5.12 FLUOPICOLIDE (235)

TOXICOLOGY

Fluopicolide is the ISO approved common name for 2,6-dichloro-N-[[3-chloro-5-(trifluoromethyl)-2-pyridinyl]methyl] benzamide (IUPAC nomenclature), which has the CAS No. 239110-15-7. Fluopicolide is a systemic fungicide of the novel chemical class of acylpicolide fungicides and targets oomycetes that cause diseases in a wide range of crops, including potatoes, vegetables and grape vines. Fluopicolide has a new mode of action, which is probably based upon delocalization of spectrin-like proteins. A number of metabolites have been detected in rotational-crop studies and are identified in the present document as M-01 (also known as BAM), M-02, M-04 and M-05. Some studies of metabolism and toxicity have been conducted to investigate the properties of these metabolites.

Fluopicolide is being reviewed for the first time by the present Meeting at the request of the CCPR. All critical studies complied with GLP. Non-GLP studies are identified as such.

Biochemical aspects

In rats given [^{14}C]fluopicolide labelled in either the pyridyl or phenyl rings as a single oral dose at 10 or 100 mg/kg bw, the radiolabel was moderately rapidly absorbed from the gastrointestinal tract (about 70% and 85% of the pyridyl and phenyl labels, respectively). Based on the results of one study of biliary excretion and only for the single dose at 10 mg/kg bw, the extent of oral absorption was 80% for the phenyl radiolabel and 62% for the pyridyl radiolabel. However, blood and plasma kinetic data show that systemic exposure was similar for both the radiolabels and for males and females. The bioavailability of the radiolabel, taking into account the material undergoing enterohepatic recirculation, was calculated to be 75–88% of the administered dose. The t_{max} calculated from plasma concentrations was 7–10 h. There were no significant differences related to sex, high or low doses or multiple doses.

Distribution investigated by dissection and liquid-scintillation counting methods and confirmed by whole-body autoradiography demonstrated that the highest concentrations of radiolabel were in the liver and kidney and, to a lesser extent, in spleen and blood. Tissue concentrations of radiolabel were consistently low and ranged from 0.46% to 1.25 % of the administered dose for the single-dose studies, with a mean of 0.38% for the repeat-dose study.

Elimination from tissues was moderately rapid such that most radioactivity was eliminated within 48 h after dosing; a subsequent slower terminal elimination phase had a a mean $t_{½}$ of about 103 h. Excretion of the 10 and 100 mg/kg bw oral doses was extensive for pyridyl (69–72%) and for phenyl (82–88%) ring radiolabels and was mainly in the faeces. More than 70% of the administered dose was eliminated within 24 h, but the rate of excretion was low thereafter. Extensive biliary excretion (90%) was demonstrated in bile-duct cannulated rats, in which there was also evidence for enterohepatic recirculation. There was a tendency towards a higher urinary excretion of the pyridyl radiolabel (approximately 20% for the dose at 10 mg/kg bw) compared with the phenyl radiolabel (approximately 10 % for the dose at 10 mg/kg bw). This suggests that a proportion of the metabolites that were formed differed between the two radiolabels and were presumably linked to the hydrolysis of the amido group and the formation of M-02 (3-chloro-5-(trifluoromethyl)pyridine-2-carboxylic acid) from the pyridyl ring moiety and M-01 (2,6-dichlorobenzamide) from the phenyl ring.

Fluopicolide was extensively metabolized in the rat. The formation of the metabolites M-01 and M-02 that are also residues in plants was confirmed during the course of the biotransformation investigations. Generally, the biotransformations observed included aromatic-ring hydroxylation, hydrolysis, dealkylation, acetylation, oxidative N-dealkylation and conjugation with glucuronic acid, sulfate and glutathione. The glutathione conjugates were further metabolized by loss of glycine and

glutamic acid to leave cysteine conjugates. The cysteine conjugates were further metabolized either by acetylation to form the mercapturic acids or by carbon–sulfur cleavage followed by S-methylation to form S-methyl metabolites. The S-methyl metabolites were oxidized to both sulfones and sulfoxides.

Toxicological data

The acute toxicity of fluopicolide is low, the oral LD_{50} being > 5000 mg/kg bw in rats. Signs of toxicity at this high dose included piloerection within 1–2.5 h after dosing in all rats. Later on day 1, piloerection was accompanied only by hunched posture and abnormal gait. Recovery was complete by day 3. The acute dermal LD_{50} of fluopicolide in rats was > 5000 mg/kg bw. The 4-h acute inhalation median lethal concentration (LC_{50}) of fluopicolide in rats was > 5.16 mg/L air (the mean achieved concentration). Fluopicolide was not irritating to rabbit skin and was only transiently, slightly irritating to the rabbit eye. Fluopicolide was not a skin sensitizer in the Magnusson and Kligman test in guinea-pigs.

Short-term studies of toxicity with fluopicolide have been performed in rats, mice and dogs. The liver was consistently identified as a target organ in short-term studies in rats, mice and, the kidney was also a target in male and female rats given higher doses. Increased liver weights were observed in mice, rats and dogs in 28-day and 3-month studies and in dogs in a 1-year study. Microscopic changes observed in the liver included centrilobular hepatocyte hypertrophy in mice and rats and an increased incidence and severity of granulated lymphocytes in rats in the 28-day dietary study. Plasma cholesterol concentrations were increased in rats in the 28-day and 3-month studies and in female dogs in the 1-year study, but they were reduced in mice in the 3-month study. Serum albumin concentrations were also reduced in mice in the latter study. The Meeting considered that these observations were suggestive of impairment of hepatic function at high doses. Renal effects were observed only in rats and consisted of kidney-weight increases in males at 28 days and at 3 months and histopathological changes (accumulation of hyaline droplets, single-cell necrosis in the proximal tubule epithelium and small foci of basophilic tubules and granular casts) in males and females at 3 months. Reversibility of the hepatic effects, but not the renal effects, was demonstrated in rats after 3 months of exposure followed by a 28-day recovery period. Other observations made in these short-term studies were restricted to a particular species, sex or treatment duration. They included treatment-related reductions in haemoglobin and erythrocyte volume fraction in male rats and increased urine volume and specific gravity and spleen weight in female rats in the 3-month study.

The NOAELs derived from short-term studies in which fluopicolide was administered orally were between 7 and 17 mg/kg bw per day in mice and rats, and the overall oral NOAEL in dogs was 70 mg/kg bw per day.

In long-term dietary studies in rats and mice, the primary target organs were the liver and kidney. In mice, liver weights were increased at 400 ppm and 3200 ppm in males after 1 year and in males and females after 18 months. Liver masses and nodules were also increased at these doses after 18 months. High incidences of centrilobular hepatocyte hypertrophy were recorded at 400 ppm and 3200 ppm in male and female mice after 18 months. Foci of altered hepatocytes (eosinophilic foci) and hepatocellular adenoma were increased in male and female mice at 3200 ppm, but there was no increase in the occurrence of hepatocellular carcinoma. In rats, liver weights were increased only in males at the highest dose at 2 years and microscopically there was a dose-related increase in the incidence and severity of centrilobular hepatocyte hypertrophy, again in males, at both 1 year and at 2 years. No cytochrome P450-related enzymes were measured in this study. Cystic degeneration of the liver was reported in males in the group at the highest dose at 2 years and there was an increase in the incidence of eosinophilic foci in both males and females at 2 years.

No significant renal changes were observed in mice. Kidney weights of rats were slightly increased at 2 years and renal lesions (cortical tubule-cell basophilia and hyaline droplets and granular and hyaline casts) were reported in male rats, mainly at the highest dietary concentration of

2500 ppm after 1 year, although an increased incidence of cortical tubule cell basophilia was also observed at 750 ppm. After 2 years, there was no further progression of these renal lesions, which were again confined to males and only at the highest dose. The NOAEL was 50 ppm, equal to 7.9 mg/kg bw per day in males and 11.5 mg/kg bw per day in females, on the basis of increased liver weights, enlarged liver, masses and nodules in the liver, and hepatocellular hypertrophy at 400 ppm, equal to 64.5 mg/kg bw per day in males and 91.9 mg/kg bw per day in females, in the 18-monthsdietary study in mice. Fluopicolide induced hepatocellular adenomas in male and female mice at 3200 ppm, equal to 551 mg/kg bw per day in male mice and 772 mg/kg bw per day in female mice. The NOAEL was 200 ppm, equal to 8.4 mg/kg bw per day, on the basis of increased centrilobular hypertrophy of the liver and increased kidney weights at 750 ppm, equal to 32 mg/kg bw per day, in the 2-year dietary study of toxicity and carcinogenicity in rats.

A short-term investigation of the neoplastic hepatic effects in mice given fluopicolide at a dietary concentration of 3200 ppm demonstrated increased cell proliferation after 7 days, but not after 28 days. Biochemical measurements made in these mice after 7 days demonstrated increases in hepatic cytochrome P450 content and hepatic activities of benzyloxyresorufin O-de-ethylase (BROD), ethoxyresorufin O-deethylase (EROD) and pentylresorufin O-dealkylase (PROD) enzymes, some of which were consistent with the induction of CYP2B. A reduction in the hydroxylation of lauric acid also occurred. This pattern of changes is almost identical to the profile reported in mice treated with phenobarbital at 80 mg/kg bw per day and is indicative of a constitutive androstane receptor (CAR)-mediated response. These data are biomarkers for a proposed mode of action for fluopicolide in mouse liver that is similar to that of phenobarbital.

The genotoxic potential of several batches of fluopicolide was investigated in a range of studies in vitro and in vivo. A small number of significant or equivocal responses were observed. A significant response with one batch in a test for mutation in bacteria was not confirmed upon repetition of the study. Another batch was associated with an equivocal response in a test for micronucleus formation in mouse bone marrow and was used in the long-term studies of toxicity and carcinogenicity in mice and rats. Current production batches are of higher purity than those used in the genotoxicity-testing programme. In conclusion, the overall weight of evidence suggested that some batches of fluopicolide can have weak mutagenic properties in vitro or in vivo at toxic doses. The Meeting considered that fluopicolide at current purity levels was unlikely to present a genotoxic hazard to humans.

