application

Application Number: 2007-4677
Application: New Active Ingredient – Maximum Residue Limits (MRLs) Only
Product: Fluopicolide Technical Fungicide
Active ingredients (a.i.): Fluopicolide (FLC)
PMRA Document Number : 1917173

Purpose of Application

The purpose of this application was to establish maximum residue limits (MRL) to cover residues of fluopicolide in/on brassica (head and stem) vegetables (crop group 5A), root and tuber vegetables (crop group 1), bulb vegetables (crop group 3), cucurbit vegetables (crop group 9), fruiting vegetables (crop group 8), leafy vegetables (crop group 4) and grapes.

Chemistry Assessment

The chemical properties of the fluopicolide technical active ingredient, Fluopicolide Technical Fungicide and the fluopicolide-containing end-use product V-10161 4 SC Fungicide are presented in the tables below.

Canada

Identity of the Active Ingredient

Active substance Fluopicolide

Function Fungicide

Chemical name

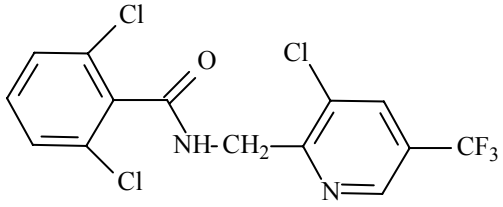
1. **International Union of Pure and Applied Chemistry (IUPAC)** 2,6-Dichloro-N-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}benzamide
2. **Chemical Abstracts Service (CAS)** 2,6-Dichloro-N-{[3-chloro-5-(trifluoromethyl)-2-pyridinyl]methyl}benzamide

CAS number 239110-15-7

Molecular formula $C_{14}H_8Cl_3F_3N_2O$

Molecular weight 383.58

Structural formula



Purity of the active ingredient 98.8%

Physical and Chemical Properties of Fluopicolide Technical Fungicide

Property	Result
Colour and physical state	Beige solid
Odour	Odourless
Melting range	149°C (135-165°C)
Boiling point or range	Not available
Specific gravity at 4°C	1.65
Vapour pressure at 20°C	3.03×10^{-7} Pa (extrapolated)
Ultraviolet (UV)-visible spectrum	λ = 203, 270, 290 nm, λ_{max} = 290 nm
Solubility in water at 20°C	3.02 mg/L
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) ethanol 19.2 n-hexane 0.20 toluene 20.5 dichloromethane 126 acetone 74.7 ethylacetate 37.7 diemthyl sulfoxide 183

n-Octanol-water partition coefficient (K_{ow})	pH log Kow 4.0 2.9 7.3 2.9 9.1 2.9
Dissociation constant (pK_a)	Not available
Stability (temperature, metal)	Stable at 54°C for 14 days in presence of aluminum or aluminum acetate.

Physical and Chemical Properties of the End-Use Product V-10161 4 SC Fungicide

Property	Result
Colour	Beige
Odour	Not available
Physical state	Liquid
Formulation type	SU (suspension)
Guarantee	39.5%
Container material and description	20 to 1000 kg, bulk, plastic, polyethylene totes
Density	1.21 g/mL at 20°C
pH of 1% dispersion in water	6.6
Oxidizing or reducing action	No chemical incompatibility if the test item comes in contact with reducing (zinc powder) or oxidizing (ammonium nitrate) agents.
Storage stability	Stable in HDPE white opaque can for at least three years at ambient temperature
Corrosion characteristics	The HDPE white opaque can shows no negative interactions with the formulation for at least three years at ambient temperature.
Explodability	The product does not present a danger of explosion under the thermal sensitivity and shock tests.

The methods provided for the analysis of the active ingredient and the impurities in Fluopicolide Technical Fungicide have been validated and assessed to be acceptable for the determinations. 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.

Health Assessments

Toxicology Summary

The PMRA conducted a detailed review of the toxicological database for fluopicolide. The database is complete, consisting of the full array of laboratory animal (*in vivo*) and cell culture (*in vitro*) toxicity studies currently required for hazard assessment purposes. The studies were

carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical.

Following acute oral exposure, Fluopicolide Technical Fungicide as well as V-10161 4 SC Fungicide were of low toxicity by the oral route of exposure in rats.

After oral dosing in rats of fluopicolide, absorption averaged 62% in both sexes and was moderately rapid with T_{max} in blood of 6-8 hours. The majority (95%) of the test material was eliminated within 48 hours in the faeces (~80%) with the rest being eliminated in the urine (~20%). No significant concentrations of radiolabel were recovered in the expired air. The mean $t_{1/2}$ in plasma was approximately 14 hours. Biliary excretion was important with more than half of the administered dose (AD) being excreted as biliary fraction. Toxicokinetics were not significantly influenced by dose, dosage regime or gender. The area under the curve (AUC) was not proportional to dosing, as the AUC increased by approximately 5-fold after a 10-fold increase in dosage. Fluopicolide was distributed in all organs and tissues. The highest concentrations were found in the main target organs: the liver, kidneys and intestines. There was no evidence of bioaccumulation. The test material was rapidly and extensively metabolized. None of the radioactivity detected in the urine was associated with the parent compound. The greatest amount of radioactivity recovered in the faeces of rats was attributed to the parent compound. The major metabolites were identified as oxidative N-dealkylation cleavage products. Many of the metabolites were the products of hydroxylation, hydrolysis, dealkylation, glucuronidation, sulfation, or glutathione conjugation.

Additional data were provided by the registrant regarding four metabolites/impurities that can be present in plants and/or mammals. AE 1344122, AE C653711 (2,6-dichlorobenzamide [BAM]), AE C657378 (metabolite of BAM) and AE C657188 (3-chloro-5-(trifluoromethyl)pyridine-2-carboxylic acid [PCA]) were evaluated for metabolism (BAM and PCA), acute toxicity, short-term toxicity (AE 1344122 and AE C657378) and genotoxic potential. With the exception of BAM, which was moderately acutely toxic, all of the other tested compounds were considered equally or less toxic than fluopicolide. All of the compounds were considered negative for genotoxicity.

