5.17 FLUOPYRAM (243)

TOXICOLOGY

Fluopyram is the International Organization for Standardization (ISO)–approved common name for *N*-(2-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]ethyl)-2-(trifluoromethyl)benzamide (International Union of Pure and Applied Chemistry [IUPAC]) (Chemical Abstracts Service [CAS] No. 658066-35-4), a novel broad-spectrum fungicide from the pyridinyl-ethyl-benzamide class. Fluopyram acts by inhibiting the enzyme succinate dehydrogenase (SDH, so-called complex II in the mitochondrial respiratory chain), which is a functional part of the tricarboxylic acid cycle, linked to mitochondrial electron transport. SDH consists of four subunits (A, B, C and D), and fluopyram, like a number of SDH inhibitors, acts by blocking the enzyme binding site for ubiquinone, which is formed by the subunits B, C and D. Fluopyram has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and was reviewed at the present Meeting at the request of the Codex Committee on Pesticide Residues (CCPR).

All pivotal studies were certified as complying with good laboratory practice (GLP) or an approved quality assurance programme.

Biochemical aspects

In rats given [^{14}C]phenyl ring–labelled or [^{14}C]pyridyl ring-labelled fluopyram orally by gavage, absorption was rapid and accounted for 93% of the total recovered radioactivity after a single dose of 5 mg/kg body weight (bw) (both labels) or 250 mg/kg bw (phenyl ring label). The maximum plasma concentrations of radio-labelled material were reached after 0.7–3 h with the pyridyl ring label and after 8–48 h with the phenyl ring label. Radiolabel was widely distributed throughout the body. Residues in tissues 168 h after a single dose of 5 mg/kg bw accounted for less than 0.5% (pyridyl ring label) or 3–5% (phenyl ring label) of the administered dose, with liver and kidney containing the highest concentrations of residues. Elimination of the radiolabel was via the faeces (39–64%) and the urine (35–60%), with evidence of significant enterohepatic circulation. In bile duct–cannulated rats, extensive biliary excretion (79–87%) was demonstrated. The terminal elimination half-lives of radio-labelled material ranged from 24 to 53 h for the phenyl ring–labelled fluopyram and from 56 to 73 h for the pyridyl ring–labelled fluopyram.

Fluopyram was extensively metabolized, and more than 20 metabolites were identified. The metabolism was principally oxidative and took place mainly at the ethylene bridge of the molecule. Hydrolytic cleavage of the molecule and subsequent oxidation were also observed, as was conjugation of several hydroxylated metabolites with glucuronic acid and, to a lesser extent, sulfate.

Toxicological data

Fluopyram was of low toxicity after oral and dermal exposure in rats (median lethal dose [LD_{50}] > 2000 mg/kg bw), and neither mortality nor systemic toxicity occurred at this limit dose. After inhalation exposure in rats, fluopyram was also of low toxicity (median lethal concentration [LC_{50}] > 5.1 mg/L), and the clinical signs observed were nonspecific and reversible within 1–5 days. Fluopyram was not a skin irritant in rabbits was only minimally irritating to the eye of rabbits and was not a skin sensitizer in the local lymph node assay in mice.

Following repeated administration of fluopyram to mice, rats and dogs, the liver was the major target organ in all species tested. The effects noted at lower doses (increased liver weights, hepatocellular hypertrophy) were consistent with the induction of hepatic cytochrome P450 (CYP), whereas effects observed at higher doses included hepatocellular degeneration or necrosis and related clinical chemistry findings (e.g., increased serum levels of liver enzymes, cholesterol and triglycerides). In mice, the adrenals were an additional target. The thyroid effects seen in mice and

rats were considered to be secondary to the enhanced hepatic clearance of thyroid hormones. The hyaline droplet nephropathy observed in male rats was considered not to be relevant to humans, as this effect is due to an accumulation of α_{2u}-globulin in the proximal tubules, a protein that is found only in trace amounts in humans.

In a 28-day range-finding study in mice, the no-observed-adverse-effect level (NOAEL) was 150 ppm (equal to 24.7 mg/kg bw per day), based on effects in liver (hepatocellular necrosis) and adrenals (hypertrophy of the zona fasciculata) at 1000 ppm and above. In a 90-day study in mice, the NOAEL was 150 ppm (equal to 26.6 mg/kg bw per day), based on effects in liver (hepatocellular necrosis) and adrenals (cortical vacuolation) at 1000 ppm.

In a 28-day range-finding study in rats, the NOAEL was 400 ppm (equal to 31 mg/kg bw per day), based on effects in the liver (increased liver weight, hepatocellular hypertrophy, enzyme induction) and the thyroid (hypertrophy of follicular cells, colloid depletion) at 3200 ppm. In a 90-day study in rats, the NOAEL was 200 ppm (equal to 12.5 mg/kg bw per day), based on effects in the liver (hepatocellular hypertrophy and vacuolation) and the thyroid (hypertrophy of follicular cells) at 1000 ppm and above. Effects at higher doses (3200 ppm, equal to 204 mg/kg bw per day) included decreased body weight gain and food consumption, decreased haemoglobin and haematocrit, clinical chemistry changes and increased levels of triiodothyronine (T_3), thyroxine (T_4) and thyroid stimulating hormone (TSH). It was noted that levels of these hormones more often change in opposite directions, with decreases in T_3 and/or T_4 being associated with increases in TSH. This pattern was subsequently observed in mechanistic studies described below.

In a 28-day range-finding study in dogs, the NOAEL was 150 mg/kg bw per day, based on treatment-related clinical signs (liquid faeces) and liver toxicity (increased liver weight, clinical chemistry changes, histopathological findings) at 750 mg/kg bw per day. In a 90-day study in dogs, the NOAEL was 800 ppm (equal to 28.5 mg/kg bw per day), based on liver toxicity (increased liver weight, histopathological findings, including necrosis, related clinical chemistry changes) at 5000 ppm and above. In a 1-year study in dogs, the NOAEL was 400 ppm (equal to 13.2 mg/kg bw per day), based on liver toxicity (hepatocellular hypertrophy, increased serum levels of alkaline phosphatase) at 2000 ppm. The overall NOAEL for the 90-day and 1-year dog studies was 28.5 mg/kg bw per day.

Long-term studies of toxicity and carcinogenicity were conducted in mice and rats. In an 18-month study of carcinogenicity in mice, the NOAEL for oncogenicity was 150 ppm (equal to 20.9 mg/kg bw per day), based on an increased incidence of follicular cell adenoma in the thyroid in males at 750 ppm. The NOAEL for non-neoplastic changes was 30 ppm (equal to 4.2 mg/kg bw per day), based on liver toxicity (hepatocellular single-cell degeneration/necrosis) and thyroid changes (follicular cell hyperplasia) in males at 150 ppm and above.

In a mechanistic study on thyroid tumorigenesis in male mice, increased liver weights, hepatocellular hypertrophy, increased hepatic CYP content and marked increases in hepatic activities of pentoxyresorufin *O*-dealkylase (PROD) (CYP2B) and benzyloxyresorufin *O*-dealkylase (BROD) (CYP3A) were observed after 3 and 14 days of exposure to fluopyram at 2000 ppm (equal to 308–314 mg/kg bw per day), whereas ethoxyresorufin *O*-deethylase (EROD) (CYP1A2) activity was only slightly increased and uridine diphosphate-glucuronosyltransferase (UDPGT) activity (using 4-nitrophenol as a substrate) was unaffected. However, decreased T_4 and increased TSH levels were noted after 3 and 14 days. The pattern of changes in the liver and thyroid end-points was similar to the profile observed in male mice treated with phenobarbital at 80 mg/kg bw per day in a parallel study.

In a 3-day study of effects on gene expression in the liver of male mice, quantitative polymerase chain reaction (PCR) analyses demonstrated that both fluopyram (2000 ppm, equivalent to approximately 286 mg/kg bw per day) and phenobarbital (80 mg/kg bw per day) induced an upregulation of the sulfotransferase and UDPGT gene transcripts. For most genes, at the doses used, effects were more pronounced with fluopyram than with phenobarbital. Further mechanistic studies in male mice demonstrated that both fluopyram (2000 ppm, equivalent to approximately

286 mg/kg bw per day) and phenobarbital (80 mg/kg bw per day) significantly increased the clearance of intravenously administered T_4. In vitro studies showed that fluopyram did not affect the thyroid peroxidase-catalysed oxidation of guaiacol.

The Meeting concluded that for the thyroid tumours in male mice, there was evidence that the mode of action was likely to be secondary to enhanced hepatic clearance of thyroxine, leading to hormone imbalance. The marked quantitative species differences in the inherent susceptibility for neoplasia in response to thyroid hormone imbalance allowed for the conclusion that the fluopyram-induced thyroid tumours in mice are not relevant to humans.