A significantly increased incidence of hepatocellular adenoma was observed in mice, but is the Meeting proposed that these were induced by a mode of action in which CAR activation is involved. The profile of hepatotoxicology of fluopicolide, including CAR activation, is similar to that observed with phenobarbital, a chemical for which there is extensive experience of exposure in humans, but no evidence for carcinogenicity in humans. The Meeting therefore considered the liver tumours in mice to be of no relevance to humans.

On the basis of the available studies, the Meeting considered that there was no evidence of carcinogenic potential for fluopicolide administered to rats.

The Meeting concluded that fluopicolide was unlikely to be carcinogenic in humans.

In a two-generation study of fluopicolide in rats, there were increased mean absolute and relative kidney and liver weights and reduced spleen weights in males and females at 2000 ppm, the highest dose, but not at lower doses. The NOAEL for systemic toxicity in the parental generation was 500 ppm, equal to 25.5 mg/kg bw per day, on the basis of increases in liver and kidney weights of rats at 2000 ppm, equal to 103.4 mg/kg bw per day. In the multigeneration study in rats, the NOAEL for reproductive toxicity was 2000 ppm, equal to 103.4 mg/kg bw per day (the highest dose tested) for F_0 rats for the period before pairing. The overall NOAEL for pups and developing offspring was 500 ppm, equal to 25.5 mg/kg bw per day, on the basis of reduced body-weight gains of pups during lactation and reduced absolute spleen and thymus weights in males and females of the F_1 and F_2 generations at 2000 ppm, equal to 103.4 mg/kg bw per day.

In a study of developmental toxicity in which rats were given fluopicolide by gavage on days 7–20 of gestation, the NOAEL for maternal toxicity and fetotoxicity was 60 mg/kg bw per day on the basis of slightly decreased body weight in dams and reduction in mean fetal body weights and crown–rump lengths in fetuses at 700 mg/kg bw per day. Further evidence for fetotoxicity at this dose was provided by increased incidences of anomalies of the thoracic vertebrae, sternebrae and ribs as well as delayed ossification.

In a study of developmental toxicity in which rabbits were given fluopicolide by gavage on days 6–28 of gestation, the NOAEL for maternal toxicity and fetotoxicity in rabbits was 20 mg/kg bw per day on the basis of mortality, a high incidence of premature delivery and reduction in body-weight gain and food consumption in dams and reduction in fetal body weights and fetal crown–rump lengths in fetuses at doses of 60 mg/kg bw per day.

The Meeting concluded that fluopicolide causes fetotoxicity and skeletal anomalies only at doses that are also maternally toxic.

In a study of neurotoxicity in rats given a single dose of fluopicolide by gavage, the NOAEL was 100 mg/kg bw on the basis of reduction in body temperature and increased incidence of excessive grooming in females at 2000 mg/kg bw. In a 90-day study of neurotoxicity in rats given diets containing fluopicolide, the NOAEL was 200 ppm, equal to 15.0 mg/kg bw per day, on the basis of impaired growth and histopathological changes in the liver and kidney at 1400 ppm, equal to 106.6 mg/kg bw per day. The NOAEL for neurotoxicity was 10 000 ppm, equal to 781 mg/kg bw per day, the highest dose tested.

The Meeting concluded that fluopicolide is unlikely to cause neurotoxicity in humans.

Toxicological data on metabolites

Some aspects of the toxicology of four metabolites of fluopicolide – M-01 (BAM) or 2,6-dichlorobenzamide, M-02 or 3-chloro-5-(trifluoromethyl)pyridine-2-carboxylic acid, M04 or 2,6-dichloro-3-hydroxybenzamide M-05 or 3-(methylsulfinyl)-5-(trifluoromethyl)pyridine-2-carboxylic acid – were reported. These metabolites are also found as residues in crops. The radiolabelled phenyl metabolite, M-01, has been subjected to kinetic and metabolic studies in rats given oral doses. The highest tissue concentrations were seen in the kidney and liver of rats at 10 mg/kg bw and in the skin and fur, kidneys and liver of rats at 150 mg/kg bw. Tissue concentrations increased by approximately five-fold for a fifteen-fold increase in dose and multiple dosing did not indicate any bioaccumulation. The radiolabel was eliminated mostly in the urine (approximately 82% of the administered dose), with low levels eliminated in the faeces (approximately 13% of the administered dose). The rate of elimination was relatively slow. Biotransformation showed no sex-specific or dose-dependent differences and consisted of hydrolysis of the amide group, hydroxylation and subsequent conjugation with either glucuronic acid or sulfate, and the loss of a chlorine atom followed by glutathione conjugation and further metabolism of the glutathione group to mercapturic acid or S-methyl metabolites.

The pyridyl metabolite, M-02, was well absorbed, with minimum mean absorption calculated to be 87%. Elimination was rapid from both male and female rats, with at least 90% of the total administered radioactivity eliminated within the first 48 h after dosing. The total recovery in urine accounted for about 80% of the administered dose, with faecal elimination accounting for about 7% of the administered dose. Unchanged M-02 accounted for most of the eliminated material.

The acute toxicity of M-01 is relatively low, with an oral LD_{50} of 2000 mg/kg bw in male rats and 500 mg/kg bw in female rats, while the acute toxicity of M-02, M-04 and M-05 can be described as very low, oral LD_{50} values being > 2000 mg/kg bw for with M-02 and M-04 in rats and > 5000 mg/kg bw for M-05. Thus, only M-01 has an acute toxicity that is higher than that of fluopicolide.

In a 28-day study of dietary toxicity with M-02 in rats, no treatment-related change was seen in mean terminal body weights, mean absolute and relative organ weights, gross post-mortem or microscopic examination. The NOAEL for M-02 was 20000 ppm, equal to 1574 mg/kg bw per day, the highest dose tested.

In a 28-day study of dietary toxicity with M-04 in rats, the NOAEL was 2000 ppm, equal to 159.2 mg/kg bw per day, on the basis of lower body weights, reduced haemoglobin concentration, increased plasma cholesterol concentration, liver and kidney weights and histological findings in the liver, kidney and thyroid at 20000 ppm, equal to 1775 and 1931 mg/kg bw per day in males and females, respectively.

In a 28-day dietary study of toxicity with M-05 in rats, the NOAEL was 2000 ppm, equal to 152 mg/kg bw per day, on the basis of clinical signs, reductions in body weight and food consumption and renal effects at 20000 ppm, equal to 1775 mg/kg bw per day. An increase in liver weight at this, the highest, dose was not accompanied by microscopic changes.

In a 13-week dietary study of toxicity with M-01 in rats, no effects on liver or kidney function were observed. The NOAEL for M-01 was 180 ppm, equal to 14 mg/kg bw per day, on the basis of reductions in food consumption and body-weight gain and reduced skeletal muscle tone at 600 ppm, equal to 49 mg/kg bw per day.

In a 13-week study of dietary toxicity with M-01 in dogs, the NOAEL was 300 ppm, equivalent to 22.5 mg/kg bw per day, on the basis of clinical signs and increases in liver weight and serum alkaline phosphatase activity at 2000 ppm, equivalent to 150 mg/kg bw per day. Increased liver weight at 300 ppm was not considered to be toxicologically significant.

In a 2-year dietary study with M-01 in dogs, the NOAEL was 180 ppm, equal to 4.5 mg/kg bw per day, on the basis of reduced body-weight gain at 500 ppm, equal to 12.5 mg/kg bw per day.

In a 2-year study with M-01 in rats, the liver was the primary target for toxicity. These effects were largely confined to females and consisted of increased incidences of vacuolation, fat deposition, hepatocyte degeneration, eosinophilic foci and basophilic foci in the liver. There was also an increased incidence of hepatocellular adenomas that was marginally statistically significant ($p = 0.05$). No relevant data on historical controls were available to assist in an evaluation of this result. The NOAEL was 60 ppm, equal to 2.0 mg/kg bw per day, based on body-weight reductions, increased incidences of eosinophilic and basophilic foci in the livers and fat deposition and cellular degeneration in the liver at 100 ppm, equal to 3.5 mg/kg bw per day.

These metabolites were tested for genotoxicity in an adequate range of assays. M-01 and M-04 were tested in vitro and in vivo, while M-02 was tested in vitro. M-05 was tested in vitro for mutagenicity in bacteria and V79 cells. No evidence of genotoxicity was observed for M-01, M-02 or, in a more limited test profile, M-05. There was no evidence for mutagenicity with M-04 in bacteria or V79 cells, although there the proportion of chromosomal aberrations was increased in treated human lymphocytes in culture. In a test for unscheduled DNA synthesis in rat liver in vivo and an assay for micronucleus formation in mouse bone-marrow cells in vivo, there was no evidence for genetic toxicity or mutagenicity with M-04. The Meeting noted, for consideration of ARfDs, that clinical signs of toxicity were observed in the dose-range finding study in mice given a single dose of 100 mg/kg bw (the lowest dose tested) by gavage. Thus the mutagenic (clastogenic) activity observed in vitro was not confirmed in vivo. The Meeting concluded that M-01, M-02 and M-04 are unlikely to be genotoxic.

In a three-generation study with M-01 in rats, the NOAEL for parental toxicity and for reproductive toxicity was 180 ppm, equal to 13.5 mg/kg bw per day (the highest dose tested), on the basis of the absence of parental toxicity and reproductive toxicity. The NOAEL for fetal toxicity was 100 ppm, equal to 7.5 mg/kg bw per day, on the basis of increased liver weights relative to body weights at 180 ppm, equal to 13.5 mg/kg bw per day.