After repeated dietary dosing with fluopicolide, the key treatment-related effects were decreased body weight/gains and liver effects across the species tested (mice, rats and dogs) and kidney effects in rats. The liver effects seen in all species seemed to reflect an adaptive response and consisted mainly of increased liver weights and centrilobular hepatocyte hypertrophy. The kidney effects in the rat were numerous with renal tubular eosinophilic proteinaceous material, granulation, hydronephrosis, hyaline droplets in the proximal tubules, single cell death in the proximal tubule epithelium, and presence of granular casts. The adverse effects observed during a 90-day dosing period in rats were similar to those noted during a 4-week treatment of rats with

the exception of hypertrophy of *zona glomerulosa* of the adrenals and trabecular hyperostosis of the bone joint in female rats over a longer period of exposure. Overall, rats were more sensitive to fluopicolide-induced toxicity than mice or dogs, and males were more sensitive than females.

The weight of evidence indicates no genotoxicity potential for fluopicolide when tested in a battery of *in vitro* and *in vivo* genotoxicity assays including reverse mutation assay, gene mutation assay, chromosomal aberration assay, micronucleus assay and unscheduled DNA synthesis.

In an 18-month mouse carcinogenicity study, there were adaptive liver effects (increased liver weight and hepatocyte hypertrophy) starting at the mid-dose and decreased body weight gains and decreased food efficiency at the high dose. There was an increase in the incidence of hepatocellular adenoma in high dose animals when compared with control animals. At this dose, with up to 20% reduction in body weight (45% decreased body weight gain) compared to controls, the maximum tolerable dose (MTD) was considered to have been exceeded. A mechanistic study performed in mice depicts fluopicolide as a potent liver enzyme inducer with a phenobarbital-like profile. Based on the weight of evidence, the increased incidence of hepatocellular adenoma was not considered relevant for the human risk assessment.

In a 2-year combined chronic/carcinogenicity study in rats, the same type of liver and kidney effects as were noted in the short-term studies were observed and were characterized by an increase in the incidence and severity of the effects suggesting that the longer duration of exposure results in greater prevalence of liver and kidney lesions. Along with liver hypertrophy, cystic degeneration, clear foci, and eosinophilic foci in males, blood cholesterol was increased because of the impaired liver function. The kidney effects were more severe at terminal sacrifice when compared to interim sacrifice. They consisted of cortical tubular basophilia with associated degenerative changes, hyaline droplets and tubular casts (males) and hyperplasia of the papillary epithelium (females) associated with mineralization of the papillary/pelvic epithelium (females) and papilla (males). The thyroid was also a target organ in this study with cystic follicular hyperplasia observed in males at the interim sacrifice, with increased severity at the terminal sacrifice. There was no evidence of carcinogenic potential in the rat.

In a 2-generation reproductive toxicity study, F_0 and F_1 parental animals were affected by decreased body weight and body weight gain, along with decreased food consumption. Kidney effects were also present including increased kidney weight in F_0 and F_1 adults, cortical tubular basophilia, medullary granular casts, and cortical scarring in F_0 and F_1 males, interstitial inflammation in F_0 males, and cortical tubular basophilia and dilatation as well as corticomedullary mineralization in F_0 and F_1 females. No treatment-related effects were noted on any of the reproduction parameters up to the highest dose tested. Other than body weight and body weight gain effects in F_1 and F_2 pups at the highest dose tested, there were no treatment-related effects observed in the offspring.

In a rat developmental toxicity study, marginal maternal toxicity was observed at the highest dose tested, namely decreased body weight gain. Developmental toxicity was observed at the highest dose tested and consisted of decreased foetal weight, crown/rump length and placental weights. There was also an increased incidence of ossification delays of sacral vertebra, sternebra, 5^{th} metacarpal and 5^{th} metatarsal bones compared to control animals. An increased

incidence of skeletal malformations of the thoracic vertebra and ribs was present, therefore there was evidence of teratogenicity in rats at the highest dose tested in presence of maternal toxicity.

In a rabbit developmental toxicity study, maternal toxicity was observed at the high dose as decreased body weight gains and food consumption, and 3 dams died on gestational days (GD) 24, 25 and 29 following hypoactivity, decreased food consumption and defecation, bristling hair coat and discoloured urine. These deaths were considered treatment-related. Also at the high dose, fifteen dams aborted or delivered prematurely between GD 22 and GD 28 presenting clinical signs similar to the dams that died. One dam from the mid dose group aborted on GD 28 and was subsequently sacrificed. Prior to aborting, this dam showed decreased defecation and hay consumption. The gross pathological observations in most of the dams that aborted included a tautly filled stomach and red fluid in the urinary bladder. Body weight gains were also markedly decreased throughout the treatment period in the high dose group. The reduction in body weight gain correlated with a reduction in food efficiency. Developmental effects included decreased foetal weight and crown-rump length. There was no evidence of teratogenicity at any dose tested in rabbits.

Fluopicolide was not neurotoxic as demonstrated in acute and 90-day neurotoxicity studies in rats. Systemic effects observed in the 90-day study were similar to these observed in other subchronic studies (decreased body weight, body weight gain, and food consumption, and liver and kidney effects). The only treatment-related neurotoxic effect was observed in the acute neurotoxicity study at the limit dose with decreased body temperature at 6 hours post-dosing. Prior to the main study, marginal toxic effects were observed in an acute neurotoxicity range-finding study, but none of them were observed in the main study up to the limit dose with the exemption of decreased body temperature. There were no triggers in the toxicological database to warrant a study to investigate developmental neurotoxicity.

Results of the acute and chronic tests conducted on laboratory animals with Fluopicolide Technical Fungicide and its associated end-use products, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Appendix I, Tables 1, 2, and 5. Results of the acute and chronic tests conducted on laboratory animals with metabolites / impurities of fluopicolide are summarized in Appendix 1, Tables 3 and 4.