In a 24-month study of toxicity and carcinogenicity in rats, the NOAEL for oncogenicity was 150 ppm (equal to 8.6 mg/kg bw per day), based on an increased incidence of liver cell tumours (adenoma and carcinoma) in females at 1500 ppm (equal to 89 mg/kg bw per day). The NOAEL for non-neoplastic changes was 30 ppm (equal to 1.2 mg/kg bw per day), based on increased incidences of findings in the liver (hepatocellular hypertrophy and eosinophilic foci in males) at 150 ppm and above. The changes in the thyroid (follicular cell hypertrophy, colloid alteration) at 150 ppm and above were attributable to the apparent susceptibility of rats to thyroid hormone imbalance and were therefore not considered relevant to humans.

In a mechanistic study on liver tumorigenesis in female rats, increased liver weights, hepatocellular hypertrophy, increased cell proliferation in the centrilobular and periportal zones of the hepatic lobules, increased hepatic CYP content and moderate to marked increases in hepatic activities of EROD, PROD, BROD and UDPGT were observed after 7 days of exposure to fluopyram (3000 ppm, equal to 193 mg/kg bw per day). The pattern of changes was similar to the profile observed in female rats treated with phenobarbital at 80 mg/kg bw per day in a parallel study.

The Meeting concluded that the relevance of the liver tumours in female rats to humans could not be discounted, as the results of the mechanistic studies were only partly sufficient to support the proposed phenobarbital-like mode of action. In particular, activation of the constitutive androstane receptor (CAR) by fluopyram has not been clearly demonstrated, and there is a lack of dose–response concordance with key precursor events and tumour incidence. However, the Meeting noted that the mode of action for the observed liver tumours is a high-dose phenomenon that would be anticipated to exhibit a threshold.

Fluopyram was tested for genotoxicity in vitro and in vivo in an adequate range of assays. It was not found to be genotoxic in mammalian and microbial test systems.

The Meeting concluded that fluopyram was unlikely to be genotoxic.

On the basis of the absence of genotoxicity, the human non-relevance of the thyroid tumours in mice and the fact that the dose–response relationship for the liver tumours in rats would be anticipated to exhibit a threshold, the Meeting concluded that fluopyram is unlikely to pose a carcinogenic risk to humans at dietary exposure levels.

In a two-generation reproductive toxicity study in rats, the NOAEL for effects on fertility was 1200 ppm (equal to 82.4 mg/kg bw per day), the highest dose tested. The NOAEL for parental toxicity was 220 ppm (equal to 13.9 mg/kg bw per day), based on decreased body weight and/or body weight gain in females and liver toxicity in both sexes at 1200 ppm. The NOAEL for offspring toxicity was 220 ppm (equal to 13.9 mg/kg bw per day), based on decreased body weight gain and decreased spleen and thymus weights at 1200 ppm.

In a prenatal developmental toxicity study in rats, the NOAEL for maternal toxicity was 30 mg/kg bw per day, based on decreased body weight gain and food consumption and increased liver weights and hepatocellular hypertrophy at 150 mg/kg bw per day and above. The NOAEL for prenatal developmental toxicity was 150 mg/kg bw per day, based on lower fetal body weights and an increased incidence of visceral and skeletal variations at 450 mg/kg bw per day.

In a prenatal developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 25 mg/kg bw per day, based on reduced body weight gain and food consumption at 75 mg/kg bw per

day. The NOAEL for prenatal developmental toxicity was 25 mg/kg bw per day, based on reduced fetal body weights and an increased number of small fetuses ("runts") at 75 mg/kg bw per day.

The Meeting concluded that fluopyram caused developmental toxicity only at doses that were maternally toxic and that it was not teratogenic.

In an acute neurotoxicity study in rats, the NOAEL for neurotoxicity was 50 mg/kg bw, based on decreased motor and locomotor activity at 100 mg/kg bw and above. In a subchronic study of neurotoxicity in rats, the NOAEL for neurotoxicity was 2500 ppm (equal to 164.2 mg/kg bw per day), the highest dose tested. The NOAEL for general toxicity was 500 ppm (equal to 33.2 mg/kg bw per day), based on decreased body weight, body weight gain and food consumption and increased liver weight at 2500 ppm.

Fluopyram-pyridyl-carboxylic acid (AE C657188), a plant metabolite of fluopyram, was of low acute oral toxicity in rats (LD_{50} > 2000 mg/kg bw) and showed no genotoxic potential in vitro in mammalian or microbial test systems. In a 28-day oral toxicity study in rats, there was no evidence of toxicity up to dietary concentrations of 20 000 ppm (equal to 1574 mg/kg bw per day), the highest dose tested.

Fluopyram-methyl-sulfoxide (AE 1344122), a plant metabolite of fluopyram, was of low acute oral toxicity in rats (LD_{50} > 2000 mg/kg bw) and showed no genotoxic potential in vitro in mammalian or microbial test systems. In a 28-day oral toxicity study in rats, the NOAEL was 2000 ppm (equal to 152 mg/kg bw per day), based on reduced body weight gain and food consumption in both sexes and kidney toxicity (tubular degeneration and single-cell necrosis, urinalysis findings) in females at 20 000 ppm.

There were no reports of adverse health effects in manufacturing plant personnel. Also, there were no reports of poisonings with fluopyram.

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

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) for fluopyram of 0–0.01 mg/kg bw, based on a NOAEL of 1.2 mg/kg bw per day for changes in liver (hepatocellular hypertrophy, eosinophilic foci) at 6.0 mg/kg bw per day in a 2-year rat study. A safety factor of 100 was applied. The ADI provides a margin of at least 860-fold relative to the NOAEL for liver tumours in rats.

The Meeting established an acute reference dose (ARfD) for fluopyram of 0.5 mg/kg bw, based on the NOAEL of 50 mg/kg bw for decreases in measures of motor and locomotor activity at 100 mg/kg bw in an acute neurotoxicity study in rats. A 100-fold safety factor was applied.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Thirteen-week study of toxicity	Toxicity	150 ppm, equal to 26.6 mg/kg bw per day	1000 ppm, equal to 188 mg/kg bw per day
	Eighteen-month study of toxicity and carcinogenicity	Toxicity	30 ppm, equal to 4.2 mg/kg bw per day	150 ppm, equal to 20.9 mg/kg bw per day
		Carcinogenicity	150 ppm, equal to 20.9 mg/kg bw per day	750 ppm, equal to 105 mg/kg bw per day
Rat	Thirteen-week study of toxicity	Toxicity	200 ppm, equal to 12.5 mg/kg bw per day	1000 ppm, equal to 60.5 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
	Two-year study of toxicity and carcinogenicity	Toxicity	30 ppm, equal to 1.2 mg/kg bw per day	150 ppm, equal to 6.0 mg/kg bw per day
		Carcinogenicity	150 ppm, equal to 8.6 mg/kg bw per day	1500 ppm, equal to 89 mg/kg bw per day
	Multigeneration study of reproductive toxicity	Fertility	1200 ppm, equal to 82.4 mg/kg bw per day[a]	—
		Parental toxicity	220 ppm, equal to 13.9 mg/kg bw per day	1200 ppm, equal to 82.4 mg/kg bw per day
		Offspring toxicity	220 ppm, equal to 13.9 mg/kg bw per day	1200 ppm, equal to 82.4 mg/kg bw per day
	Developmental toxicity study[b]	Maternal toxicity	30 mg/kg bw per day	150 mg/kg bw per day
		Embryo and fetal toxicity	150 mg/kg bw per day	450 mg/kg bw per day
	Acute neurotoxicity study[b]	Neurotoxicity	50 mg/kg bw	100 mg/kg bw
	Subchronic neurotoxicity study	Neurotoxicity	2500 ppm, equal to 164.2 mg/kg bw per day[a]	—
Rabbit	Developmental toxicity study[b]	Maternal toxicity	25 mg/kg bw per day	75 mg/kg bw per day
		Embryo and fetal toxicity	25 mg/kg bw per day	75 mg/kg bw per day
Dog	Thirteen-week and 1-year studies of toxicity[c]	Toxicity	800 ppm, equal to 28.5 mg/kg bw per day	2000 ppm, equal to 66.1 mg/kg bw per day

[a] Highest dose tested.

[b] Gavage administration.

[c] Two or more studies combined.