In a study of developmental toxicity in rabbits given M-01 by gavage on days 7–19 of gestation, the NOAEL for maternal toxicity and fetoxocity was 30 mg/kg bw per day on the basis of maternal mortality and abortions in dams and slightly reduced birth weights at 90 mg/kg bw per day. M-01 was not teratogenic in the study of developmental toxicity in rabbits. Data for individual rabbits were examined for effects that may have been produced by a single or small number of doses, but none were found.

In conclusion, in studies of acute toxicity and in long-term studies of toxicity, M-01 is more toxic than fluopicolide, while the data show that the metabolites M-02, M-04 and M-05 are less toxic than parent fluopicolide. In the case of M-04, there are clear similarities with the toxicity profile of fluopicolide. A weak tumorigenic response to M-01 in the liver of female rats would appear to have no significance for an interpretation of the fluopicolide-associated liver tumours, which were found in male and female mice, but not in rats. In view of the lack of genotoxicity and the occurrence of benign tumours only at a high dose, the Meeting concluded that M-01 was unlikely to be carcinogenic in humans at estimated dietary levels of exposure.

No reported incidents of adverse reactions during the pilot-scale manufacture or formulation of fluopicolide. No further information on medical surveillance or poisoning incidents was available.

The Meeting concluded that the existing database on fluopicolide was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

Fluopicolide and M-01 (2,6-dichlorobenzamide)

Fluopicolide

An ADI of 0–0.08 mg/kg bw was established for fluopicolide based on the NOAEL of 7.9 mg/kg bw per day, identified on the basis of organ weight increases and gross and microscopic changes in the liver and kidneys in an 18-month dietary study of toxicity and carcinogenicity in mice, supported by the NOAEL of 8.4 mg/kg bw per day identified on the basis of histopathological changes in the liver and increased kidney weights in a 2-year dietary study of toxicity and carcinogenicity in rats, and with a safety factor of 100.

An ARfD of 0.6 mg/kg bw was established for women of child-bearing age based on a NOAEL of 60 mg/kg bw per day identified on the basis of a marginally increased incidence of skeletal defects of the vertebrae and sternebrae, which might be attributable to a single exposure to fluopicolide at 700 mg/kg bw per day in a study of developmental toxicity in rats, and with a safety factor of 100.

The Meeting concluded that the establishment of an ARfD for the general population was not necessary for fluopicolide on the basis of its low acute toxicity, the lack of evidence for any acute neurotoxicity and absence of any other toxicologically relevant effect that might be attributable to a single dose.

M-01 (2,6-dichlorobenzamide)

An ADI of 0–0.02 mg/kg bw was established for the fluopicolide metabolite M-01 based on the NOAEL of 2.0 mg/kg bw per day identified on the basis of microscopic changes in the liver in a 2-year dietary study of toxicity and carcinogenicity in rats, supported by the NOAEL of 4.5 mg/kg bw per day, identified on the basis of reduced body weight gain in a 2-year dietary study of toxicity in dogs, and with a safety factor of 100.

The Meeting concluded that the establishment of an ARfD for the general population should be considered based on the finding of mortality at single oral doses of less than 500 mg/kg bw in

female rats. An LOAEL of 100 mg/kg bw was identified on the basis of clinical signs of toxicity in a dose range-finding study in mice given a single dose of M-01, but this study did not provide sufficient detail for it to be used as the basis for an ARfD by itself. In the absence of adequate data, an ARfD for the general population was established for the metabolite, based on the value of 0–0.6 mg/kg bw for the parent compound. This value is derived from a study of developmental toxicity in rats and a safety factor of 100, as described above. The ARfD derived from a study with fluopicolide is sufficiently protective for application to the metabolite M-01, owing to the large dose-spacing between the LOAEL and the NOAEL.

A toxicological monograph was prepared.

Levels relevant to risk assessment for fluopicolide

Species	Study	Effect	NOAEL	LOAEL
Mouse	18-month study of toxicity and carcinogenicity	Toxicity	50 ppm equal to 7.9 mg/kg bw per day	400 ppm equal to 64.5 mg/kg bw per day
		Carcinogenicity	400 ppm equal to 64.5 mg/kg bw per day	3200 ppm equal to 552 mg/kg bw per day
Rat	Two-year studies of toxicity and carcinogenicity	Toxicity	200 ppm equal to 8.4 mg/kg bw per day	750 ppm equal to 32 mg/kg bw per day
		Carcinogenicity	2500 ppm equal to [a]109.4 mg/kg bw per day	—
	Two-generation study of reproductive toxicity	Reproductive toxicity	2000 ppm equal to [a]103.4 mg/kg bw per day	—
		Parental toxicity	500 ppm equal to 25.5 mg/kg bw per day	2000 ppm equal to 103.4 mg/kg bw per day
		Offspring toxicity	500 ppm equal to 25.5 mg/kg bw per day	2000 ppm equal to 103.4 mg/kg bw per day
	Developmental toxicity	Maternal toxicity	60 mg/kg bw per day	700 mg/kg bw per day
		Embryo and fetal toxicity	60 mg/kg bw per day	700 mg/kg bw per day
Rabbit	Developmental toxicity	Maternal toxicity	20 mg/kg bw per day	60 mg/kg bw per day
		Embryo and fetal toxicity	20 mg/kg bw per day	60 mg/kg bw per day
Dog	Three-month study of toxicity	Toxicity	70 mg/kg bw per day	1000 mg|kg bw per day

[a] Highest dose tested.

Levels relevant to risk assessment for M-01 (2,6-dichlorobenzamide)

Species	Study	Effect	NOAEL	LOAEL
Mouse	Dose-range finding study of toxicity for a test of micronucleus formation	Toxicity	—	100 mg/kg bw
Rat	Two-year studies of toxicity and carcinogenicity	Toxicity	60 ppm, equal to 2.0 mg/kg bw per day	100 ppm, equal to 3.5 mg/kg bw per day
		Carcinogenicity	180 ppm equal to 5.7 mg/kg bw per day	500 ppm equal to 17.6 mg/kg bw per day
	Two-generation study of reproductive toxicity	Reproductive toxicity	180 ppm equal to 13.5 mg/kg bw per day	—
		Parental toxicity	180 ppm equal to 13.5 mg/kg bw per day	—
		Offspring toxicity	100 ppm equal to 7.5 mg/kg bw per day	180 ppm equal to 13.5 mg/kg bw per day
Rabbit	Developmental toxicity	Maternal toxicity	30 mg/kg bw per day	90 mg/kg bw per day
		Embryo- and fetal toxicity	30 mg/kg bw per day	90 mg/kg bw per day
Dog	Two-year study of toxicity	Toxicity	180 ppm, equal to 4.5 mg/kg bw per day	500 ppm, equal to 12.5 mg/kg bw per day

Estimate of acceptable daily intake for humans

Fluopicolide	0–0.08 mg/kg bw
M-01[33]	0–0.02 mg/kg bw

Estimates of acute reference doses

Fluopicolide	0.6 mg/kg bw for women of child-bearing age
	Unnecessary for the general population
M-01	0.6 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

[33] 2,6-dichlorobenzamide

Critical end-points for setting guidance values for exposure to fluopicolide and its metabolite M-01 (2,6-dichlorobenzamide)

Absorption, distribution, excretion and metabolism in mammals		
Rate and extent of oral absorption	Moderately rapid and moderately extensive, at least 80%	
Distribution	Distributed throughout the body; higher concentrations in liver, kidney and blood	
Potential for accumulation	No evidence for accumulation	
Rate and extent of excretion	Moderately rapid, > 70% within 24 h, but subsequently low rate with 95% within 48 h, mainly in faeces	
Metabolism in animals	Extensively metabolised; biotransformations observed included aromatic ring hydroxylation, hydrolysis, dealkylation, acetylation, oxidative N-dealkylation and conjugation with glucuronic acid, sulfate and glutathione. Up to 46 radiolabelled components in urine and faeces	
Toxicologically significant compounds (animals, plants and environment)	Parent, M-01	
Acute toxicity	Fluopicolide	2,6-Dichlorobenzamide (M-01)
Rat, LD_{50}, oral	> 5000 mg/kg bw	2000 mg/kg bw in males, 500 mg/kg bw in females
Rat, LC_{50}, inhalation	> 5.2 mg/L[a] (4 h)	No data
Rat, LD_{50}, dermal	> 5000 mg/kg bw[a]	No data
Rabbit, dermal irritation	Not an irritant	No data
Rabbit, ocular irritation	Slightly, transiently irritating	No data
Guinea-pig, dermal sensitization	Not sensitizing (Magnusson and Kligman test)	No data
Short-term studies of toxicity		
Target/critical effect	Liver, kidney	Body-weight gain; muscle tone
Lowest relevant oral NOAEL	7.4 mg/kg bw per day (3-month study in rats) 300 mg/kg bw per day (1-year study in dogs)	14 mg/kg bw per day (3-month study in rats 4.5 mg/kg bw per day (2-year study in dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day[a] (28-day study in rats)	No data
Genotoxicity	A small number of inconsistent positive or equivocal responses were observed, but the overall weight of evidence is that it is unlikely to be genotoxic.	Not genotoxic

Long-term studies of toxicity and carcinogenicity		
Target/critical effect	Liver	Liver
Lowest relevant NOAEL	7.9 mg/kg bw per day (18-month study in mice)	60 ppm equal to 2 mg/kg bw per day (2-year study in rats
Carcinogenicity	Benign liver tumours in mice that are of no human relevance, based on mode of action	Benign liver tumours in rats that are unlikely to pose a risk to humans
Reproductive toxicity		
Reproductive target/critical effect	No reproductive toxicity	No reproductive toxicity
Lowest relevant reproductive NOAEL	2000 ppm equal to 103 mg/kg bw per day	180 ppm equal to 13.5 mg/kg bw per day
Developmental target/critical effect	Not teratogenic; abortions, total litter loss, reduced fetal body weight and pup body weight during lactation, delayed ossifications, vertebral and sternebral defects	Not teratogenic; abortions, reduced fetal body weight, increased relative liver-to-body weight
Lowest relevant developmental NOAEL	60 mg/kg bw per day (rat),	30 mg/kg bw per day (rabbit)
	20 mg/kg bw per day (rabbit)	
Neurotoxicity/delayed neurotoxicity		
	No signs of neurotoxicity	No data
Other toxicological studies		
	Induction of liver xenobiotic metabolizing enzymes in female mice and male and female rats	No data
	Several metabolites that are also crop residues have been investigated, but only M-01 (2,6-dichlorobenzamide) was more toxic than fluopicolide in a single-dose and a long-term study.	
Medical data		
	No reports of toxicity in workers exposed during pilot scale manufacture or formulation	