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* (PCPA) requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data and potential prenatal and postnatal toxicity with respect to the exposure of and toxicity to infants and children. 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, extensive data were available for fluopicolide including developmental toxicity studies in rats and rabbits and a 2-generation rat reproductive toxicity study.

With respect to effects relevant to the assessment of risk to infants and children, there was no indication of increased susceptibility in the offspring compared to parental animals in the reproduction study and offspring effects were limited to effects on body weight. In the rat developmental toxicity study, malformations were observed at the maternal LOAEL. The

malformations were considered serious endpoints although the concern was tempered by the presence of maternal toxicity (i.e. decreased body weight gain). The maternal toxicity effect was considered marginal, and therefore, increased qualitative susceptibility of the foetus was apparent in the rat. The database for fluopicolide is complete, there were no data deficiencies and a clear NOAEL has been identified for this developmental rat study. On the basis of this information, the PCPA factor was reduced to 3-fold, where the malformations were selected as the endpoint of concern for risk assessment. Furthermore, abortions were observed in dams from the rabbit developmental study at the high dose. The abortions were considered serious endpoints although the concern was tempered by the presence of maternal toxicity (i.e. deaths). The database for fluopicolide is complete, there were no data deficiencies and a clear NOAEL has been identified for this developmental rabbit study. On the basis of this information, the PCPA factor was reduced to 3-fold, where the abortions were selected as the endpoint of concern for risk assessment.

An acute reference dose (ARfD) for fluopicolide was not determined for the general population because an endpoint of concern attributable to an acute exposure was not identified in the toxicity studies.

The ARfD for fluopicolide in females aged 13-49 is based on the NOAEL of 60 mg/kg bw/day from the developmental toxicity study in rats based on malformations at the LOAEL of 700 mg/kg bw/day. Uncertainty factors of 10-fold for interspecies extrapolation as well as a 10-fold for intraspecies variability were applied in the setting of the ARfD. As indicated in the PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold for seriousness of endpoint in presence of maternal toxicity, resulting in a composite assessment factor (CAF) of 300-fold.

The ARfD (females aged 13-49) is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{60 \text{ mg/kg bw}}{300} = 0.2 \text{ mg/kg bw of fluopicolide}$$

The recommended acceptable daily intake (ADI) for fluopicolide is based on the NOAEL of 20 mg/kg bw/day from the developmental toxicity study in rabbits based on abortions, deaths and decreased body weight gains at the LOAEL of 60 mg/kg bw/day. Uncertainty factors of 10-fold for interspecies extrapolation as well as a 10-fold for intraspecies variability were applied in the setting of the ADI. As indicated in the PCPA Hazard Characterization section, the PCPA factor was reduced to 3-fold for seriousness of endpoint in the presence of maternal toxicity, resulting in a CAF of 300-fold.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{20 \text{ mg/kg bw/day}}{300} = 0.067 \text{ mg/kg bw/day of fluopicolide}$$

Dietary Assessment

The nature of fluopicolide in plants is adequately understood based on the submitted plant metabolism studies on lettuce, grape and potato. The general metabolic pathway in plants involves the cleavage of the bond between the carbon attached to the pyridine ring and the amide nitrogen of the parent compound to give rise to the metabolites BAM and PCA. Based on these studies, the residue definition for fluopicolide in/on plant matrices is outlined in Appendix 1, Table 6.

The analytical methods, using liquid chromatography with dual mass selective detectors (LC-MS/MS), are adequate to quantitate residues of fluopicolide in/on the imported crops. Based on acceptable method validation and independent laboratory validation, these methods are deemed adequate for data gathering and enforcement purposes.

Frozen storage stability of fluopicolide was demonstrated in four diverse matrices for 30 months.

Crop field trials were conducted in NAFTA representative growing regions in the United States of America (U.S.A.) on grapes, head lettuce, leaf lettuce, potatoes, tomatoes, bell peppers, chili peppers, cucumbers, squash and cantaloupes; and in the European Union (E.U.) on grapes alone. Trials were conducted at 0.7-fold maximum U.S.A. label rates, and the E.U. trials on grapes were conducted at 1.0-fold of the Greek Good Agricultural Practices (GAP). Data on grapes, head lettuce, leaf lettuce and potato, as well as the representative crops of crop group 8 (fruiting vegetables) and crop group 9 (cucurbit vegetables) were provided and are summarized in Appendix 1, Table 7.

Processing studies were conducted on grapes and tomatoes. Concentration was only observed in tomato paste (2.7-fold), tomato puree (1.4-fold) and raisins (3.4-fold). However, an MRL will only be required for raisins (4.1 ppm); residues in tomato paste and puree will be covered by the MRL for fruiting vegetables.

Based on the residue data provided, MRLs to cover residues of fluopicolide in/on imported grapes, head and leaf lettuce, tuberous and corm vegetables (except potatoes; crop subgroup 1D), fruiting vegetables (crop group 8), and cucurbit vegetables (crop group 9) will be recommended as shown below. The MRL calculations for fluopicolide are summarized in Appendix 1, Table 8.

Crop	Proposed MRL (ppm)
Grape	1.4
Fruiting vegetables (crop group 8)	1.6
Cucurbit vegetables (crop group 9)	0.5
Head and Leaf Lettuce	16
Tuberous and Corm vegetables (except potatoes; crop group 1D)	0.02
Grape, Raisin	4.1

The basic acute and refined chronic dietary exposure assessments, using consumption estimates coupled with proposed MRLs, median residue values and experimental processing factors, demonstrates that consumption of the above imported crops treated with fluopicolide as per GAP will not pose a concern to human health for any segment of the population, including infants, children and seniors. For a summary of chronic and acute dietary exposure and risk for

fluopicolide, see Appendix 1, Table 9.

Environmental and Value Assessment

Environmental and value assessments are not required for applications to establish import MRLs.