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

0.5 mg/kg bw

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

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

Critical end-points for setting guidance values for exposure to fluopyram

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption	Rapid; approximately 93%
Distribution	Wide; highest concentrations in liver and kidney
Rate and extent of excretion	> 95% within 168 h (35–60% in urine; 39–64% in faeces; up to 79–87% in bile)

Potential for accumulation	None
Metabolism in animals	Extensive; hydroxylation, oxidation and hydrolytic cleavage of the molecule, followed by conjugation (glucuronic acid, sulfate)
Toxicologically significant compounds (animals, plants and the environment)	Fluopyram
Acute toxicity	
Rat, LD_{50}, oral	> 2000 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.1 mg/L (4 h, nose-only exposure)
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Minimally irritating
Mouse, dermal sensitization	Not sensitizing (local lymph node assay)
Short-term studies of toxicity	
Target/critical effect	Liver (enzyme induction, hypertrophy, single-cell necrosis) in mice, rats and dogs, adrenals (cortical hypertrophy and vacuolation) in mice
Lowest relevant oral NOAEL	12.5 mg/kg bw per day (90-day study in rats)
Lowest relevant dermal NOAEL	300 mg/kg bw per day (28-day study in rats)
Lowest relevant inhalation NOAEC	No data
Long-term toxicity and carcinogenicity	
Target/critical effect	Liver (hypertrophy, single-cell degeneration/necrosis) in mice and rats
Lowest relevant NOAEL	1.2 mg/kg bw per day (2-year study in rats)
Carcinogenicity	Unlikely to pose a carcinogenic risk to humans at levels of dietary exposure
Genotoxicity	
	No genotoxic potential
Reproductive toxicity	
Reproductive target/critical effect	No effects on fertility at highest dose tested; decreased body weight gain in pups at parentally toxic dose
Lowest relevant reproductive NOAEL	13.9 mg/kg bw per day for offspring toxicity (two-generation study in rats)
Developmental target/critical effect	Decreased fetal weight and increased number of small fetuses at maternally toxic dose
Lowest relevant developmental NOAEL	25 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity	Decrease in motor and locomotor activity; NOAEL: 50 mg/kg bw
Subchronic neurotoxicity	No evidence of neurotoxicity at highest dose tested
Other toxicological studies	
Mechanistic studies	Studies on liver enzyme induction (rats, mice) and thyroid hormone levels (mice) suggest a non-genotoxic threshold

	mechanism for carcinogenicity
Studies on plant metabolites	Fluopyram-pyridyl-carboxylic acid (AE C657188): lower toxicity than parent compound, not genotoxic in vitro
	Fluopyram-methyl-sulfoxide (AE 1344122): lower toxicity than parent compound, not genotoxic in vitro
Medical data	
	Limited data; no adverse health effects reported in manufacturing plant personnel

Summary

	Value	Study	Safety factor
ADI	0–0.01 mg/kg bw	Two-year study of toxicity in rat	100
ARfD	0.5 mg/kg bw	Acute neurotoxicity study in rat	100

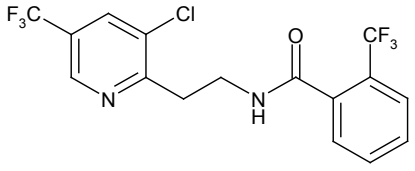
RESIDUE AND ANALYTICAL ASPECTS

Fluopyram, a pyridylethylamide broad spectrum fungicide, is being developed for protection against a range of Ascomycete and Deuteromycete diseases in many horticultural and arable crops. Fungicidal action is by the inhibition of succinate dehydrogenase (complex II) within the fungal mitochondrial respiratory chain, thus blocking electron transport. Fluopyram inhibits spore germination, germ tube elongation, mycelium growth and sporulation. Within plants, fluopyram shows translaminar activity and some upwards movement within the xylem.

Authorisations exist for the use of fluopyram (SC formulation) in China and registration has recently been granted in Romania for use on grapes. Other uses are currently being progressed in Europe and North America.

Residue and analytical aspects of fluopyram were considered for the first time by the present meeting. The manufacturer submitted studies on metabolism, analytical methods, supervised field trials, processing, freezer storage stability, environmental fate in soil and rotational crop residues.

Fluopyram is N-{2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethyl}-2-(trifluoromethyl)benzamide. It is relatively insoluble in water (15 mg/L), stable to hydrolysis, of low volatility (1.2 x 10^{-6} Pa at 20 °C), has a log P_{OW} of 3.3 and is soluble (> 250 g/L) in methanol, dichloromethane, acetone, ethyl acetate and dimethyl sulfoxide.



Fluopyram (AE C656948)

The following abbreviations are used for the metabolites discussed below:

BZM	-benzamide	2-(trifluoromethyl)benzamide
PAA	-pyridyl-acetic acid	[3-chloro-5-(trifluoromethyl)pyridin-2-yl]acetic acid
PCA [a]	-pyridyl-carboxylic acid	3-chloro-5-(trifluoromethyl)pyridine-2-carboxylic acid
7-OH	-7-hydroxy	N-{2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-2-hydroxyethyl}-2-trifluoromethyl) benzamide
8-OH	-8-hydroxy	N-{2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1-hydroxyethyl}-2-

	trifluoromethyl) benzamide
E-olefine	N-{(E)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl}-2-trifluoromethyl) benzamide
Z-olefine	N-{(Z)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-trifluoromethyl) benzamide
GA	glucuronic acid
glyc	glycoside
glc	glucoside

[a] Also a metabolite of fluopicolide (M05)

Animal metabolism

The Meeting received information on the metabolism of radio-labelled fluopyram (separately ^{14}C-labelled at the [pyridyl-2,6-^{14}C]- and [phenyl-U-^{14}C]-rings) in rats, lactating goats and laying hens.

In rats, absorption was rapid and residues in tissues at 168 h accounted for < 0.5% (pyridyl ring-label) or 3–5% (phenyl ring-label) of the administered dose, with liver and kidney containing the highest concentrations of residues. Elimination of the radiolabel was via the faeces (39–64%) and the urine (35–60%).

The metabolism of fluopyram in rats was principally oxidative and took place mainly at the ethylene bridge of the molecule. Also, hydrolytic cleavage of the molecule and subsequent oxidation was observed, as was conjugation of several hydroxylated metabolites with glucuronic acid and to a lesser extent with sulphate. Somewhat higher levels of unchanged parent compound in tissues of female rats compared to male rats indicated that the metabolic transformation of the parent compound was generally more pronounced in males.

Lactating goats were orally dosed with [pyridyl-2,6-^{14}C]- or [phenyl-U-^{14}C]-fluopyram at doses equivalent to approximately 45 ppm in the feed for 5 consecutive days and sacrificed 24 hours after the last dose.

The majority of the administered dose was recovered in excreta (29–36% in faeces, 52–53% in urine) with an estimated 7–18% assumed to have remained in the gastro-intestinal tract. Radioactivity retained in tissues or secreted in milk accounted for about 5% (phenyl-label) and less than 1% (pyridyl-label) of the administered dose. Overall 82–93% of administered radioactivity was accounted for.

Radio-labelled residues (fluopyram equivalents) in the phenyl-label study were highest in liver (8.4 mg/kg) and kidney (2.3 mg/kg) and were 0.74 mg/kg in muscle, 0.4 mg/kg in fat and 0.25 mg/kg in milk. Except for fat, much lower residues (but a similar distribution) occurred in the pyridyl-label study, with highest residues in liver (1.4 mg/kg) and kidney (0.4 mg/kg) and were 0.04 mg/kg in muscle and 0.05 mg/kg in milk. In fat, residues reported in the two studies were comparable (0.37–0.4 mg/kg).

In the phenyl-label study, the TRR-values in milk increased continuously over the 5 day dosing period without reaching a plateau, suggesting ongoing absorption, rapid distribution and delayed excretion. The equivalent concentrations in milk samples ranged from 0.05 (8 hours after the first dose) to 0.45 mg/kg (24 hours after the last of 5 doses), with a cumulative total representing 0.56% of the total applied dose. However, in the pyridyl-label study, TRR-values increased during the 8 hour period after each dosing and then decreased (suggesting rapid absorption, distribution and elimination) and reached plateau-levels within 24 hours. The highest TRR-value in milk (0.063 mg/kg) was detected 32 hours after the first dose, with a cumulative total TRR of 0.08% of the total applied dose.

The two metabolism studies were combined using appropriate scaling to obtain an overall picture of the metabolism and the scaled results indicated that residues of BZM represented 98% of the TRR in muscle, 89% TRR in milk, 81% TRR in liver, 73% TRR in kidney and 48% in fat. The Z- and E-olefine isomers made up about 13% and 8% TRR in fat respectively. Residues of the parent compound were about 18% TRR in fat and were less than 1% TRR in all other matrices. Other metabolites were present at less than 10% in any matrix.

Laying hens were orally dosed with [pyridyl-2,6-^{14}C]- or [phenyl-U-^{14}C]-fluopyram at doses equivalent to approximately 26 ppm in the feed for 14 consecutive days and sacrificed 24 hours after the last dose.

The majority of the administered dose was recovered in excreta (83–95%) with an estimated 4–5% assumed to have remained in the gastro-intestinal tract. Radioactivity retained in tissues or found in eggs accounted for about 12% (phenyl-label) and less than 1% (pyridyl-label) of the administered dose. Overall 95–96% of administered radioactivity was accounted for.

Radio-labelled residues in the pyridyl-label study were considerably lower than those in the phenyl-label study (consistent with the results of the goat metabolism studies). Total residues were highest in liver (9.5 mg/kg in the phenyl-label study, 0.54 mg/kg in the pyridyl-label study). In kidney, the phenyl-label residues were 5.8mg/kg and the pyridyl-label residues were 0.24 mg/kg. In muscle, total radioactive residues were 3.3 mg/kg (phenyl-label) and 0.05 mg/kg (pyridyl-label) and were 2.5 mg/kg (phenyl-label) and 0.15 mg/kg (pyridyl-label) in skin. Residues in fat were 1.7 mg/kg in the phenyl-label study and 0.5 mg/kg in the pyridyl-label study.