[a] Highest dose tested

Summary

Fluopicolide	**Value**	**Study**	**Safety factor**
ADI	0–0.08 mg/kg bw	Mouse, 18-month study of toxicity and carcinogenicity	100
ARfD	0.6 mg/kg bw for women of child-bearing	Rat, study of developmental toxicity	100

	age		
M-01 (2,6-dichlorobenzamide)			
ADI	0–0.02 mg/kg bw	Rat, 2-year study of toxicity and carcinogenicity	100
ARfD	0.6 mg/kg bw general population	Rat, study of developmental toxicity on the parent compound	100

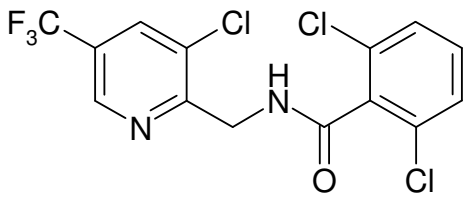
[a] Only dose tested.

RESIDUE AND ANALYTICAL ASPECTS

Fluopicolide belongs to the benzamide and pyridine class of fungicide. It is a meso-systemic fungicide; it translocates toward the stem tips via the xylem but it does not translocate toward the roots. Fluopicolide is effective against a wide range of Oomycete (Phycomycete) diseases including downy mildews (Plasmopara, Pseudoperonospora, Peronospora and Bremia), late blight (Phytophthora), and some Pythium species. The Meeting received information on fluopicolide metabolism and environmental fate, methods of residue analysis, freezer storage stability, national registered use patterns, supervised residue trials, farm animal feeding studies and fates of residues in processing.

The 2009 JMPR established ADIs for fluopicolide and 2,6-dichlorobenzamide of 0–0.08 and 0–0.02 mg/kg bw respectively. For fluopicolide the ARfD is 0.6 mg/kg bw for women of child-bearing age with an ARfD not necessary for other groups of the population. The Meeting set an ARfD for 2,6-dichlorobenzamide of 0.6 mg/kg bw for the general population.

Fluopicolide is 2,6-dichloro-N-{[3-chloro-5-(trifluoromethyl)-2-pyridinyl]methyl}benzamide.



The following abbreviations are used for the metabolites discussed below:

M-01 or BAM:	2,6-dichlorobenzamide
M-02:	3-chloro-5-(trifluoromethyl)pyridine-2-carboxylic acid
M-04:	2,6-dichloro-3-hydroxybenzamide
M-05:	3-(methylsulfinyl)-5-(trifluoromethyl)pyridine-2-carboxylic acid
M-06:	2,6-dichloro-N-[(3-chloro-5-trifluoromethylpyridin-2-yl) methyl]-3-hydroxybenzamide
M-07	2,6-dichloro-N-[(3-chloro-5-trifluoromethylpyridin-2-yl) methyl]-4-hydroxybenzamide

M-18: 2,4-dichloro-3-[({[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}amino)carbonyl] phenyl hydrogen sulphate or 3,5-dichloro-4-[({[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}amino)carbonyl] phenyl hydrogen sulfate

M-19: 3,5-dichloro-4-[({[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}amino)carbonyl] hydroxyphenyl hydrogen sulfate

Animal metabolism

Radiolabelled fluopicolide (separately ^{14}C-labelled at the [pyridyl-2,6-^{14}C]- and [phenyl-U-^{14}C]-rings) was used in the metabolism and environmental studies. The metabolism of laboratory animals was qualitatively the same as for farm animals though some species-related differences were noted.

Lactating cows were orally dosed with [pyridyl-2,6-^{14}C]- or [phenyl-U-^{14}C]-fluopicolide at doses equivalent to approximately 1 or 10 ppm in the feed for 7 consecutive days.

The majority of the administered doses were recovered in excreta (55–69% in faeces, 11–19% in urine) with an additional 0.87–2.1% recovered from the cage wash. Radioactivity retained in tissues, bile or secreted in milk accounted for less than 1% of the administered dose. Overall 76–84% of administered radioactivity was accounted for.

Radiocarbon content in various tissues were highest in liver followed by kidney, fat and muscle while in milk radioactive residues were low, being lower than those observed in muscle. Following dosing equivalent to 10 ppm in the diet radioactivity was 0.45–0.64 mg/kg in liver, 0.2–0.3 mg/kg in kidney, 0.04 mg/g in fat, 0.01–0.02 mg/kg in muscle and 0.01–0.02 mg/kg in milk. Fluopicolide was the major component of the extracted radioactivity identified in muscle (5.1%), fat (64–78%) and milk (37%) samples and was also present in liver (0.9–2.9%) and kidney (0.7–1.8%). A large number of metabolites were present in extracts of liver and kidney, each accounting for less than 10% of the TRR, most notably mono- and di-hydroxy-glucuronides of fluopicolide as well as mono- and dihydroxy-sulphate conjugates of fluopicolide (M-18, M-19).

Investigations into polar metabolites in liver and kidney demonstrated that they were associated with amino acids, peptides and proteins. There was no significant association of the radioactive residues of fluopicolide with RNA or DNA.

Laying hens were orally dosed with [pyridyl-2,6-^{14}C]- or [phenyl-U-^{14}C]-fluopicolide at doses equivalent to approximately 1 or 10 ppm in the feed for 14 days. The majority of the administered radioactivity was excreted (82–95% over the 14 day dosing period), with 0.6–2.8% recovered from cage wash and approximately 0.08–0.13% in eggs (white and yolks). In tissues from the 10 ppm dose groups, the highest concentrations of radioactivity were in liver (0.28–0.98 mg/kg), followed by fat (0.03–0.06 mg/kg) and muscle (0.01–0.04 mg/kg). Fluopicolide represented 11% of the radioactivity in yolks and 0–2.5% in egg whites. The major component of the radioactivity in egg whites (51%) was tentatively assigned to a methylsulphone conjugate of fluopicolide; the conjugate was also present in fat (38% TRR). A large number of degradates were present in the eggs and tissues, most notably M-01 (37% liver TRR), M-06 in liver (5.4% TRR) and skin plus fat (38% TRR), M-07 in egg white (41% TRR), egg yolk (9.6–16% TRR), liver (5.9% TRR) and fat (47% TRR). Monohydroxy-sulphate (M-18 10% TRR in yolk and liver) and dihydroxy-sulphate conjugates (M-19 23% egg white TRR, 15–34% yolk TRR) were also observed but no mono- and dihydroxy-glucuronides.

As with lactating cows, investigations into polar metabolites in liver demonstrated that they were associated with amino acids, peptides and proteins and that there was no significant association of the radioactive residues of fluopicolide with RNA or DNA.

In summary, in livestock the majority of the administered radioactivity was recovered in the excreta (75–95% of dose) leaving only low levels of radioactivity in the tissues (0.06–0.78%), milk

(0.08–0.14%) and eggs (0.08–0.13%). The highest tissue concentrations were consistently observed in the liver of cow and hen at both dose levels. There was no evidence of any accumulation of radioactivity in milk, eggs or edible tissues.

The identified metabolites of fluopicolide in the cow and hen are thought to be formed by hydroxylation of the chlorophenyl ring in the meta- and para- positions to give metabolites M-07 and M-06, respectively. Each of these metabolites is conjugated with sulphate or hydroxylated in a second position to give a proposed dihydroxy intermediate, which is further metabolised to a sulphate conjugate. In the cow, conjugation with glucuronic acid was also observed. Additionally a methyl sulphone conjugate of fluopicolide and M-01 have been observed in the hen.

Plant Metabolism

The Meeting received information on the fate of [^{14}C]fluopicolide after foliar application to grapes, lettuce and potato and also as a soil drench to lettuce.

Metabolism studies in grapes, lettuce and potato demonstrated that following foliar application, fluopicolide was not metabolised to any great extent. With up to three consecutive foliar applications of fluopicolide to grapes, lettuce and potato, parent compound was the major component of the radioactive residues at 87–95%, 96% and 51–70% of the TRR respectively for grapes (berries), lettuce (leaves) and potato (tubers). When applied as a soil drench to lettuce parent compound was the major component of the TRR in lettuce at harvest (72% TRR). Minor metabolites (< 0.035 mg/kg) identified in the studies were M-01 (1.3–25% TRR), M-02 (0.6–26% TRR) and M-06 (0.1–2.8% TRR) with the higher levels of metabolites resulting from uptake from soil (lettuce following a soil drench or in potato tubers following foliar sprays). Surface washes of samples removed the majority of the residue, decreasing with time after spraying.

Metabolism of fluopicolide is proposed to occur through hydrolysis of the amide bond of fluopicolide to form metabolites M-01 and M-02 and hydroxylation in position 3 of the phenyl ring to form metabolite M-06.

Environmental fate

Photolytic degradation of fluopicolide occurs to some extent and may contribute to its degradation. Fluopicolide is considered stable to hydrolysis.

The aerobic degradation of fluopicolide in soil is primarily via oxidative cleavage to produce, M-01 and M-02. Ultimately mineralisation to $^{14}CO_2$ occurs. The half-life for disappearance of parent fluopicolide in soil is estimated to be > 200 days. Fluopicolide is considered to be persistent.