Conclusion

Following the review of all available data, import MRLs have been established in/on grapes (1.4 ppm), head and leaf lettuce (16 ppm), tuberous and corm vegetables (except potatoes; crop subgroup 1D; 0.02 ppm), fruiting vegetables (crop group 8; 1.6 ppm), cucurbit vegetables (crop group 9; 0.5 ppm) and raisins (4.1 ppm). Residues of fluopicolide on the above noted crops will not pose a concern to human health for any segment of the population, including infants, children and seniors.

List of Abbreviations

AD	administered dose
ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
AUC	area under the curve
bw	body weight
BAM	2,6-dichlorobenzamide
BROD	benzoxyresorufin O-debenzylase
CAF	composite assessment factor
CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
EU	European Union
F	female
g	gram(s)
GAP	Good Agricultural Practices
GD	gestational day
ha	hectare(s)
HAFT	highest average field trial
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
Kow	*n*-octanol-water partition coefficient
L	litre(s)
LC	liquid chromatography
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level

M	male
MAS	maximum average score
mg	milligram(s)
MIS	maximum irritation score
mL	millilitre(s)
MOE	margin of exposure
MRL	Maximum Residue Limit
MS	mass spectrometry
MTD	maximum tolerable dose
NAFTA	North American Free Trade Agreement
nm	nanometre(s)
NOAEL	no observed adverse effect level
Pa	Pascal
PCA	3-chloro-5-(trifluoromethyl)pyridine-2-carboxylic acid
PCPA	*Pest Control Product Act*
PHI	pre-harvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
PROD	pentoxyresorufin O-dependentylase
ROLD	repeated oral low dose
SOHD	single oral high dose
SOLD	single oral low dose
t½	half-life
Tmax	time after administration of a dose when maximum plasma concentration is reached
UF	uncertainty factor
U.S.A	United States of America
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Acute Toxicity of Fluopicolide and Its Associated End-use Product (V-10161 4 SC Fungicide)

Study Type	Species	Result	Comment	Reference
Acute Toxicity of Fluopicolide (Technical)				
Oral	Rat	LD_{50} >5000 mg/kg bw	Low Toxicity	1446247
Acute Toxicity of End-Use Product - V-10161 4 SC Fungicide				
Oral	Rat	LD_{50} >5000 mg/kg bw	Low Toxicity	1446378, 1446379

a MAS = maximum average score for 24, 48 and 72 hours

b MIS = maximum irritation score

Table 2 Toxicity Profile of Technical Fluopicolide

Study Type	Species	Results[a] / Comments	Reference
28-day dietary (supplemental)	Mouse	Effect levels were not established since this study was considered to be supplemental. Treatment-related effects consisted of decreased body weights and body weight gains, increased liver weights with centrilobular hepatocyte hypertrophy.	1446284
28-day dietary	Rat	NOAEL: 17.4/17.9 mg/kg bw/day (M/F) LOAEL: 174/184 mg/kg bw/day (M/F) based on kidney effects: renal tubular eosinophilic proteinaceous material and granulation (M). Decreased body weight gains and food conversion (F).	1446285
28-day dietary (Supplemental; non-guideline)	Dog	Effect levels were not established since this study was considered to be supplemental. Treatment-related effects consisted of increased liver weights and liver hypertrophy, increased cholesterol levels.	1446282
90-day dietary	Mouse	NOAEL:161/207 mg/kg bw/day (M/F) LOAEL: 770/965 mg/kg bw/day (M/F) based on body weight gain effects and liver effects (increased liver weights and centrilobular liver hypertrophy (M+F) and oval cell proliferation (F)	1446264, 1446263
90-day dietary	Mouse	NOAEL: 944 mg/kg bw/day LOAEL was not determined. There were no treatment-related effects.	1446262
90-day dietary	Rat	NOAEL: 7.4/8.4 mg/kg bw/day (M/F) LOAEL: 109/119 mg/kg bw/day (M/F) based on decreased body weights, body weight gains, liver effects (centrilobular hepatocytic hypertrophy, increased activated partial thromboplastin time, increased gamma-glutamyl transferase activity, increased liver weights), and kidney lesions (hyaline droplets in the proximal tubules, single cell death in the proximal tubule epithelium, foci of regenerating tubules, and granular casts) (M). Trabecular hyperostosis of the bone joints, and hypertrophy of the *zona glomerulosa* of the adrenals (F).	1446261
90-day gavage	Dog	NOAEL: 1000 mg/kg bw/day LOAEL was not determined. There were no treatment-related effects.	1446266

12-month gavage	Dog	NOAEL:300/1000 mg/kg bw/day (M/F) LOAEL: 1000/not determined mg/kg bw/day (M/F) based on decreased body weight and body weight gain effects	1446268, 1446269
Carcinogenicity (18-month dietary)	Mouse	NOAEL: 64.5 mg/kg bw/day LOAEL: 551 mg/kg bw/day based on decreased body weights, body weight gains, food consumption, and overall food efficiency, increased liver weights and altered liver cell foci. Increased incidence of hepatocellular adenoma at the high dose, which exceeded the maximum tolerable dose (MTD). No increase in the number of tumour at the mid-dose.	1446292
Chronic/ Carcinogenicity (2-year dietary)	Rat	NOAEL: 8.4/10.8 mg/kg bw/day (M/F) LOAEL: 31.5/41.0 mg/kg bw/day (M/F) based on liver and kidney lesions. Liver lesions centrilobular hepatocytic hypertrophy, cystic degeneration, clear foci and eosinophilic foci (M). Kidney lesions included cortical tubular basophilia with hyaline droplets and casts (M), hyperplasia and mineralization of the papillary epithelium (F). **Not carcinogenic.**	1446293, 1446295
Two-generation reproduction (supplemental)	Rat	Effect levels were not established since this study was considered to be supplemental. **Parental:** treatment-related effects consisted of decreased body weight gains and food consumption in F_0. **Offspring toxicity:** treatment-related effects consisted of decreased body weights, body weight gains and food consumption in F_1 **Reproductive toxicity:** there were no treatment-related effects.	1446299