In eggs, after 8 days, the TRR values in eggs increased to 3.2 mg/kg (phenyl-label study) and to 0.32 mg/kg (pyridyl-label study), reaching a plateau after 8–10 days. The residue-level in the eggs collected from the ovary and oviduct were about 1.5× (phenyl-label) and about 3× (pyridyl-label) higher than those in the laid eggs at the test end, suggesting that the egg yolk was probably the preferred site for the secretion.

The two metabolism studies were combined using appropriate scaling to obtain an overall picture of the metabolism and the scaled results indicated that the BZM metabolite was the major component of the extracted radioactivity identified in muscle (98% TRR), liver (89% TRR), eggs (90% TRR) and fat (68% TRR). The only other metabolite found above 10% TRR was the Z-olefine isomer, found in fat at about 26% TRR. Fluopyram was found in fat at about 2.5% TRR and made up less than 1% TRR in other matrices.

In summary, BZM was the main residue component in edible livestock matrices, making up more than about 90% of the residues in milk, eggs and muscle, about 80–90% of the residues in liver and about 73% of the residues in kidney. The predominant residues in fat were the BZM metabolite (48–68%), the E-/Z-olefine isomers (21–26%) and to a lesser extent fluopyram (18% of the residues in ruminant fat).

The proposed metabolic pathway in livestock (hen and goat) includes hydroxylation of the parent compound to the 7-OH and 8-OH metabolites, the formation of the Z/E-olefines, cleavage of the fluopyram molecule to produce BZM (from the phenyl-label) and PAA (from the pyridyl-label) and conjugation of the hydroxylated parent compound, mainly with glucuronic acid.

These main metabolic reactions are also observed in the rat metabolism studies.

Plant metabolism

The Meeting received information on the metabolism of radio-labelled fluopyram (separately ^{14}C-labelled at the [pyridyl-2,6-^{14}C]- and [phenyl-U-^{14}C]-rings) in grapes, potatoes, and beans after two or three spray applications at a maximum annual application rate of 0.5 kg ai/ha and on red bell pepper applying 5 mg ai/plant through the drip irrigation system. To facilitate metabolite identification in bell pepper a 4× overdose experiment was also performed at an application rate of 20 mg ai/plant.

In grapes treated three times at 42–49 day intervals up to the start of ripening (total 0.5 kg ai/ha) and sampled 18–19 days later, 77–80% (1.3–1.5 mg/kg fluopyram equivalents) of the radioactive residue in grapes was found in the acetonitrile surface wash and a further 19–20% (0.34 mg/kg) was obtained by triple-extraction in acetonitrile/water. Residues in leaves sampled immediately after the second application were 28–64 mg/kg and were 43–48 mg/kg at harvest 19 days after the third application.

Between 94% and 99% of the TRR was identified, mostly as the unchanged fluopyram (96–98% in grapes and 91–92% in leaves) with minor components being the BZM, the 7-OH (and its glycoside), the 8-OH and the PCA metabolites, all present in grapes or leaves at 1% TRR or less.

In potatoes foliar treated three times at 11–16 day intervals up to berry development (total 0.5 kg ai/ha) and sampled 51 days later, total radioactive residues in tubers were very low (0.008–0.012 mg/kg) and were 22–48 mg/kg in leaves.

Between 74% and 99% of the TRR was identified, mostly as the unchanged fluopyram (23–69% in tubers and 98% in leaves) with the PCA metabolite (pyridyl-label) also present in tubers at about 50% TRR (0.006 mg/kg) and 0.5% (0.11 mg/kg) in leaves. Minor residue components were the BZM and the 7-OH metabolites, present in tubers or leaves at 7% TRR or less.

In beans treated twice at the equivalent of 0.25–0.27 kg ai/ha, 28 days apart (total 0.5 kg ai/ha) and sampled as green beans and foliage (4 days after the last application), as succulent beans (without pods) and straw (29 days after the last application) and as dry beans (29 days after the last application and a further 11 days drying), total radioactive residues were 1.4–3.9 mg/kg (green beans), 0.07–0.17 mg/kg (succulent beans), 0.12–0.31 mg/kg (dry beans), 37–39 mg/kg (foliage) and 17–19 mg/kg in straw (vines and empty pods).

Between 76% and 99% of the TRR was identified, mostly as the unchanged fluopyram (92–99% in green beans and foliage and 87–90% in straw), as the BZM metabolite (52% in succulent beans and 64% in dry beans) or as the PAA and PCA metabolites (30–31% in succulent beans and 23–33% in dry beans). Glycoside-glucuronic acid conjugates of the hydroxylated fluopyram were also found at up to 10% TRR in dry and succulent beans.

In sweet peppers treated with a single drip irrigation application of 5 mg ai/plant and harvested at fruit maturity, 55–96 days later, total radioactive residues were 0.04–0.06 mg/kg (fruit) and 2.3–3.5 mg/kg (plants without fruit). In plants treated at 20 mg ai/plant (4×), TRRs were 6.2–18 mg/kg in plants sampled 33 days after treatment.

Between 78% and 98% of the TRR was identified, mostly as the unchanged fluopyram (16–49% in fruit, 64–70% in plants (without fruits) and 87–88% in the 4× plants), as the BZM metabolite (16% TRR in fruit and 10% in plants or as the PCA metabolite (20–44% TRR) and PAA-glycoside isomers (individually ranging from 13–24% TRR).

In summary, residues of unchanged fluopyram account for the major part of the residues in grapes and green beans and also occur at lower levels in potatoes, drip-irrigated red peppers, dry and succulent beans (without pods), where the commodities are not directly exposed to fluopyram spray applications. In these latter commodities, significant levels of the cleavage products BZM and to a lesser extent the PCA and PAA metabolites also occur, generally at concentrations close to the combined fluopyram plus BZM levels. The PCA metabolite residues were up to 0.1 mg/kg in dry beans, less than 0.05 mg/kg in succulent beans (without pods) and peppers (drip irrigated) and less than 0.01 mg/kg in potatoes. Residues of the PAA metabolite in beans were 0.05–0.07 mg/kg in both the fresh and dry beans (without pods).

The proposed metabolic pathway in plants involves hydroxylation of the parent compound to the 7-OH and 8-OH metabolites and subsequent conjugation (mainly with sugars), cleavage of the parent molecule to produce the BZM, PAA and PCA metabolites.

With the exception of PCA and its methyl-sulfoxide derivative, the main metabolites in plants are also observed in the rat, goat and poultry metabolism studies.

Environmental fate in soil

The Meeting received information the environmental fate and behaviour of fluopyram, including hydrolytic stability, aerobic degradation in soil, photolysis on the soil surface, field dissipation and confined and field rotational crop studies. Radio-labelled fluopyram (separately ^{14}C-labelled at the [pyridyl-2,6-^{14}C]- and [phenyl-U-^{14}C]-rings) were used in the confined soil degradation and rotational crop studies.

Hydrolysis

Fluopyram was stable in sterile aqueous buffered solutions at pH 4, 7 and 9 when stored at 50 °C in the dark for 5 days. One minor degradate was measured, at up to 1.6% applied radiolabel, in the pH 7 and pH 9 solutions at the end of the test period.

Photolysis

After exposure to continuous artificial sunlight for 13 days, radio-labelled fluopyram residues in sterile buffer solutions decreased to 64–72% of the applied phenyl and pyridyl ring radiolabels. In both studies, the one major degradation product was the lactame degradate, comprising 12–13% of the applied radiolabel. A number of minor degradation products were reported, all at less than 4.2% of the applied amount. Based on simple first order degradation kinetics, experimental DT_{50} values of 21–25 days and DT_{90} values of 70–83 days were calculated.

In soil treated with the equivalent of 0.25 kg ai/ha and exposed to artificial irradiation for 23 days, phenyl ring radio-labelled fluopyram was stable, with no organic volatiles or degradation products being detected, about 0.2% of the applied radio-label being mineralised to $^{14}CO_2$ and non-extractable residues increasing to a maximum of 2.3%.

Aerobic soil metabolism

Studies were conducted in four European soils (2 loam soils, a silt-loam and a sandy-loam) with radio-labelled (phenyl ring) fluopyram at a target rate of 0.67 mg/kg soil (equivalent to 250 g/ha, mixed to 2.5 cm depth). In these studies, soils were incubated in the dark for 121–128 days at 20 °C and samples were collected at intervals up to 128 days after application.

Fluopyram was slowly degraded with an estimated single first order (SFO) half-lives of 165–339 day (mean 239 days). The identified soil metabolites were BZM (maximum 1.1%TARafter 30 days), 7-OH (maximum 3.3–4.2%TARafter 30–60 days), PCA (maximum 0.7%TARafter 30 days) and the methyl sulfoxide (maximum 1%TARat 128 days). The estimated single first order half-lives for the 7-OH metabolite ranged from 7.5–16 days..