Residues in succeeding crops

The log K_{ow} of fluopicolide (log K_{ow} 2.9) and the results of the lettuce and potato metabolism studies suggest fluopicolide may be translocated in plants. In confined and field rotational crop studies, residues of fluopicolide were found in leafy and brassica vegetables, root vegetables, and cereal and pulse grain at harvest. In confined rotational crop studies with radiolabelled fluopicolide metabolites M-01, M-02 and M-04 occurred at levels higher than fluopicolide in some matrices, principally wheat grain and forage. In lettuce and radish (root and tops), the main residues were fluopicolide and M-01. Residues of M-06, M-08 and M-09 were also detected but the levels were lower than for fluopicolide. The levels of fluopicolide and metabolites in field rotational crop studies on wheat were < 0.01–0.12 mg/kg for fluopicolide, < 0.01–0.06 mg/kg for M-01, < 0.01–0.02 mg/kg for M-02, < 0.01–0.09 mg/kg for M-04 and < 0.01–0.08 mg/kg for M-05 in forage, straw and grain. For cabbage, faba beans (shoots, pods and dried seed) and radish (root and tops) residues were < 0.01–0.03 mg/kg for fluopicolide, < 0.01–0.10 mg/kg for M-01 and < 0.01–0.02 mg/kg for M-02. It is concluded that rotational crops may contain low levels of residues of fluopicolide and metabolites.

Analytical methods

Several different analytical methods have been reported for the analysis of fluopicolide and selected metabolites/degradates in plant material (M-01, M-02) and fluopicolide in animal commodities. The basic approach employs extraction by homogenisation with acetonitrile:water, and column clean-up using SPE. Residues are determined by liquid chromatography with mass spectra detection. The methods for fluopicolide and selected metabolites have been validated with for a range of substrates with LOQs of 0.01 mg/kg for each analyte. Studies on extraction efficiency indicated greater than 80% of the residue is able to be extracted with acetone:water.

The official German multi-residue method (DFG-S19) with LC-MS/MS detection was validated for fluopicolide; M-01, M-02 in plant, and fluopicolide in animal commodities. LOQs were also 0.01 mg/kg for each analyte.

Stability of pesticide residues in stored analytical samples

Freezer storage stability was tested for a range of representative substrates. Fluopicolide, M-01 and M-02 residues are stable in grapes, potatoes, cabbages and wheat grain for at least 30 months frozen storage. Fluopicolide, M-01, M-04 and M-05 are stable in wheat straw for at least 18 months frozen storage. Data on freezer storage stability showed that fluopicolide, M-01 and M-02 residues are stable in milk for at least 2 months, in fat and muscle for at least 4 months and in liver and kidney for at least 9 months.

Definition of the residue

The metabolism of fluopicolide in a range of crops has been studied following both foliar and soil drench application. Studies were conducted with leafy vegetables (lettuce), root vegetables (potatoes) and fruit crops (grape vine). Each was conducted with both phenyl- and pyridyl-radiolabelled fluopicolide. The rate of degradation on plants is low and the parent compound was always the major component (51–96% TRR). Metabolites M-01 and M-02 were present at 1.3–25% and 0.6–26% respectively. Minor metabolites M-04, M-05, M-08 and M-09 were found in plant matrices at low levels ($\leq$ 2.8% TRR) but not in rat metabolism studies.

In rotational crop studies fluopicolide and M-01 were generally the main components of the residue. The Meeting considered the acute and long term toxicity of M-01 is higher than fluopicolide while the available data show that the metabolites M-02, M-04 and M-05 are less toxic than the parent compound. The Meeting decided to include M-01 in the residue definition for risk assessment. However, the metabolite M-01 is not unique to fluopicolide, e.g. M-01 is also a metabolite of dichlobenil. Therefore, it was proposed not to include M-01 in the residue definition for compliance. The Meeting considered the majority of dietary exposure to residues of toxicological concern would be accounted for when measuring residues of fluopicolide and M-01.

In the lactating cow metabolism study, fluopicolide is the major component of the residue in muscle (5.1%), fat (64–78%) and milk (37%) and was also present in liver (0.9–2.9%) and kidney (0.7–1.8%) and in the laying hen study represented 11% of the radioactivity in yolks and 0–2.5% in egg whites. Parent fluopicolide is present in most tissues and considered a good indicator compound for enforcement purposes.

The Meeting recommended that the residue definition for plant and animal commodities for compliance with MRLs should be fluopicolide.

The Meeting recommended that the residue definition for plant and animal commodities for dietary risk assessment should be fluopicolide and M-01.

The log K_{ow} of fluopicolide (log K_{ow} 2.9, pH 7) suggests that fluopicolide might be borderline fat soluble. The ratio of fluopicolide residues in muscle and fat observed in the livestock metabolism studies (lactating cow 1:32–1:49) support the conclusion that fluopicolide is fat soluble.

Proposed definition of the residue (for compliance with MRL for plant and animal commodities): *fluopicolide.*

Proposed definition of the residue (for estimation of dietary intake for plant and animal commodities): *fluopicolide and 2,6-dichlorobenzamide measured separately*.

The residue is fat soluble.

Results of supervised trials on crops

Dietary risk assessment requires separate STMR and HR values for fluopicolide and M-01. Supervised trials were available for the use of fluopicolide on: grapes, onions, leeks, Brassica vegetables (broccoli, Brussels sprouts, cabbage and cauliflower), cucumber, melon and summer squash including zucchini, chilli peppers, sweet peppers, tomatoes, lettuce, spinach, carrots, radish, and celery. Residue trial data was made available from Brazil, Canada, member states of the European Union and the USA.

The NAFTA calculator was used as a tool in the estimation of the maximum residue levels from the selected residue data sets obtained from trials conducted according to GAP. As a first step, the Meeting reviewed all relevant factors related to each data set in arriving at a best estimate of the maximum residue level with the calculator using expert judgement. Then, the NAFTA calculator was employed. If the statistical calculation spreadsheet suggested a different value than that recommended by the JMPR, a brief explanation of the deviation was supplied. Some common factors that may lead to rejection of the statistical estimate include when the number of data points in a data set is < 15 or when there are a large number of values < LOQ.

Grapes

Data were available from supervised trials on grapes in member states of the European Union, Canada and the USA.

The GAPs of Italy and Slovenia are similar at one to three sprays at 133 g ai/ha and a PHI of 28 days. Residues in grapes from trials in southern Europe matching GAP of Italy and Slovenia were (n=20): 0.11, 0.11, 0.15, 0.16, 0.20, 0.21, 0.21, 0.21, 0.27, 0.35, 0.38, 0.39, 0.40, 0.46, 0.54, 0.60, 0.69, 0.97, 1.1 and 1.2 mg/kg. M-01 residues were < 0.01 (12), 0.014, 0.015, 0.02 (2), 0.026, 0.03, 0.037 and 0.04 mg/kg. Residues in grapes from trials in northern Europe matching GAP of Italy and Slovenia were (n=19): 0.18, 0.20, 0.21, 0.24, 0.27 (0.013), 0.32, 0.32, 0.33, 0.33, 0.38, 0.44, 0.48 (0.01), 0.50, 0.51 (0.01), 0.52, 0.56, 0.66, 0.83 and 0.96 mg/kg. Residues of M-01 were: < 0.01 (16), 0.01 (2) and 0.013 mg/kg. The residue populations for trials conducted in northern and southern Europe were similar (Mann-Whitney U test) and the Meeting decided to combine the data for the purposes of estimating a maximum residue level (n=39) 0.11, 0.11, 0.15, 0.16, 0.18, 0.2, 0.2, 0.21, 0.21, 0.21, 0.21, 0.24, 0.27, 0.27, 0.32, 0.32, 0.33, 0.33, 0.35, 0.38, 0.38, 0.39, 0.4, 0.44, 0.46, 0.48, 0.5, 0.51, 0.52, 0.54, 0.56, 0.6, 0.66, 0.69, 0.83, 0.96, 0.97, 1.1 and 1.2 mg/kg. Residues of M-01 were: ≤ 0.01 (28), 0.01 (2), 0.013, 0.014, 0.015, 0.02 (2), 0.026, 0.03, 0.037 and 0.04 mg/kg.

The GAP of the USA was used to evaluate trials on grapes from Canada and the USA (USA GAP: 140 g ai/ha, PHI 21 days with a maximum seasonal application of 420 g ai/ha). The intervals between sprays in the trials were 4 to 5 days compared with the minimum specified for GAP of 7 days. The meeting noted the DT_{50} for residues in grapes from trials in Europe were approximately 21 days and concluded the shorter interval between sprays would have minimal impact on observed residues at harvest. Residues of fluopicolide in grapes from 16 trials in Canada and the USA approximating GAP of the USA, in rank order, were: 0.07, 0.10, 0.10, 0.13, 0.13, 0.14, 0.19, 0.21, 0.25, 0.26, 0.32, 0.44, 0.53, 0.56, 0.99 and 1.1 mg/kg. No residues of M-01 were detected, LOQ = 0.01 mg/kg.

Residues according to the GAP of Canada and the USA were similar to those for Italy and Slovenia and the larger dataset of trials conducted in Europe was used to estimate residue values. The

Meeting considered a value of 2 mg/kg appropriate as a maximum residue using a mixture of expert judgement and information on initial residue deposits. Use of the NAFTA calculator yielded a value of 1.4 mg/kg which agreed with the estimate of 2 mg/kg made by the Meeting (after rounding up to one figure). The Meeting estimated a maximum residue level for fluopicolide in grapes of 2 mg/kg. The corresponding HR values are 1.2 mg/kg for fluopicolide and 0.04 mg/kg for M-01, and STMRs are 0.38 mg/kg for fluopicolide and 0.01 mg/kg for M-01.

Bulb vegetables

Data were available from supervised trials on onions in member states of the European Union and the USA. Details of GAP for countries from the European Union were not available and the data from these trials were not further evaluated.