Two-generation reproduction	Rat	**Parental toxicity** NOAEL: 36.4 mg/kg bw/day LOAEL: 145 mg/kg bw/day based on decreased body weights and body weight gains in F_0 and F_1 animals, decreased food consumption in F_0 and F_1, cortical tubular basophilia, medullary granular casts, and cortical scarring in F_0 and F_1 males, interstitial inflammation in F_0 kidneys of males, cortical tubular basophilia and cortical tubular dilatation in F_0 and F_1 in females, corticomedullary mineralization in F_0 and F_1 females. **Offspring toxicity** NOAEL: 36.4 mg/kg bw/day LOAEL: 145 mg/kg bw/day based on decreased body weights and body weight gains. **Reproductive toxicity** NOAEL: 180 mg/kg bw/day LOAEL was not determined. There were no treatment-related effects.	1446296, 1449297, 1446298, 1446299
Developmental toxicity (supplemental)	Rat	Effect levels were not established since this study was considered to be supplemental. **Maternal effects:** There were no treatment-related effects. **Developmental effects:** Foetal and litter incidences of resorptions were markedly increased at the high dose. One total litter loss at the high dose.	1446311

Developmental toxicity	Rat	**Maternal:** NOAEL: 60 mg/kg bw/day LOAEL: 700 mg/kg bw/day based on decreased corrected and not corrected for gravid uterus weights body weight gains during gestational day 7 to 21. **Developmental:** NOAEL: 60 mg/kg bw/day LOAEL: 700 mg/kg bw/day based on decreased foetal weights and crown/rump length, increased incidences of ossification delays and skeletal malformations compared to control animals. **No evidence of increased susceptibility of foetuses compared to adults.**	1446312
Developmental toxicity (supplemental)	Rabbit	Effect levels were not established since this study was considered to be supplemental. **Maternal effects:** decreased body weight gains and food efficiency, death and abortion accompanied by impairments of mobility and consciousness, decreased defecation and hay consumption, hyperactivity and discoloured urine.	1446313
Developmental toxicity	Rabbit	**Maternal:** NOAEL: 20 mg/kg bw/day LOAEL: 60 mg/kg bw/day based on death, abortions and decreased body weight gains **Developmental:** NOAEL: 20 mg/kg bw/day LOAEL: 60 mg/kg bw/day based on abortions and decreased foetal weights and crown-rump length. **No evidence of increased susceptibility of foetuses compared to adults.**	1446314
Reverse gene mutation assay	*Salmonella typhimurium* strains, *E. Coli*	Positive	1446316
Reverse gene mutation assay	*Salmonella typhimurium* strains, *E. Coli*	Negative	1446318, 1446317

Reverse gene mutation assay	*Salmonella typhimurium* strains, *E. Coli*	Negative	1446319
Reverse gene mutation assay	*Salmonella typhimurium* strains, *E. Coli*	Negative	1446321, 1446320
Reverse gene mutation assay	*Salmonella typhimurium* strains, *E. Coli*	Negative	1446323, 1446322
Gene mutations in mammalian cells in vitro	Chinese hamster Lung Cells	Negative	1446327
In vitro unscheduled DNA synthesis	Rat hepatocytes	Negative	1446335
In vitro mammalian chromosomal aberration	Chinese hamster Lung Cells	Positive	1446325
In vitro mammalian chromosomal aberration	Human lymphocytes	Negative	1446326
In vivo mammalian cytogenetics	Mouse	Equivocal	1446333
In vivo mammalian cytogenetics	Mouse	Negative	1446334
In vivo mammalian cytogenetics	Mouse	Negative	1446336
Acute neurotoxicity (supplemental)	Rat	Effect levels were not established since this study was considered to be supplemental. **Systemic effect:** hunched posture, partial palpebral closure, tremor during handling, decreased arousal, decreased activity. **Neurotoxicity:** decreased body temperature at the mid-high and highest dose tested.	1446307, 1446306

Acute neurotoxicity	Rat	**Systemic:** NOAEL: 2000 mg/kg bw LOAEL was not determined. There were no treatment-related effects. **Neutoxicity:** NOAEL: 100 mg/kg bw LOAEL: 2000 mg/kg bw based on decreased body temperature.	1446302, 1446301
90-day neurotoxicity	Rat	**Systemic:** NOAEL: 15 mg/kg bw/day LOAEL: 107 mg/kg bw/day based on decreased body weights, body weight gains and food efficiency, and kidney effects (centrilobular hepatocytic hypertrophy, cortical tubules with hyaline droplets and associated inflammation, medullar casts and tubular dilatation). **Neutoxicity:** NOAEL: 781 mg/kg bw/day LOAEL was not determined. There were no treatment-related effects.	1446304, 1446303, 1446308