In two US soils (silty clay loam and sandy loam), radio-labelled fluopyram was applied to soil at 0.11–0.13 mg ai/kg (equivalent to 250 g/ha mixed to 15 cm depth), the soils were incubated in the dark at 25 °C for 365 days and sampled at 12 regular intervals during the 1 year study period.

Fluopyram (parent) residues decreased to 60–71 % in the two soils and the SFO model half-lives were 922 days and 484 days. Apart from CO_2, no metabolite of significance was detected in either soil and volatile residues were insignificant. No intermediate metabolites accumulated in the aerobic soil system.

The proposed metabolic pathway of fluopyram in soil includes hydroxylation to form the 7-OH metabolite, cleavage of the parent molecule and the formation of the BZM and the PCA metabolites, the latter being further metabolized to the methyl-sulfoxide. Microbial breakdown leads to the formation of carbon dioxide and soil bound residues and all degradation products were either further transformed to their metabolic downstream products, mineralized (5–24% AR), or substantially integrated into the soil matrix as non-extractable residues (9–15%) after 128 days incubation.

Soil dissipation

In six European field studies involving bare soil (pre-emergent - grass) treatments equivalent to 0.25 kg ai/ha, about 50% of the total applied fluopyram disappearing within 21 to 347 days after treatment in the different soils. Dissipation then proceeded more slowly until the end of the 2-year study when residues remaining were 3–27% of the total applied amount. The time required for dissipation of 90% of the initial concentration of fluopyram ranged from 497 to more than 1000 days.

Interim results of a 4-year soil dissipation study in Europe (two sites) involving annual applications of 0.25 kg ai/ha report an increase in fluopyram residues at the end of each year, from 23–47% of the annual application rate just before the 2nd application to 46–66% of the annual application rate just before the 3rd application.

Five field dissipation studies were conducted in USA with fluopyram (0.5 kg ai/ha) being applied to bare soil. Fluopyram showed biphasic degradation behaviour (double first order in parallel (DFOP) kinetics model) with estimated DT_{50} values of 24 days, 87 days and 166–537 days with 21–44% of the applied residue remaining after 18–22 months. DT_{75} values in these studies ranged from 500 to more than 1000 days.

The observed transformation products were 7-OH, BZM, and PCA metabolites, only found above the LOQ (1.0 µg/kg) in the top 15 cm segment. The highest concentrations found were 3.0 µg/kg (7-OH), 9.7 µg/kg (BZM) and 10 µg/kg (PCA). Residues of BZM and PCA were below the LOQ (1 µg/kg) at all sites within 30 days after treatment. In four of the sites, residues of 7-OH were below the LOQ after 9 months and at one site, were present at about 1.6 µg/kg (mostly in the top 15 cm segment) at the end of the 22-month study period.

Residues in succeeding crops

In rotational crop metabolism studies involving wheat, Swiss chard and turnips as representative crops (small grains, leafy crops and root crops respectively), 1st, 2nd and 3rd rotation crops were planted 30, 139 and 280 days after a single bare-soil spray treatment at a nominal rate of 0.5 kg ai/ha radio-labelled fluopyram (separately ^{14}C-labelled at the [pyridyl-2,6-^{14}C]- and [phenyl-U-^{14}C]-rings).

Total radioactive residues (fluopyram equivalents) were found in all matrices from the 1st rotation crops, at levels ranging from 0.04–0.07 mg/kg (turnip roots) to 6.1–6.7 mg/kg (wheat straw). Total residues decreased in the 2nd rotation crops (0.01–3.5 mg/kg) and decreased further to < 0.01–1.6 mg/kg in the 3rd rotation crops.

Fluopyram was the major residue in most commodities, accounting for 20–95% of the TRR in wheat matrices, Swiss chard, turnip leaves and roots.

The 7-OH metabolite was a significant residue in Swiss chard (21–39% TRR in all rotations), with the BZM metabolite occurring at close to 10% TRR in Swiss chard and turnip leaves of the first rotation. In all other commodities the BZM metabolite was only a minor component. The PCA metabolite was the main residue component in wheat grains from the first rotation, accounting for about half the TRR and the methyl-sulfoxide metabolite, a degradation product of PCA, was a significant residue in wheat grains in the second rotation (49% TRR).

Rotational crop field studies were conducted in Europe where wheat, turnip/carrot and lettuce were planted as representative crops in bare soil treated with 0.5 kg ai/ha or following harvest of lettuce (primary crop) treated with 0.5 kg ai/ha. Plant-back intervals in these trials were 28–49 days (1st rotation), 90–240 days (2nd rotation) and 286–320 days (3rd rotation).

Fluopyram was found in all commodities with highest residues present in wheat straw and forage (0.28 mg/kg and 0.12 mg/kg respectively). Residues were also present in wheat grain, lettuce, turnip and carrot tops and roots at levels of 0.01–0.05 mg/kg.

Residues of the 7-OH metabolite were only found in wheat straw at levels of 0.11–0.08 mg/kg with residues of the BZM and the methyl-sulfoxide metabolites also present at 0.14 mg/kg and 0.07 mg/kg respectively.

In rotational crop studies in North America where alfalfa and cotton were planted 12–14 days after the last of two applications of fluopyram (total 0.5 kg ai/ha), fluopyram residues were not found in cotton seed, were less than 0.02 mg/kg in cotton gin trash and were generally less than 0.1 mg/kg in alfalfa forage (except in 2 of the 12 sites where residues in 1st cut forage were up to 0.39 mg/kg and up to 0.19 mg/kg in 3rd cut forage). Residues in alfalfa hay, sampled at the same times as the forage showed a similar pattern (taking into account the increased dry matter content).

In a limited rotational crop study in North America where wheat, turnip and mustard greens were planted in rotation with cover crops treated with 2× 0.25 kg ai/ha fluopyram (plant-back interval of about 240 days), residues of fluopyram were found in all commodities except wheat grain and turnip roots. Maximum residues found were 0.12 mg/kg in wheat straw, 0.09 mg/kg in wheat hay, 0.05 mg/kg in wheat forage and 0.04 mg/kg in turnip tops and in fresh mustard leaves.

In summary, at plant-back intervals of more than 28 days, residues of fluopyram can be expected at low levels (0.01–0.05 mg/kg) in root crops, cereal grain crops and in leafy vegetables grown as rotational crops, with higher levels likely to occur in cereal forage (up to 0.12 mg/kg) and feed commodities (up to 0.28 mg/kg in straw). Levels of up to 0.11 mg/kg of the 7-OH metabolite and up to 0.14 mg/kg of the BZM metabolite could occur in cereal straw and residues of the methyl-sulfoxide metabolite may also occur in cereal grain (up to 0.09 mg/kg), cereal forage (up to 0.06 mg/kg) and cereal straw (up to 0.07 mg/kg).

Methods of analysis

Several analytical methods have been reported for the analysis of fluopyram and for selected metabolites and in animal commodities. The basic approach employs extraction by homogenisation with acetonitrile/water and in some methods, additional clean-up using SPE or liquid/liquid partition. Residues are determined by liquid chromatography with mass spectrometric detection.

The methods for fluopyram and selected metabolites have been validated for a range of substrates with LOQs of 0.01 mg/kg for each analyte (0.05 mg/kg for wheat straw). Studies on extraction efficiency indicated that in most matrices, greater than 80% of the residue can be extracted with acetonitrile/water with single and double extraction and that comparable results can be achieved for fluopyram using acetone/water extraction (as used in the DFG S19 multi-residue method).

In the methods used to measure fluopyram metabolites in plant commodities, dilution under acid conditions allowed the determination of the PCA metabolite and its methyl-sulfoxide derivative while a parallel dilution under basic conditions allowed the determination of fluopyram and the BZM, 7-OH and PAA metabolites.

For analysis of animal commodities, extracts are cleaned-up on a C18 cartridge and further diluted with methanol/water (containing the corresponding internal standards) before analysis for fluopyram, the BZM metabolite and the sum of the two olefine isomers (because of internal inter-conversion between the E-isomer and the Z-isomer).

Based on the results of validation studies and the concurrent recovery rates achieved in the supervised field trials, the available analytical methods fulfilled the following criteria:-

- adequate limit of quantification
- mean recovery 70–110%
- relative standard deviation of recovery rates < 20%
- interfering blanks lower than 30% of the limit of quantification.

The European multi-residue method DFG S19 method used in combination with GC/MS was validated as a multi-residue enforcement method to monitor residues of fluopyram in both plant and animal matrices, but is not applicable as an enforcement method for the BZM metabolite. The US-FDA PAM 1 multi-residue methods (E1 extraction and DG17 detection without Florisil cleanup) are also suitable for detection and enforcement of fluopyram in non-fatty matrices but are also not suitable for measuring the BZM residues. For animal tissues, milk and eggs, a modification of the data collection method was validated as an enforcement method for measuring fluopyram and its BZM metabolite.