The GAP of the USA is foliar application at a maximum rate of 140 g ai/ha, PHI 2 days with a maximum seasonal application of 420 g ai/ha and a minimum interval between sprays of 7 days. In trials conducted in the USA the interval between sprays was lower (4–6 days) than the minimum; however, the meeting noted that the DT_{50} for residues in decline trials from Europe was of the order of 4 days and therefore it is the last spray that has the greatest influence on residues. Residues of fluopicolide in onions from seven trials in the USA complying with GAP were (in rank order, median underlined): 0.01, 0.05, 0.05, 0.07, 0.08, 0.11 and 0.58 mg/kg. No residues of M-01 were detected, < 0.01 (7) mg/kg.

The Meeting suggested a value of 1 mg/kg would be appropriate noting the size of the dataset and variability in residues. Using the NAFTA calculator a proposal of 0.51 mg/kg was derived assuming a lognormal distribution however, inspection of plots indicated the data did not follow this distribution type. The Meeting estimated maximum residue level for fluopicolide in onions of 1 mg/kg. The corresponding HR values are 0.58 mg/kg (fluopicolide) and 0.01 mg/kg (M-01) and STMR values of 0.07 mg/kg for fluopicolide and 0.01 mg/kg for M-01.

Additionally three trials were available on bunching onions (Welsh onions). Residues according to the GAP of the USA for bulb vegetables were: 1.7, 2.1 and 4.5 g/kg. Corresponding residues of M-01 were < 0.01, < 0.01 and 0.01 mg/kg respectively. The Meeting noted the small dataset and suggested a value of 10 mg/kg would be suitable as a maximum residue level. The value derived from use of the the NAFTA calculator was 8.3 mg/kg. The Meeting considered the uncertainty of estimates based on very small datasets and considered the higher estimate more appropriate.

The Meeting estimated maximum residue level for fluopicolide in Welsh onions of 10 mg/kg, HR values of 4.5 mg/kg (fluopicolide) and 0.01 mg/kg (M-01) and STMRs of 2.1 mg/kg for fluopicolide and 0.01 mg/kg for M-01.

Residue trials were provided from Europe for use of fluopicolide on leeks but no GAP was available.

Brassica vegetables

In Estonia and Lithuania, fluopicolide is registered for use on cabbage at a maximum of three sprays of 100 g ai/ha with a PHI of 14 days. Residues in head cabbage from northern Europe complying with GAP were: < 0.01, < 0.01, 0.01, 0.01, 0.03, 0.03, 0.08 and 0.18 mg/kg. Residues of M-01 were not detected. Residues in head cabbage from southern Europe complying with GAP were: 0.01, 0.01, 0.02, and 0.03 mg/kg. Residues of M-01 were not detected. The residue populations for trials conducted in northern and southern Europe were similar (Mann-Whitney U test) and the Meeting decided to combine the data for the purposes of estimating a maximum residue level (n=12): < 0.01, < 0.01, 0.01, 0.01, 0.01, 0.01, 0.02, 0.03, 0.03, 0.03, 0.08 and 0.18 mg/kg.

Fluopicolide is registered in the USA for use on cabbage (Brassica vegetables) at 140 g ai/ha, PHI 2 days with a maximum seasonal application of 420 g ai/ha. Trials were available from the USA

in which crops were treated three times at four to six day intervals at 133 g ai/ha with harvest 2 days after the last spray. Residues in head cabbage (with wrapper leaves) were: 0.31, 0.36, 0.61, 1.2, 1.9, 2.3 and 3.9 mg/kg. Residues of M-01 were < 0.01 (6) and 0.02 mg/kg.

The Meeting noted the data from the US for head cabbage had the higher residues and decided to use this dataset to estimate a maximum residue level. The Meeting considered a value of 7 mg/kg appropriate as a maximum residue using a mixture of expert judgement and initial residue deposits. Use of the NAFTA calculator yielded a value of 8.85 mg/kg. The Meeting estimated a maximum residue value for fluopicolide in head cabbages of 7 mg/kg. The corresponding HR values are 4.0 and 0.02 mg/kg respectively for fluopicolide and M-01. The STMRs are 1.2 mg/kg for fluopicolide and 0.01 mg/kg for M-01.

Trials reported from Europe on Brussels sprouts were assessed according to the GAP of Estonia (maximum of three sprays of 100 g ai/ha with a PHI of 14 days). Residues that approximated GAP of Estonia were (n=8): 0.01, 0.03, 0.03, 0.04, 0.04, 0.05, 0.05 and 0.13 mg/kg. Residues of M-01 were < 0.01 (8) mg/kg.

The Meeting considered a value of 0.2 mg/kg appropriate as a maximum residue noting the distribution of residue values. The value derived from use of the the NAFTA calculator was also 0.2 mg/kg. The Meeting estimated maximum residue level for fluopicolide in Brussels sprouts of 0.2 mg/kg, HR values of 0.13 and 0.01 mg/kg for fluopicolide and M-01 respectively, and STMRs of 0.04 mg/kg for fluopicolide and 0.01 mg/kg for M-01.

In Estonia and Lithuania, fluopicolide is registered for use on cauliflower and broccoli at a maximum of three sprays of 100 g ai/ha with a PHI of 14 days. Residues in broccoli from northern Europe trials complying with GAP were: < 0.01, 0.01, 0.02, and 0.10 mg/kg. Corresponding residues of M-01 were all < 0.01 mg/kg. Residues in broccoli from southern Europe trials complying with GAP were: < 0.01, 0.04, 0.06 and 0.11 mg/kg. Corresponding residues of M-01 were all < 0.01 mg/kg.

In Estonia and Lithuania, fluopicolide is registered for use on cauliflower at a maximum of three sprays of 100 g ai/ha with a PHI of 14 days. Residues in cauliflower from northern Europe trials complying with GAP were: < 0.01, < 0.01, < 0.01, and 0.01 mg/kg. Corresponding residues of M-01 were all < 0.01 (4) mg/kg. Residues in cauliflower from southern Europe trials complying with GAP were: < 0.01, < 0.01, 0.01 and 0.06 mg/kg. Corresponding residues of M-01 were all < 0.01 (4) mg/kg.

Fluopicolide is registered in the USA for use on broccoli (Brassica vegetables) at 140 g ai/ha, PHI 2 days with a maximum seasonal application of 420 g ai/ha. Trials were available from the USA in which crops were treated three times at four to six day intervals at 133 g ai/ha with harvest 2 days after the last spray. Residues in broccoli were: 0.18, 0.21, 0.32, 0.45, 0.50 and 0.69 mg/kg. Residues of M-01 were not detected (< 0.01 (6) mg/kg).

The Meeting agreed to extrapolate the USA data for broccoli to establish a maximum residue level for Flowerhead brassicas. The Meeting considered a value of 2 mg/kg appropriate as a maximum residue. The value derived from use of the NAFTA calculator agreed with the estimate of 2 mg/kg made by the present Meeting (after rounding up to one figure (NAFTA = 1.2 mg/kg). The Meeting estimated a maximum residue level, HR and an STMR value of 2 mg/kg for fluopicolide in Flowerhead brassicas. The corresponding HR values are 0.69 mg/kg for fluopicolide and 0.01 mg/kg for M-01. The STMRs are 0.385 mg/kg for fluopicolide and 0.01 mg/kg for M-01.

Fruiting vegetables, Cucurbits

Fluopicolide is registered in Estonia for use on cucumbers at 100 g ai/ha or 10 g ai/hL, PHI 3 days for field use. Trials were available from northern Europe that complied with GAP of Estonia. Residues in field grown cucumbers were: 0.02, 0.02, 0.03 and 0.08 mg/kg. Residues of M-01 were not detected (< 0.01 mg/kg).

In Lithuania, fluopicolide is registered for use on cucumbers grown under protected cover at a maximum of three sprays at 8.8 g ai/hL with a PHI of 1 day. Trials were available from Europe that complied with GAP of Lithuania with residues of: 0.02, 0.02, 0.03, 0.03, 0.04, 0.04, 0.08 and 0.09 mg/kg. Residues of M-01 were not detected (< 0.01 mg/kg).

Trials on cucumber were reported from the USA (USA GAP for cucurbits: 140 g ai/ha, PHI of 2 days and a maximum application per season of 420 g ai/ha). Fluopicolide residues on cucumbers in six trials from the USA matching GAP in rank order were: 0.01, 0.02, 0.03, 0.03, 0.03 and 0.06 mg/kg. Residues of M-01 were not detected (< 0.01 mg/kg).

Residue trials were provided from Europe for use of fluopicolide on melons but no GAP was available.

Residues on melons (cantaloupe) in nine trials from the USA matching GAP in rank order were: < 0.01, 0.05, 0.06, 0.06, 0.07, 0.07, 0.10, 0.26 and 0.30 mg/kg. Residues of M-01 were not detected (< 0.01 mg/kg).

Trials were available from Greece, Italy and Spain on zucchini but did not match GAP.

Fluopicolide residues on summer squash (including zucchini) in six trials from the USA matching GAP in rank order were: 0.01, 0.03, 0.04, 0.04, 0.05 and 0.06 mg/kg. Residues of M-01 were not detected (< 0.01 mg/kg).

The use-pattern in the USA is for fruiting vegetables, (cucurbits) and the Meeting decided to use the data on the crop with the highest residues (melons) to estimate a maximum residue level for the group. The Meeting considered a value of 0.5 mg/kg appropriate as a maximum residue using a mixture of expert judgement and initial residue deposit data. The value derived from use of the NAFTA calculator was 0.5 mg/kg, which agreed with the estimate of the Meeting. The Meeting estimated a maximum residue level for fluopicolide in fruiting vegetables, cucurbits of 0.5 mg/kg.

The commodity group encompasses fruit with both edible and inedible peel. For fruit with edible peel the HR and STMRs listed above should be used. Data on residues in the edible portion for melons in trials complying with USA GAP were not available; however, in trials from Europe with similar residues in melons, no residues of fluopicolide or M-01 were detected in the edible portion (LOQ 0.01 mg/kg). For fruit with inedible peel the HR and STMRs are all 0.01 mg/kg and for fruit with edible peel the HR and STMRs are 0.3, 0.07 (fluopicolide) and 0.01, 0.01 (M-01) mg/kg respectively. This is consistent with fluopicolide being a surface residue on crops if applied by foliar application.