Metabolism		**Absorption:** Fluopicolide was readily absorbed. Absorption and excretory patterns did not exhibit gender-related variability, but blood/plasma kinetic studies suggest near-saturation of absorption at the high dose (100 mg/mg bw). Absorption was estimated to be 59.0% for males and 64.0% for females. **Distribution:** Fluopicolide was distributed in all organs and tissues and its metabolites do not appear to undergo any significant tissue sequestration. With the exception of transiently higher levels in the liver, kidneys, and intestines during the elimination phase, radioactivity concentrations in any given tissue consistently represented <1% of the administered dose within 24 hours of administration of AE C638206. **Excretion:** Faecal elimination accounted for 68.8% to 72.3% of the AD, whereas urinary excretion for 18.8% to 21.4% of the AD in both sexes. Bile excretion studies confirmed that 51.7% of the AD in both sexes was excreted in duct bile duct with a possible entero-hepatic circulation. The majority of the radioactivity was almost entirely dissipated within 48 hours followed by a slower biphasic elimination phase. The mean $t_{1/2}$ in plasma was ~14 hours following elimination of a major portion of the AD at 48 hours. There were no significant sex differences. A 10-fold increase of the dose resulted in an AUC ~5-fold higher rather than being 10-fold. **Metabolism:** Fluopicolide was extensively metabolized. The parent compound was absent from urine samples, but present in faecal samples (11% at SOLD, 81% at SOHD, 36% at ROLD). The major metabolites identified were oxidative N-dealkylation cleavage products. Other identified metabolites were sulfate conjugates, aglycones of glucuronide conjugates, one was an aglycone for both sulfate and glucuronide conjugate, some fractions contained both sulfate and glucuronide conjugates, and other stable fractions were aglycones of a sulfate conjugate.	1446346, 1446347, 1446348, 1446349, 1446350, 1446351, 1446352, 1446353, 1446355, 1446356, 1446357, 1446358, 1446359, 1446360, 1446361, 1446362, 1446363, 1446364, 1446365, 1446366, 1446367, 1446369, 1446370, 1446371, 1446372

SPECIAL STUDIES			
Study Type	**Species**	**Results[a] / Comments**	**Reference**
28-day dietary (supplemental mechanistic study)	Mouse	Effect levels were not established since this study was conducted to determine the potential liver changes caused by fluopicolide in mice and, therefore was considered to be supplemental. Treatment-related effects consisted of decreased body weights, body weight gains, and food consumption, increased liver weights with microscopic diffuse, perilobular to panlobular hepatocellular hypertrophy accompanied by decreased vacuaolation. There was an increased hepatocellular proliferation, increased total cytochrome P-450 with increased activities of microsomal benzoxyresorufin O-debenzylase (BROD) and pentoxyresorufin O-depentylase (PROD). Changes similar to those resulting from treatment with phenobarbital.	1446283

a Effects observed in males as well as females unless otherwise reported

Table 3 Acute Toxicity of Metabolites/Impurities of Fluopicolide

Study Type	Species	Result	Comment	Reference
Acute Toxicity of AE 1344122 (plant metabolite)				
Oral	Rat	LD_{50} >5000 mg/kg bw	Low Toxicity	1446249
Acute Toxicity of AE C653711 (BAM, impurity/metabolite)				
Oral	Rat	LC_{50} ♂ = 2000 mg/kg bw ♀= 500 mg/kg bw	Moderately Toxicity **WARNING-POISON**	1446251
Acute Toxicity of AE C657378 (metabolite of BAM)				
Oral	Rat	LD_{50} >5000 mg/kg bw	Low Toxicity	1446250
Acute Toxicity of AE C657188 (PCA, rat/plant metabolite)				
Oral	Rat	2000 mg/kg bw < LD_{50} < 4000 mg/kg bw	Low Toxicity	1446248

Table 4. Toxicity Profile of Metabolites/Impurities of Fluopicolide

Study Type	Species	Results[a] / Comments	Reference
SHORT TERM TOXICITY – AE 1344122 (plant metabolite)			
28-day dietary	Rat	NOAEL: 152 mg/kg bw/day LOAEL: 1495 mg/kg bw/day based on decreased body weights and body weight gains, increased urinary volume and granular casts, tubular degeneration/regeneration and single cell necrosis	1446291
GENOTOXICITY – AE 1344122 (plant metabolite)			
Reverse gene mutation assay	*Salmonella typhimurium* strains	Negative	1446338
Gene mutations in mammalian cells in vitro	Chinese hamster Lung Cells	Negative	1446329
GENOTOXICITY – C653711 (BAM, impurity/metabolite)			
Reverse gene mutation assay	*Salmonella typhimurium* strains	Negative	1446328
Reverse gene mutation assay	*Salmonella typhimurium* strains	Negative	1446340
Gene mutations in mammalian cells in vitro	Chinese hamster Lung Cells	Negative	1446330
SHORT TERM TOXICITY – AE C657378 (metabolite of BAM)			
28-day dietary	Rat	NOAEL: 159 mg/kg bw/day LOAEL: 1775 mg/kg bw/day based on decreased body weight and body weight gain, cytoplasmic changes in periportal hepatocytes accompanied by reduction in periportally stored fat, increased cholesterol, increased kidney weight and increased incidences and severity of basophilic cortical tubules, and decreased urine volume, alteration of the thyroid follicular colloid and flattening of the epithelium of the peripherally located follicles.	1446289
GENOTOXICITY – AE C657378 (metabolite of BAM)			
Reverse gene mutation assay	*Salmonella typhimurium* strains	Negative	1446339
Gene mutations in mammalian cells in vitro	Chinese hamster Lung Cells	Negative	1446331

In vitro unscheduled DNA synthesis	Rat hepatocytes	Negative	1446332
In vitro mammalian chromosomal aberration	Human lymphocytes	Positive	1446344
In vivo mammalian cytogenetics	Mouse	Negative	1446345
GENOTOXICITY – AE C657188 (PCA, rat/plant metabolite)			
Reverse gene mutation assay	*Salmonella typhimurium* strains, *E. coli*	Negative	1446324
Gene mutations in mammalian cells in vitro	Chinese hamster Lung Cells	Negative	1446341
In vitro mammalian chromosomal aberration	Human lymphocytes	Negative	1446342
METABOLISM – AE C657188 (PCA, rat/plant metabolite)			
Metabolism (supplemental)		**Absorption:** From the urine and cage wash recovered at 24 hours post-dosing (87% of AD), it was assumed that PCA was absorbed quickly and was highly bioavailable. **Distribution:** Only the residual carcass and skin and fur retained detectable radioactivity **Excretion:** Most of the AD was excreted in the urine within the first 24 hours (~75%). **Metabolism:** The parent compound was the only significant radioactive peak was detected in both urine (74-79%) and faecal (5.2-7.0%).	1446377
METABOLISM – AE C653711 (BAM, impurity/metabolite)			