Stability of residues in stored analytical samples

Freezer storage stability was tested for a range of representative substrates covering those with a high water content (lettuce), a high starch content (wheat grain), a high protein content (dry pea seed), a high oil content (rape seed) and a high acid content (orange).

Fluopyram and major metabolites (BZM, PAA and PCA) are stable in these representative substrates for at least 24 months in frozen storage. Residues of the PCA metabolite are stable in grapes potato tubers, cabbage leaves and wheat grain for at least 30 months in frozen storage and residues of the methyl-sulfoxide metabolite in wheat forage, straw and grain are stable for at least 25 months in frozen storage.

Definition of the residue

In animal commodities, BZM is the main residue in edible animal tissues, milk and eggs, with the combined E/Z olefine isomers and the parent compound being major components only in fat of ruminants and poultry.

Although a suitable multi-residue method was not available to measure these components, an HPLC-MS/MS method measuring fluopyram and the BZM metabolite has been validated for MRL-compliance and the Meeting recommended that for MRL-compliance, the residue definition should be fluopyram and its BZM metabolite.

For animal commodity dietary intake estimation, in addition to the parent compound and the BZM metabolite, the E/Z olefine isomers contributes about 30% to the final residue in ruminant and poultry fat.

Both BZM (2-(trifluoromethyl)benzamide) and to a much lesser extent the E/Z olefine isomers (N-{(E)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-trifluoromethyl) benzamide and N-{(Z)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-trifluoromethyl) benzamide) also occur in rats and are adequately covered in the derived toxicological reference doses and the Meeting agreed that these metabolites should be included in the residue definition.

The compound fluopyram has a log K_{ow} of 3.3, suggesting that it is fat-soluble, and this is supported by the preferential partitioning into milk fat (cream) and fat reported in a cow feeding study. Analysis of skim milk and heavy cream in the cow feeding study also indicated that the combined E/Z olefine isomers also show preferential partitioning into fat (0.12:1). However the BZM metabolite (the major component of the residue in eggs, milk and animal tissues) is not fat-soluble. The Meeting therefore concluded that fluopyram (as defined in the residue definitions for animal commodities) is not fat-soluble.

Fluopyram is the major residue in treated plant commodities and where residues occur in rotational crops, fluopyram is also the major residue. The Meeting also noted that multi-residue analytical methods exist to measure the parent residues and agreed that for MRL-compliance, the residue definition for plant commodities should be fluopyram.

Metabolites identified in the plant metabolism studies at more than 10% TRR are BZM, PCA and PAA. While these metabolites were generally present at not more than 1% TRR and below

0.02 mg/kg in most edible commodities, higher percentages (up to 60% TRR but at relatively low concentrations up to 0.1 mg/kg) were found in commodities not directly exposed to spray applications (drip irrigated peppers, potato tubers and beans without pods). In wheat grown as a rotational crop, PCA was found in grain at up to 56% TRR and 0.23 mg/kg.

In supervised crop field trials, residues of BZM, PCA and to a lesser extent PAA were sometimes detected in a number of commodities, mostly at longer PHIs of 10–21 days and generally at levels below 0.02 mg/kg. Higher levels of BZM and less frequently, PCA and its methyl sulfoxide (up to about 0.1 mg/kg) and PAA (rarely more than 0.05 mg/kg) were found occasionally in some legumes and brassicas, rape seed, grapes, lettuce and strawberries. The related parent residues are usually more than twice the metabolite levels.

Two of the main metabolites in plants (BZM and PAA) are also observed in the animal metabolism studies and the toxicology of these metabolites are addressed in the rat studies and are covered by the derived reference doses. Sufficient toxicology information is available to confirm that the PCA metabolite and its methyl sulfoxide, common metabolites with fluopicolide, are significantly less toxic than fluopyram

The Meeting therefore agreed that the BZM, PCA and PAA metabolites need not be included in the plant commodity residue definitions for MRL enforcement or estimation of dietary intake.

Proposed definition of the residue (for compliance with the MRL and for estimation of dietary intake for plant commodities): *fluopyram.*

Proposed definition of the residue (for compliance with the MRL for animal commodities): *sum of fluopyram and 2-(trifluoromethyl) benzamide, expressed as fluopyram.*

Proposed definition of the residue (for estimation of dietary intake for animal commodities: *sum of fluopyram, 2-(trifluoromethyl)benzamide and the combined residues of N-{(E)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-trifluoromethyl) benzamide and N-{(Z)-2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethenyl}-2-trifluoromethyl) benzamide, all expressed as fluopyram.*

The residue is not fat-soluble.

Results of supervised trials on crops

The Meeting received supervised trial data for foliar applications of fluopyram (SC formulations) on a wide range of fruit, vegetable, cereal, tree nut, oilseed, hops and herb crops and for drip-line irrigation treatments to strawberries and cucurbits and for seed treatment to cereals. These trials were conducted mainly in Europe and/or North America.

The NAFTA calculator was used as a tool in the estimation the maximum residue level from the selected residue data set 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.

The Meeting noted that GAP has been authorised for the use of fluopyram (500 SC) on table and wine grapes in Romania and on cucumbers in China.

Grapes

GAP for fluopyram in Romania is 2× 0.25 kg ai/ha (max), PHI 21 days for wine grapes and 3 days for table grapes. Residues in trials in South Europe matching the Romanian wine grape GAP (i.e., PHI 21 days) in wine grapes were: 0.26, 0.34, 0.35, 0.36, 0.44, 0.46 and 0.56 mg/kg (n = 7) and in table

grapes were: 0.13, 0.22, 0.28, 0.41, 0.44, 0.61 and 0.63 mg/kg (n = 7). As these data sets were not from different populations, the Meeting agreed to combine the results, giving a data set of: 0.13, 0.22, 0.26, 0.28, 0.34, 0.35, 0.36, 0.41, 0.44, 0.44, 0.46, 0.56, 0.61 and 0.63 mg/kg (n = 14).

In trials matching the GAP for table grapes in Romania (i.e., PHI of 3 days), residues in trials from Europe (on table grapes) were: 0.3, 0.34, 0.55, 0.6, 0.66, 0.96 and 1 mg/kg (n = 7) and on wine grapes were: 0.36, 0.51, 0.57, 0.58, 0.58, 0.63 and 0.63 mg/kg (n = 7). As these data sets were not from different populations, the Meeting agreed to combine the results, giving a data set of: 0.3, 0.34, 0.36, 0.51, 0.55, 0.57, 0.58, 0.58, 0.6, 0.63, 0.63, 0.66, 0.96 and 1 mg/kg (n = 14).

The Meeting agreed to use the data from the European trials on grapes matching the Romanian GAP for table grapes (PHI 3 days) and estimated a maximum residue level of 2 mg/kg, an STMR of 0.58 mg/kg and an HR of 1 mg/kg for fluopyram on grapes. The value derived from use of the NAFTA Calculator was 1.3 mg/kg (unrounded).

Cucumber

Supervised residue trial data and GAP information on the use of fluopyram as a foliar spray on cucumber in China were provided to the Meeting. The GAP for use in China is for up to 3 foliar applications of 0.075 kg ai/ha at 7–10 day intervals and the PHI is 2 days.

In six trials matching this GAP, fluopyram residues were 0.05, 0.07, 0.08, 0.14, 0.17 and 0.19 mg/kg.

The Meeting estimated an STMR of 0.11 mg/kg, an HR of 0.19 mg/kg and recommended a maximum residue level of 0.5 mg/kg. The value derived from use of the NAFTA Calculator was 0.36 mg/kg (unrounded).

Estimation of residues in plant commodities grown as potential succeeding crops

Although the results of the rotational crop studies indicate that potential residues could occur in root crops, cereals and leafy vegetables planted in rotation with cucumbers, the Meeting noted that interim soil accumulation studies suggested that residues could build up following repeat applications and concluded there was insufficient information to estimate a residue plateau level for fluopyram in soil. As this is a prerequisite for estimating possible residues in rotational crops (according to the principles outlined in the JMPR Report 2008, General consideration 2.9), the Meeting was not able to recommend maximum residue levels for fluopyram in rotational crops.

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. Fluopyram was shown to be stable under these conditions.

The fate of fluopyram residues has been examined in a number of studies reflecting household washing, peeling and cooking practices and also simulated commercial processing. Estimated processing factors and STMR-Ps for the commodities considered at this Meeting are summarised below.

Summary of relevant processing factors and STMR-P values for fluopyram residues.