Fruiting vegetables, other than Cucurbits

Trials on tomatoes were made available from Brazil but did not match GAP for that country. Fluopicolide is registered in Italy for use on tomatoes at 100 g ai/ha or 10 g ai/hL, PHI 3 days for field use, and 125 g ai/ha or 10 g ai/hL, PHI 3 days for crops grown under protected cover. Trials were available from Europe that complied with GAP of Italy. Residues in field grown tomatoes from trials conducted in northern Europe were: 0.015, 0.14, 0.22, and 0.23 mg/kg. Residues of M-01 were not detected (< 0.01 mg/kg). Residues in field grown tomatoes from trials conducted in southern Europe were: 0.019, 0.046, 0.05, 0.055, 0.09, 0.10, 0.14 and 0.28 mg/kg. Residues of M-01 were not detected (< 0.01 mg/kg). The residue populations for trials conducted in northern and southern Europe were similar (Mann-Whitney U test) and the Meeting decided to combine the data for the purposes of estimating a maximum residue level (n=12): 0.015, 0.019, 0.046, 0.05, 0.055, 0.09, 0.10, 0.14, 0.14, 0.22, 0.23 and 0.28 mg/kg.

In Lithuania, fluopicolide is registered for use on tomatoes grown under protected cover at a maximum of three sprays at 8.8 g ai/hL with a PHI of 1 day. Trials were available from Europe that complied with GAP of Lithuania with residues of: 0.063, 0.08, 0.085, 0.093, 0.14, 0.18, 0.20 and 0.21 mg/kg. Residues of M-01 were not detected (< 0.01 mg/kg).

Trials on tomatoes (including cherry tomatoes) were reported from the USA (USA GAP: 140 g ai/ha, PHI of 2 days and a maximum application per season of 420 g ai/ha). Fluopicolide residues in twelve trials from the USA matching GAP in rank order were: 0.05, 0.06, 0.08, 0.10, 0.15, 0.15[c], 0.17[c], 0.17, 0.19, 0.19, 0.28 and 0.42[c] mg/kg ([c] = cherry tomatoes). Residues of M-01 were not detected (< 0.01 mg/kg).

Trials on sweet peppers were reported from the USA (GAP: 140 g ai/ha, PHI of 2 days and a maximum application per season of 420 g ai/ha). Fluopicolide residues in seven trials on sweet peppers (including Bell peppers) from the USA matching GAP in rank order were: 0.04, 0.05, 0.09, 0.15, 0.17, 0.19 and 0.57 mg/kg. Residues of M-01 were not detected (< 0.01 mg/kg).

Fluopicolide residues in chilli peppers in three trials from the USA matching GAP in rank order were: 0.10, 0.36 and 0.58 mg/kg. Residues of M-01 were not detected (< 0.01 mg/kg).

The Meeting decided that the trials in tomatoes, sweet and chilli peppers could be used to support a group maximum residue level for fruiting vegetables other than cucurbits except mushrooms and sweet corn. The Meeting decided to use the data on the crop with the highest residues (sweet and chilli peppers) to estimate a maximum residue level for the group (fluopicolide residues: 0.04, 0.05, 0.09, 0.10, 0.15, 0.17, 0.19, 0.36, 0.57 and 0.58 mg/kg; M-01 residues < 0.01 (10) mg/kg).

The Meeting considered a value of 1 mg/kg appropriate as a maximum residue using a mixture of expert judgement and initial residue deposit data. Use of the NAFTA calculator yielded a value of 0.8 mg/kg. The Meeting estimated a maximum residue level for fluopicolide in fruiting vegetables other than cucurbits (except mushrooms and sweet corn) of 1 mg/kg. The HR values are 0.58 mg/kg for fluopicolide and 0.01 mg/kg for M-01. The STMRs are 0.16 mg/kg for fluopicolide and 0.01 mg/kg for M-01.

Leafy vegetables

In Romania, fluopicolide is registered for use on lettuce grown under protected cover at a maximum of two sprays at 7 day intervals and at 8.8 g ai/hL (88 g ai/ha) with a PHI of 14 days. Noting that growth dilution would ensure a spray made 28 days before harvest would make a negligible contribution to the final residues; the Meeting agreed that the trials from Europe with three sprays at 7 day intervals could be evaluated against the GAP of Romania. Trials were available from Europe that complied with GAP of Romania with residues of: 0.40, 0.40, 0.63, 0.68, 1.5, 2.7, 4.0 and 4.9 mg/kg. Corresponding residues of M-01 were: < 0.01, 0.018, 0.017, 0.017, 0.022, 0.014, 0.020 and 0.011 mg/kg).

Trials on lettuce and spinach were reported from the USA (GAP: 140 g ai/ha, PHI of 2 days and a maximum application per season of 420 g ai/ha). Fluopicolide residues in seven trials on head lettuce from the USA matching GAP in rank order were: 0.62, 2.3, 2.3, 2.4, 4.2, 4.3 and 7.2 mg/kg. Corresponding residues of M-01 were: < 0.01 (5) and 0.01 (2) mg/kg.

Residues of fluopicolide in seven trials on leaf lettuce from the USA matching GAP were higher than in head lettuce and were (in rank order): 4.3, 5.0, 5.3, 7.6, 7.6, 10 and 12 mg/kg. Corresponding residues of M-01 were: 0.01, 0.01, < 0.01, 0.02, 0.04, < 0.01 and 0.02 mg/kg.

Residue trials were provided from Europe for use of fluopicolide on spinach but no GAP was available.

Fluopicolide residues in seven trials on spinach from the USA matching GAP in rank order were: 6.8, 6.8, 6.9, 8.6, 12, 16 and 17 mg/kg. Corresponding residues of M-01 in rank order were: 0.02, 0.03, 0.06, 0.07, 0.07, 0.09 and 0.19 mg/kg.

The Meeting noted that the registered use of fluopicolide in the USA is for leafy vegetables and decided to recommend a group MRL. The Meeting decided to use the data on the crop with the highest residues (spinach) to estimate a maximum residue level for the group. The Meeting

considered a value of 30 mg/kg appropriate as a maximum residue using a mixture of expert judgement and initial residue deposit data. Use of the NAFTA calculator yielded a value of 25.3 mg/kg which, on rounding, also leads to a value of 30 mg/kg. The Meeting estimated a maximum residue level for fluopicolide in leafy vegetables of 30 mg/kg. The HR values are 17 mg/kg for fluopicolide and 0.19 mg/kg for M-01, while the STMRs are 8.6 mg/kg for fluopicolide and 0.07 mg/kg for M-01.

Root and tuber vegetables

Trials on carrot and radish were made available from the USA. No carrot trials matched GAP (no GAP available) and one trial on radish matched GAP in the USA (GAP: 140 g ai/ha, PHI of 2 days and a maximum application per season of 420 g ai/ha) with residues of 0.11 mg/kg (M-01 < 0.01 mg/kg). The Meeting decided that a single trial constitutes an insufficient dataset to estimate a maximum residue level.

Celery

Fluopicolide residues in seven trials on celery from the USA matching GAP (the USA crop group 'leafy vegetables' includes celery) in rank order were (median underlined): 0.16, 0.76, 1.0, 1.4, 5.2, 6.7 and 14 mg/kg. Residues of M-01 were < 0.01 (4), 0.01, 0.03 and 0.04 mg/kg. The Meeting considered a value of 20 mg/kg appropriate as a maximum residue using a mixture of expert judgement. Use of the NAFTA calculator yielded a value of 10.15 mg/kg, which is less than the highest observed residues. The Meeting estimated a maximum residue level for fluopicolide in celery of 20 mg/kg. The HR values are 14 mg/kg for fluopicolide and 0.04 mg/kg for M-01, and STMRs 1.4 mg/kg for fluopicolide and 0.01 mg/kg for M-01.

Rotational crops

Residues of fluopicolide are persistent in soil and may be taken up by succeeding crops. In the USA the total seasonal application rate for crops is 420 g ai/ha. Studies of residues in rotational crops were made available to the meeting where in confined rotational crop studies bare soil was treated at 400 g ai/ha, and in field studies preceding potato crops were treated four times at 100 g ai/ha (400 g ai/ha). It is likely that soil residues would require several years to reach plateau levels and residues in succeeding crops could be higher than those observed in the rotational crop following a single season of applications.

Residues in brassica vegetables grown as a rotational crop were < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, < 0.01 (0.02) and < 0.01 (0.04) mg/kg in cabbage (figures in brackets are for M-01). The levels in brassica vegetables from rotational crops are adequately covered by the recommendations for Head cabbages (5 mg/kg), Flowerhead brassicas (2 mg/kg) and Brussels sprouts (0.2 mg/kg). In addition, if the levels found in cabbage are representative of those taken up by leafy vegetables, considering the magnitude of the maximum residue level recommended for leafy vegetables, it is concluded that residues taken up from soil are a minor contribution for leafy vegetables and adequately covered by the recommendation for leafy vegetables.

Residues in follow-crop cereal grains were < 0.01 mg/kg in 17 trials on wheat. No residues of M-01 were detected. As the residues were all below the LOQ, the Meeting decided it is not necessary to recommend a maximum residue level for cereals grown as rotational crops.

Corresponding residues in cereal forage (wheat) were: < 0.01, < 0.01, < 0.01, < 0.01, < 0.01, 0.01, 0.01, 0.01, 0.01, 0.02, 0.02, 0.02, 0.02, 0.02, 0.03, 0.04 and 0.04 mg/kg. The Meeting decided to recommend STMR and highest residue values of 0.015 and 0.04 mg/kg respectively for forage of cereals (or 0.06 and 0.16 mg/kg on a dry weight basis respectively and assuming 25% dry matter content).