Metabolism		**Absorption:** No differences were observed in male and females rats as patterns for absorption, distribution, metabolism, and elimination of the test substance were similar. **Distribution:** At the SOLD, the highest concentrations were found in kidneys and liver. At SOHD, the highest concentration was found in the skin and fur, kidneys, and liver. In the ROLD, the highest concentrations were noted in the skin and fur, kidneys, liver and adrenal. The amount of radioactivity present in tissues at 6-7 days post-dosing was low (1-2% of the AD). No significant metabolism differences were noted regarding the dose levels and repeated administration. **Excretion:** The major route of elimination was urinary for the three protocols tested (53-84%), while the rest was eliminated via the faeces (12-19%). Elimination of the majority of the radioactivity recovered occurred during the first 72 hours post-dosing at the SOLD or on Day 10 after the last dose in the ROLD. During the repeat dose study, elimination by the urine was decreased in favour of faecal elimination. **Metabolism:** The major metabolites identified in urine samples of all doses tested were the unchanged parent (8-18%), mercapturic acid conjugate of hydroxychlorobenzamide (16-26%), cysteine conjugate of hydroxyl-cholorobenzamide (2-12%), and cysteine and O-glucuronide conjugate of chlorobenzamide (3-7%). In the faecal samples, except for the single high dose study in which AE C657378 (~5%) was present, the only major metabolite identified was the unchanged parent (4-10%).	1446374, 1446375, 1446376

a Effects observed in males as well as females unless otherwise reported

Table 5 Toxicology Endpoints for Use in Health Risk Assessment for Fluopicolide

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	UF/CAF[1] or Target MOE[2]
Acute dietary, females aged 13+	NOAEL = 60	Rat developmental toxicity study	Skeletal malformations at maternally toxic dose	300
	ARfD = 0.2 mg/kg bw			
Chronic Dietary	NOAEL = 20	Rabbit developmental toxicity study	Deaths, abortions, and decreased body weight gains in the dams	300
	ADI = 0.067 mg/kg bw/day			
Short-term Dermal	*Not needed at this time*			
Intermediate-term Dermal	*Not needed at this time*			

[1] Dietary scenarios
[2] Exposure scenarios

Table 6 Summary of Residue Definition for Fluopicolide

Matrix		Dietary Exposure Assessment	Enforcement
Plants	Tuberous and Corm vegetables (based on potato)	Parent, BAM, PCA	Parent Only
	All other primary crops	Parent, BAM	Parent Only

Table 7 Summary of fluopicolide Residue Data from Crop Field Trials*

Commodity	Formulation	Total Rate (g a.i./ha)	PHI [1] (days)	Residue Levels (ppm)					
				n	Min.	Max.	HAFT [2]	Median	Std. Dev.
Fruiting vegetables (crop group 8) - U.S.A. label rate: 403-560 g a.i./ha/season; PHI = 2 days									
Tomato	40% SC	399-413	2	24	0.02	0.42	0.38	0.15	0.09
Bell pepper	0.48 kg a.i./L SC	391-401	2	14	0.04	0.56	0.52	0.10	0.16
Chili pepper	40% SC	398-407	2	6	0.08	0.58	0.52	0.30	0.20
Cucurbit vegetables (crop group 9) - U.S.A. label rate: 403-560 g a.i./ha/season; PHI = 2 days									
Cantaloupe	40% SC	395-406	2	18	<0.01	0.26	0.18	0.06	0.06

Summer Squash	40% SC	399-411	2	12	0.01	0.05	0.04	0.03	0.01
Cucumber	40% SC	391-405	2	12	<0.01	0.06	0.05	0.02	0.01
Grape - U.S.A. label rate: 403-560 g a.i./ha/season; PHI = 21 days Greece label rate: 396 g a.i./ha/season; PHI = 28 days									
Grape (US)	40% SC	387-449	20-21	32	0.07	1.10	0.99	0.21	0.29
Grape (EU)	95 g/L EC	386-413	20-22	16	0.11	1.20	1.20	0.39	0.30
Grape (US+EU)	40% SC + 95 g/L EC	386-449	20-22	48	0.07	1.20	1.20	0.24	0.30
Head and leaf lettuce - U.S.A. label rate: 403-560 g a.i./ha/season; PHI = 2 days									
Head Lettuce	0.48 kg a.i./L SC	392-414	2	14	0.46	7.15	6.34	2.39	2.06
Leaf Lettuce	40% SC	391-408	2	14	0.44	11.7	9.78	6.43	2.96
Tuberous and Corm vegetables (except potato) (crop group 1D) - U.S.A. label rate: 403-560 g a.i./ha/season; PHI = 7 days									
Potato (extended to sweet potato)	40% SC	392-417	6-8	38	<0.01	0.02	<0.01	<0.01	0.01

[1] Pre-harvest Interval

[2] Highest Average Field Trial

*The U.S.A. field trials were conducted with a use pattern of 3 applications, yet the use pattern on the registered U.S.A. label allows for a fourth application to these crops. Hence the use pattern from the field trials accounted for 0.7-fold the U.S.A. GAP. The recommended MRLs are expected to encompass any anticipated residues from a fourth application of the product, since the recommended MRLs are higher than the maximum residues from the crop field trials.

The E.U. grape field trials were conducted with a use pattern of 3 applications and 20-22 day PHIs. These PHIs are shorter than the 28 day PHI on the registered Greek label. Residues in grapes from the crop field trials are thus expected to be higher than the residues in grapes treated according to the Greek GAP. Therefore the recommended MRL for grapes is expected to encompass the residues in grapes treated according to the Greek GAP.