Raw agricultural commodity	Processed commodity	Calculated processing factors [a]	Processing factor (mean or median)	RAC STMR (mg/kg)	STMR-P (mg/kg)
Grape	Juice	< 0.02, < 0.02, < 0.02, < 0.03,	< 0.02 (median)	0.58	< 0.012
	Red wine (young)	0.1, 0.14, 0.16, 0.22	0.16	0.58	0.093
	Red wine [b]	0.14, 0.17, 0.2, 0.2	0.18	0.58	0.104
	Pomace (wet)	2.2, 3.1, 3.6, 3.9	3.2	0.58	1.86

Raw agricultural commodity	Processed commodity	Calculated processing factors [a]	Processing factor (mean or median)	RAC STMR (mg/kg)	STMR-P (mg/kg)
	Raisins	2.0, 2.4, 2.9, 3.2, 6.6	2.9 (median)	0.58	1.68

[a] Each value represents a separate study where residues were above the LOQ in the RAC. The factor is the ratio of the total residue in the processed item divided by the total residue in the RAC.

[b] Wine at first taste (approximately 132 days bottled storage)

In four grape processing studies conducted in Europe, fluopyram residues decreased in juice median processing factor of < 0.02) and in wine (mean processing factor of 0.18) with residues increasing about 3-fold in raisins and wet pomace.

The Meeting agreed to estimate a maximum residue level for dried grapes of 5 mg/kg based on a highest residue for grapes of 1 mg/kg and a median processing factor of 2.9 (1 mg/kg × 2.9 PF). The STMR-P for residues of fluopyram in dried grapes is 1.68 mg/kg and the HR-P is 2.9 mg/kg.

The STMR-P for grape pomace (wet) is 1.86 mg/kg and assuming a default 15% dry matter content, the STMR-P for grape pomace (dry) is 12.4 mg/kg.

The STMR-P for grape juice is 0.012 mg/kg and is 0.1 mg/kg for wine.

The Meeting agreed that for commodities not being considered for maximum residue levels at this meeting, the relevant processing studies would not be reviewed and processing factors would not be estimated at this meeting.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of fluopyram in farm animals on the basis of the diets listed in Annex 6 of the 2009 JMPR Report (OECD Feedstuffs Derived from Field Crops). Based on the estimated STMR-P of 12.4 mg/kg for grape pomace (dry) and the 20% contribution to the Australian dairy and beef cattle diets, the maximum and mean residue contribution is 2.48 mg/kg. Grape pomace is not a significant component of poultry diets.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef and dairy cattle, calculated using the animal diets from US/CAN, EU and Australia in the OECD Table (Annex 6 of the 2006 JMPR Report) are summarised below.

		Animal dietary burden, fluopyram, ppm of dry matter diet		
		US/CAN	EU	Australia
Beef cattle	max	0.0	0.0	2.48 [a]
	mean	0.0	0.0	2.48 [c]
Dairy cattle	max	0.0	0.0	2.48 [b]
	mean	0.0	0.0	2.48 [d]
Poultry – broiler	max	0.0	0.0 [e]	0.0
	mean	0.0	0.0 [f]	0.0
Poultry – layer	max	0.0	0.0 [g]	0.0
	mean	0.0	0.0 [h]	0.0

[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 fluopyram dietary burdens for animal commodity MRL and STMR estimation (residue levels in animal feeds expressed on dry weight) are: 2.48 ppm for beef and dairy cattle and 0.0 ppm for poultry.

Farm animal feeding studies

The Meeting received information on the residue levels arising in animal tissues and milk when dairy cows were dosed with fluopyram for 29 days at the equivalent of 1.5, 14.4, 44 and 133 ppm in the diet. A separate dose group (146 ppm) was used to estimate residue depuration of fluopyram and its major metabolites.

In milk, average residues of fluopyram were not detectable in the 1.5 ppm dose group and increased to 0.12 mg/kg in the highest dose group (133 ppm). In skim milk, fluopyram residues were 0.02 mg/kg and 1.3 mg/kg in centrifuged 'cream' (71–78% milk fat). Residues of BZM, the predominant residue component in milk, increased from 0.04–1.7 mg/kg over the four dose groups while residues of the total-olefine metabolites were above the LOQ only in the two higher dose groups (0.03 mg/kg and 0.12 mg/kg respectively).

In muscle, residues of fluopyram did not exceed 0.03 mg/kg at any dose level and the predominant residue was the BZM metabolite, found at up to 1.4 mg/kg. Residues of the total-olefine metabolites were found above the LOQ (0.02 mg/kg) only in the two higher dose groups, up to 0.04 mg/kg.

In fat, residues of fluopyram were < LOQ in the lowest dose group and increased to 0.58 mg/kg in the 133 ppm dose group and a similar pattern was observed with BZM (up to 0.86 mg/kg). Total-olefine residues were found at up to 0.77 mg/kg.

In liver, fluopyram residues were found in all dose groups, up to 4.0 mg/kg with higher residues of the BZM metabolite also being found in the top three dose groups (1.2–6.9 mg/kg). Residues of the total-olefine isomers were found in the top three dose groups at levels of 0.04–0.5 mg/kg.

In kidney, fluopyram residues were above the LOQ in the two higher dose groups (44 ppm and 133 ppm) at levels of 0.03 mg/kg and 0.07 mg/kg respectively. The predominant residue was the BZM metabolite, present at 0.03–1.6 mg/kg over the four dose groups and residues of the total-olefine metabolites above the LOQ were found in the two higher dose groups at 0.04 mg/kg and 0.13 mg/kg respectively.

Residue depletion was studied in cows dosed orally for 29 days with the equivalent of 146 ppm fluopyram. Fluopyram residues in milk had depleted to < 0.01 mg/kg within 2 days after the last dose and were not detectable after 5 days with residues of BZM and the total-olefine metabolites being < LOQ within 21 days. In tissues, fluopyram residues decreased to less than the LOQ within 7 days (muscle) and within 14 days (fat, liver and kidney). Tissue residues of BZM decreased to less than the LOQ within 14 days in fat and within 21 days in milk with residues of 0.42 mg/kg (liver), 0.19 mg/kg (muscle) and 0.05 mg/kg (kidney) remaining at the end of the study period (21 days after the last dose). Residues of the total-olefine metabolites also remained in fat (0.17 mg/kg) and liver (0.04 mg/kg) at the end of the study period and were < 0.02 mg/kg (LOQ) in muscle within 7 days and within 21 days in kidney.

The Meeting also received information on the residues in tissues and eggs when laying hens were dosed with fluopyram for 28 days at levels equivalent to 0.05, 0.49, 1.6 and 4.8 ppm in the diet.

Fluopyram residues were not detected in eggs or any tissues from any dose groups and residues of the total-olefine metabolites were either not detectable or were at or below 0.02 mg/kg (LOQ) except in skin/fat from the highest (4.8ppm) dose group. The BZM metabolite was the predominant residue and was found in eggs and all tissues up to 1.4 mg/kg in liver, 0.72 mg/kg in eggs, 0.41 mg/kg in skin/fat and 0.29 mg/kg in muscle from the highest dose group.

In the residue depuration dose group (4.8 ppm), residues of the total-olefine metabolites in skin/fat were not detectable within 21 days after the last dose and residues of the BZM metabolite decreased to 0.01 mg/kg in muscle, 0.02 mg/kg in skin/fat, 0.03 mg/kg in eggs and 0.05 mg/kg in liver at the end of the study (21 days after the last dose).

Animal commodity maximum residue levels

The maximum and the mean dietary burden for beef and dairy cattle is 2.48 ppm and residue levels in tissues were obtained by interpolation between the 1.5 ppm and the 14.4 ppm feeding levels.

Dietary burden (mg/kg)[a]		Combined Fluopyram, BZM and Total olefine residues, mg/kg (fluopyram equivalents)[c]								
Feeding level [ppm][b]		Milk	Fat		Muscle		Liver		Kidney	
		mean	high	mean	high	mean	high	mean	high	mean
MRL beef	2.48		*< 0.049*		*< 0.053*		*0.551*		*< 0.057*	
	[1.5:14.4] F [1.5:14.4] B		< 0.01:0.07 0.01:0.33		0:< 0.01 0.02:0.44		0.26:0.98 0.1:1.9		0:< 0.01 0.03:0.38	
MRL dairy	2.48	*0.037*								
	[1.5:14.4] F [1.5:14.4] B	0:0.01 0.02:0.24								
Hi-res cattle			*< 0.076*		*< 0.054*		*< 0.574*		*< 0.059*	
	[1.5:14.4] F [1.5:14.4] B [1.5:14.4] O		< 0.01:0.07 0.01:0.33 < 0.02:0.12		0:< 0.01 0.02:0.44 0:< 0.02		0.26:0.98 0.1:1.9 < 0.02:0.06		0:< 0.01 0.03:0.38 0:< 0.02	
STMR beef	2.48			*< 0.061*		*< 0.043*		*0.472*		*< 0.051*
	[1.5:14.4] F [1.5:14.4] B [1.5:14.4] O			< 0.01:0.04 0.01:0.18 < 0.02:0.09		0:< 0.01 0.02:0.29 0:< 0.02		0.25:0.71 0.1:1.21 0:0.04		0:< 0.01 0.03:0.28 0:< 0.02
STMR dairy	2.48	*< 0.039*								
	[1.5:14.4] F [1.5:14.4] B [1.5:14.4] O	0:0.01 0.02:0.24 0:< 0.02								

[a] Values in parentheses are the estimated dietary burdens

[b] Values in square brackets are the actual feeding levels in the transfer study

[c] Residue values in italics are interpolated from the dietary burden, feeding levels and the residues found in the transfer studies (F = fluopyram, B = BZM, O = total olefins)

High is the highest individual animal tissue residue in the relevant feeding group.