Corresponding residues in cereal straw (wheat) were: < 0.01, 0.01, 0.02, 0.02, 0.03, 0.04, 0.05, 0.05, 0.06, 0.06, 0.06, 0.07, 0.07, 0.07, 0.08, 0.09 and 0.12 mg/kg. The estimated STMR and highest residue values for straw of cereals are 0.06 (or 0.07 mg/kg on a dry weight basis) and 0.12 (or 0.14 mg/kg on a dry weight basis assuming 88% dry matter content) mg/kg respectively. The Meeting recommended a maximum residue level for straw and hay of cereals of 0.2 mg/kg.

Eight trials on residues in pulses (faba bean) grown as rotational crops were available with residues in seed of < 0.01(8) mg/kg. No residues of M-01 were detected. The Meeting decided it is not necessary to recommend a maximum residue level for pulses grown as rotational crops. Residues in forage were < 0.01 (5), 0.01, 0.02 and 0.03 mg/kg. The Meeting also estimated STMR and highest residue values of 0.01 and 0.03 mg/kg respectively for legume animal feeds, or 0.04 and 0.12 mg/kg on a dry weight basis respectively, assuming 25% dry matter content.

Metabolism studies on rotational crops suggested residues of fluopicolide and metabolites would be present in root and tuber crops; however, no field studies were available. The Meeting did not have sufficient information to evaluate residue levels in root and tuber crops or other rotational crops not mentioned above.

Fate of residues during processing

The effect of processing on the nature of residues was investigated in buffer solutions under conditions simulating pasteurisation, boiling and sterilisation. Fluopicolide was shown to be stable under these conditions.

The fate of fluopicolide residues has been examined in grapes and tomato processing studies. Processing of tomatoes into purée and paste showed an increase of fluopicolide residues in the processed commodities compared to the raw commodity, whilst there was a decrease in residues found in the corresponding juice and ketchup. Grapes showed a decrease in residues found in wine, but an increase in pomace. Estimated processing factors and STMR-Ps are summarised below.

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors	PF (Mean, median or best estimate)	Fluopicolide RAC-STMR (mg/kg)	Fluopicolide STMR-P (mg/kg)	M-01 STMR-P (mg/kg)[a]
Grape	Pomace wet	1.6 1.8 2.3 5.0 6.3 6.6	3.65 (median)	0.38	1.387	0.01
	Raisin	2.2, 6.5	6.5 (highest)		2.47	0.045
	White wine (np)	0.40 0.43 0.61	0.43 (median)		0.1634	0.01
	Red wine	0.28 0.31 0.38	0.31 (median)		0.1178	0.01
Tomato	Preserve	0.1 0.1 0.1 0.1 0.1	0.1 (median)	0.16[c]	0.016	0.01
	Juice	0.2 0.2 0.3 0.3 0.3	0.3 (median)		0.048	0.01
	Purée[b]	(0.3 0.3 0.4 0.5 0.5) 1.5 1.8 2.2	1.8 (median US)		0.288	0.01
	Paste	1.9 2.2 3.5	2.2 (median)		0.352	0.01

np = non-pasteurised

[a] values in brackets are for 2,6-dichlorobenzamide residues observed in processed commodities from processing trials. Residues were scaled to the application rate for GAP for the crop from which the RAC was derived.

[b] higher tomato values are from US study

[c] STMR for USA tomato trials

On processing tomatoes, fluopicolide concentrated in tomato purée and paste. For grapes, residues concentrated in raisins and pomace. The Meeting decided to estimate a maximum residue level for dried grapes of 10 mg/kg based on a highest residue for grapes of 1.2 mg/kg and a processing factor of 6.5 (1.2 mg/kg × 6.5 = 7.8 mg/kg). The highest residue observed for M-01 in

grapes from vines treated according to GAP and processed was 0.06 mg/kg. The STMR-P for residues of fluopicolide in dried grapes is 2.47 mg/kg while that for M-01 is 0.045 mg/kg (average of the two residue values for M-01 observed in the trials that processed grapes into raisins).

Residues in grape pomace were estimated to be 0.785 mg/kg on a wet weight basis and 5.2 mg/kg (assuming a default 15% dry matter content) when expressed on a dry weight basis. The Meeting decided to recommend a maximum residue level for grape pomace (dry) of 7 mg/kg.

The Meeting also decided to estimate a maximum residue for chilli pepper (dried) of 7 mg/kg following application of a default dehydration factor of 7 to the estimated maximum residue level of 1 mg/kg for chilli pepper (7 × 1 mg/kg = 7 mg/kg). The STMR for residues of fluopicolide in chilli peppers (dry) is estimated to be 7 × 0.13 mg/kg = 0.91 mg/kg. As residues of M-01 were < 0.01 in peppers, the HR and STMR for chilli pepper (dried) is also estimated to be 0.01 mg/kg.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of fluopicolide in farm animals on the basis of the diets listed in Annex 6 of the 2006 JMPR Report (OECD Feedstuffs Derived from Field Crops). Residues of M-01 are extremely low and considered unlikely to transfer from feed to tissues, milk and eggs. Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed as dry weight.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. The calculations were made according to the animal diets from US-Canada, EU and Australia in the OECD Table (Annex 6 of the 2006 JMPR Report).

		Animal dietary burden, fluopicolide, ppm of dry matter diet		
		US-Canada	EU	Australia
Beef cattle	max	0.08	5.1[a]	2.0
	mean	0.03	1.1	1.9[c]
Dairy cattle	max	0.09	5.1[b]	2.0
	mean	0.05	1.1	1.9[d]
Poultry – broiler	max	0.01	1.3[e]	0.01
	mean	0.01	0.28[f]	0.01
Poultry – layer	max	0.01	0.03[g]	0.01
	mean	0.01	0.02[h]	0.01

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian tissues

[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 tissues.

[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 tissues.

[f] Highest mean poultry dietary burden suitable for STMR estimates for poultry tissues.

[g] Highest maximum poultry dietary burden suitable for MRL estimates for poultry eggs.

[h] Highest mean poultry dietary burden suitable for STMR estimates for poultry eggs.

The fluopicolide dietary burdens for animal commodity MRL and STMR estimation (residue levels in animal feeds expressed on dry weight) are: beef cattle 5.1 and 1.1 ppm, dairy cattle 5.1 and 1.9 ppm and poultry 1.3 and 0.28 ppm (for eggs 0.03 and 0.02 ppm).

Farm animal feeding studies

The Meeting received information on the residue levels arising in animal tissues and milk when dairy cows were dosed with fluopicolide for 28 days at the equivalent of 0.5, 1.7 and 5.7 ppm in the diet. Average residues of fluopicolide in milk for the 5.7 ppm dose group were < 0.01 mg/kg. Residues of fluopicolide in milk were detected for one sample at day 4 and one at day 28 of dosing; levels were 0.01 and 0.02 mg/kg respectively. No residues of the metabolites M-01 and M-02 were detected in milk (LOQ 0.01 mg/kg). No residues of fluopicolide or the metabolites M-01 and M-02 were detected in tissues (LOQ 0.02 mg/kg).

The Meeting also received information on the residue levels arising in tissues and eggs when laying hens were dosed with [^{14}C]fluopicolide for 14 days at levels equivalent to 1 and 10 ppm in the diet. At the high dose residues of fluopicolide in eggs and tissues were below the LOQ (0.01 mg/kg) for the analytical method.

Animal commodity maximum residue levels

The maximum dietary burden for beef and dairy cattle is 5.1 ppm, so the levels of residues in tissues can be obtained directly from the 5.7 ppm feeding level. Maximum residues expected in tissues are: fat, muscle, liver and kidney are 0 mg/kg and the mean residue for milk 0 mg/kg. The Meeting estimated maximum residue levels for meat (from mammals other than marine mammals) 0.01(*) mg/kg; edible offal (mammalian) 0.01(*) mg/kg and milks 0.02 mg/kg. Estimated HRs for short term intake estimations for fluopicolide are all 0 mg/kg for tissues. No residues of M-01 are expected, HR values are 0 mg/kg.

No residues are expected to be detected on exposure to the mean dietary burden and estimated STMRs for fluopicolide and M-01 are 0 mg/kg for meat (from mammals other than marine mammals), fat (from mammals other than marine mammals), edible offal (mammalian) and milk.

The maximum dietary burden for broiler poultry is 1.3 ppm. No residues above the LOQ of the analytical method are expected for fluopicolide or M-01.

The Meeting estimated maximum residue levels for poultry meat 0.01(*) mg/kg; poultry offal 0.01(*) and eggs 0.01* mg/kg. The mean dietary burden for poultry is 0.28 ppm. No residues are expected in poultry tissues and eggs of birds at the mean dietary burden. HRs and STMRs for fluopicolide and M-01 in poultry meat, skin/fat, edible offal and eggs are all 0 mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intake (IEDI) for fluopicolide was calculated for the food commodities for which STMRs or HRs were estimated and for which consumption data were available. The results are shown in Annex 3.

The International Estimated Daily Intakes of fluopicolide and 2,6-dichlorobenzamide for the 13 GEMS/Food Consumption Cluster Diets, based on estimated STMRs were 1–10% of the maximum ADI of 0.08 mg/kg bw for fluopicolide and 0–1% of the maximum ADI of 0.02 mg/kg bw for 2,6-dichlorobenzamide (Annex 3). The Meeting concluded that the long-term intake of residues of fluopicolide from uses that have been considered by the JMPR is unlikely to present a public health concern.

Long-term intake

The International Estimated Short-term Intake (IESTI) for fluopicolide was calculated for the food commodities for which STMRs or HRs were estimated and for which consumption data were available. The results are shown in Annex 4 of the 2009 Report of the JMPR.

For fluopicolide the IESTI varied from 0–70% of the ARfD (0.6 mg/kg bw) for women of child bearing age when using intake figures for the general population. An ARfD was unnecessary for the other groups of the population. For 2,6-dichlorobenzamide the IESTI varies from 0–1% of the ARfD (0.6 mg/kg bw) for the general population and 0–2% for children. The Meeting concluded that the short-term intake of residues of fluopicolide from uses considered by the Meeting is unlikely to present a public health concern.