Table 8 Fluopicolide MRL Calculations

Crop	Formulation	Rate (g a.i./ha)	PHI	n	MRL Calc. (ppm)	U.S. Tolerance (ppm)	Proposed MRL (ppm)
Grape	40% SC + 95 g/L EC	386-449	20-22	48	1.4	2.0	1.4
Tomato	40% SC	399-413	2	24	0.7	Fruiting vegetables (CG 8)	Fruiting vegetables (CG 8)
Bell Pepper	0.48 kg a.i./L SC	391-401	2	14	0.6		
Chili Pepper	40% SC	398-407	2	6	1.6	1.6	1.6

Cantaloupe	40% SC	395-406	2	18	0.4	Cucurbit vegetables (CG 9) 0.5	Cucurbit vegetables (CG 9) 0.5
Squash	40% SC	399-411	2	12	0.08		
Cucumber	40% SC	391-405	2	12	0.08		
Head Lettuce	0.48 kg a.i./L SC	392-414	2	14	14	Leafy vegetables (CG 4) 25	Head and Leaf lettuce 16
Leaf lettuce	40% SC	391-408	2	14	16		
Potato (extended to sweet potato)	40% SC	392-417	6-8	38	N/A	Tuberous and Corm vegetables (except potatoes; CG 1D) 0.02	Tuberous and Corm vegetables (except potatoes; CG 1D) 0.02
Grape, Raisin	Based on the grape field trial HAFT and processing factor					6.0	4.1

N/A – Not applicable – The MRL calculator was not used based on the residue data.

Table 9 Summary of Chronic and Acute Dietary Exposure and Risk for Fluopicolide

Population Subgroup	% ADI (Refined)
Total Population	2.5
All Infants (<1 year old)	2.7
Children 1-2 years old	4.2
Children 3-5 years old	3.5
Children 6-12 years old	2.4
Youth 13-19 years old	1.8
Adults 20-49 years old	2.4
Adults 50+ years old	2.6
Females 13-49 years old	2.5
Population Subgroup	**% ARfD (Basic; 95th percentile)**
Females 13-49 years old	28.9

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1446247	2000, AE C638206: Rat Acute Oral Toxicity, DACO: 4.2.1
1446248	2000, AE C657188 (Plant metabolite of AE C638206) Rat Acute Oral Toxicity, DACO: 4.2.1

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1446251	2003, AE C653711 (Metabolite of AE C638206) Acute Toxicity in the Rat After Oral Administration, DACO: 4.2.1
1446261	2000, AE C638206: Rat 90-Day Dietary Toxicity Study with 4 Week Off-Dose Period, DACO: 4.3.1
1446262	2000, AE C638206: Mouse 90-Day Dietary Toxicity Study, DACO: 4.3.1
1446263	2001, AE C638206: 90-Day Toxicity Study in the Mouse by Dietary Administration, DACO: 4.3.1 CBI
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1446268	2002, AE C638206: 52-Week Toxicity Study by Oral Route (Gavage) in Beagle Dogs, DACO: 4.3.2 CBI
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1446282	2000, AE C638206 Dog 28-day oral toxicity study, DACO: 4.3.3
1446283	2004, AE C638206: 28-Day Explanatory Toxicity Study in the C57BL/6 Female Mouse, DACO: 4.3.3
1446284	2000, Mouse 28-day dietary toxicity study AE C638206, DACO: 4.3.3
1446285	2000, Rat 28-day dietary toxicity study AE C638206, DACO: 4.3.3
1446287	2003, A Subacute Dermal Toxicity Study in Rats with AE C638206, DACO: 4.3.3
1446289	2003, AE C657378 Subacute Toxicity in Rats (Administration in Diet for 4 Weeks), DACO: 4.3.3
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1446292	2003, AE C638206: Carcinogenicity Study by Oral Route (Dietary Admixture) in C57BL/6 Mice, DACO: 4.4.4
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1446304	2002, AE C638206: Neurotoxicity Study by Dietary Administration to CD Rats for 13 Weeks, DACO: 4.5.12,4.5.13
1446306	2002, AE C638206: Dose Range and Time to Peak Effect in Rats by Acute Oral Administration, DACO: 4.5.12,4.5.13 CBI
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1446312	2004, AE C638206: Rat Oral Developmental Toxicity (Teratogenicity) Study (Including Addendum), DACO: 4.5.2
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1446316	2004, AE C638206: Bacterial Reverse Mutation Test (Including Amendment 2), DACO: 4.5.4
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1446333	2003, AE C638206: Induction of Micronuclei in the Bone Marrow of Treated Mice, DACO: 4.5.7
1446334	2003, AE C638206: Micronucleus-Test on the Male Mouse, DACO: 4.5.7
1446335	2000, AE C638206: In vivo rat liver unscheduled DNA synthesis (DNA repair) test (Including First Addendum), DACO: 4.5.7
1446336	2005, AE C638206: Mouse erythrocyte micronucleus test, DACO: 4.5.7
1446338	2003, AE 1344122 Salmonella / Microsome Test Plate Incorporation and Preincubation Method, DACO: 4.5.8
1446339	2003, AE C657378 Salmonella/Microsome Test Plate Incorporation and Preincubation Method, DACO: 4.5.8
1446340	2003, Salmonella/Microsome Test Plate Incorporation and Preincubation Method, DACO: 4.5.8
1446341	2003, AE 1C657188 V79/HPRT - Test in Vitro for the Detection of Induced Forward Mutations, DACO: 4.5.8
1446342	2003, AE C657188 (metabolite of AE C638206) Induction of Chromosome Aberrations in Cultured Human Peripheral Blood Lymphocytes, DACO: 4.5.8
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1446434	2002, Determination of the Residues of AE C638206 and Metabolites in Wheat (Straw and Grain), Grapes and Cabbage Using LC/MS/MS: Method Validation, DACO: 7.2.1
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1446439	2004, Extraction Efficiency (Radiovalidation) of the Residue Method for the Determination of AE C638206 Residues in Plant Samples Using Aged Radioactive Residues, DACO: 7.2.1
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1446447	2005, Storage Stability of AE C638206 and Metabolites in Potato, Sugar Beet, Tomato and Wheat Processed Commodities, DACO: 7.3
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B. Additional Information Considered

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