Mean is mean animal tissue residue in the relevant feeding group.

Combined residues of fluopyram and BZM (expressed as fluopyram equivalents) expected in cattle milk and tissues for use in estimating maximum residue levels are: < 0.049 mg/kg (fat), < 0.053 mg/kg (muscle), 0.551 mg/kg (liver) and < 0.057 mg/kg (kidney) and the mean residue for milk is 0.037 mg/kg.

The Meeting estimated maximum residue levels of 0.1 mg/kg for fluopyram in meat (from mammals other than marine mammals), 0.7 mg/kg for edible offal (mammalian), 0.1 mg/kg for fat and 0.07 mg/kg for milks.

Estimated HRs for dietary intake estimation for fluopyram (and including residues of BZM and total olefins) are 0.076 mg/kg for mammalian fat, 0.054 mg/kg for mammalian muscle, 0.574 mg/kg for liver and 0.059 mg/kg for kidney.

Estimated STMRs for dietary intake estimation for fluopyram (and including residues of BZM and total olefins) are 0.061 mg/kg for mammalian fat, 0.043 mg/kg for mammalian muscle, 0.472 mg/kg for mammalian liver, 0.051 mg/kg for mammalian kidney and 0.039 mg/kg for milks.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intake (IEDI) for fluopyram 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 fluopyram for the 13 GEMS/Food regional diets, based on estimated STMRs were 1–6% of the maximum ADI of 0.01 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of fluopyram from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The International Estimated Short-term Intake (IESTI) for fluopyram was calculated for the food commodities for which STMRs or HRs were estimated and for which consumption data were available (Annex 4).

For fluopyram the IESTI varied from 0–4% of the ARfD (0.5 mg/kg bw) for the general population and 0–10% for children. The Meeting concluded that the short-term intake of residues of fluopyram from uses considered by the Meeting is unlikely to present a public health concern.

5.18 MEPTYLDINOCAP (244)

TOXICOLOGY

Meptyldinocap is the International Organization for Standardization (ISO)–approved name for 2-(1-methylheptyl)-4,6-dinitrophenyl crotonate (International Union of Pure and Applied Chemistry [IUPAC]), with Chemical Abstracts Service (CAS) No. 131-72-6. Meptyldinocap is a new dinitrophenolic fungicidal compound, which acts by uncoupling mitochondrial oxidative phosphorylation. Meptyldinocap was reviewed for the first time by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) on the request of the Codex Committee on Pesticide Residues (CCPR).

Meptyldinocap is one of the six structural analogues present in the existing active substance dinocap. Dinocap was evaluated previously by the JMPR in 1969, 1974, 1989, 1998 and 2000. In 1998, the acceptable daily intake (ADI) and the acute reference dose (ARfD) for dinocap were established at 0–0.008 mg/kg body weight (bw) and 0.008 mg/kg bw, respectively. In 2000, two ARfDs were established for dinocap, one for women of childbearing age, at 0.008 mg/kg bw, and another for the general population, at 0.03 mg/kg bw. Dinocap contains approximately 22% meptyldinocap.

The database supporting meptyldinocap consists of some new studies performed with meptyldinocap together with earlier studies performed with dinocap. Previously evaluated studies with dinocap were reviewed at the Meeting but are summarized only briefly. Most of the pivotal studies met the basic requirements of the relevant Organisation for Economic Co-operation and Development (OECD) or national test guidelines, although the level of detail in some of the older reports of studies performed with dinocap did not always meet current requirements. A number of studies using dinocap did not contain certificates of compliance with good laboratory practice (GLP).

Biochemical aspects

No new absorption, distribution, metabolism and excretion (ADME) studies on meptyldinocap in mammals have been conducted. However, in a number of the ADME studies with dinocap, the radiolabel was present on the methylheptyl analogue, which is the primary component of meptyldinocap. The Meeting considered that these ADME studies were applicable to meptyldinocap.

Meptyldinocap is relatively well absorbed, with approximately 60–70% of the radiolabel absorbed in rabbits. Absorption is rapid, with peak plasma radioactivity seen 1–6 h after oral administration. Radiolabel was widely distributed, with tissue levels generally low and below those in blood. The compound did not tend to concentrate in any particular organ or tissue; highest levels were found in the liver, kidneys and skin. Metabolism was extensive, consisting of hydrolytic cleavage to release the crotonate moiety and subsequent oxidation of the methylheptyl chain. The basic metabolic pathways are similar in rats and mice. Excretion of radiolabel was extensive via urine (39–58% in mice; 31–50% in rats) and faeces and mainly occurred within 48 h.

Toxicological data

Meptyldinocap is of low acute toxicity when administered orally or dermally (median lethal dose [LD_{50}] > 2000 mg/kg bw) but is of moderate toxicity by inhalation (median lethal concentration [LC_{50}] 1.2 mg/L). Meptyldinocap is a slight irritant to skin and a moderate irritant to the eye; it has been found to produce skin sensitization in a local lymph node assay in mice.

Short-term studies of toxicity with meptyldinocap were performed in mice, rats and dogs. Yellow urine staining was a consistent finding, but this is considered not to be adverse, as it is associated with the excretion of coloured metabolites of meptyldinocap. In a 28-day dietary study of meptyldinocap in mice, there were increases in liver weight (approximately 10–15%) at 750 ppm (equal to 126 mg/kg bw per day), with a NOAEL of 200 ppm (equal to 33 mg/kg bw per day). In a

90-day dietary study of meptyldinocap in rats, altered clinical chemistry parameters and mononuclear cell infiltration of the lacrimal glands were seen at 2000 ppm (equal to 122 mg/kg bw per day), with a NOAEL of 650 ppm (equal to 40 mg/kg bw per day).

In a 90-day dietary study, groups of dogs were exposed to meptyldinocap at 0, 15, 60 or 120 ppm, with a positive control group receiving 60 ppm dinocap. Reduced body weight gain was seen in males after the first week of dosing with 120 ppm (equal to 3.9 mg/kg bw per day), following a gradual introduction to the treated diets. These initial body weight effects showed no consistency between animals or with food consumption patterns. The body weight gain over 90 days was 41% lower in males receiving 120 ppm than in controls. Ocular changes seen in the dinocap-exposed group were not evident in the meptyldinocap-treated groups. The NOAEL for meptyldinocap was 60 ppm (equal to 1.6 mg/kg bw per day), based on the effects on body weight gain over the duration of the study. In an extension to this 90-day study, a satellite group was exposed to meptyldinocap for 1 year at 120 ppm (equal to 3.5 mg/kg bw per day). The examinations were limited to tibial nerves, eyes and heart. This segment of the study showed that there were no significant eye, heart or nerve lesions evident after exposure to meptyldinocap for 1 year. The reduced body weight gain seen in the 90-day phase was not evident over the extended dosing period. The 1-year study was not designed to permit the identification of a NOAEL.

No evidence of carcinogenicity was seen in long-term studies of toxicity and carcinogenicity with dinocap at the highest doses tested, 150 ppm (equal to 23 mg/kg bw per day) in mice and 2000 ppm (equal to 71 mg/kg bw per day) in rats. The NOAEL for general toxicity in the chronic study in mice with dinocap was 15 ppm (equivalent to 2.8 mg/kg bw per day), based on body weight deficits in females. In the 30-month study of dinocap in rats, there was a significant increase in survival in both sexes at the top dose of 2000 ppm (equal to 71 mg/kg bw per day), which had an impact on the incidences of a number of age-related changes. The NOAEL for general toxicity of dinocap was 200 ppm (equal to 6.4 mg/kg bw per day).

The potential genotoxicity of meptyldinocap has been investigated in an adequate range of tests in vitro and in vivo. No evidence of mutagenicity or clastogenicity was noted.

The Meeting concluded that meptyldinocap is unlikely to be genotoxic.

The Meeting concluded that dinocap is not carcinogenic and that this conclusion could be extrapolated to meptyldinocap.

No effects on fertility, reproductive parameters, sperm or reproductive tissues were seen in a two-generation dietary study with dinocap at doses up to 400 ppm (equal to 27 mg/kg bw per day), the highest dose tested over both generations. At 1000 ppm (equal to 65 mg/kg bw per day), reduced pup survival in the first generation led to a reduction in the dose level to 400 ppm, which was without effect on pups in the second generation. The NOAEL for pup development and parental toxicity was 200 ppm (equal to 13 mg/kg bw per day).

In a developmental toxicity study in mice investigating effects on the palate and inner ear, meptyldinocap did not produce any such effects on fetuses at the highest dose of 500 mg/kg bw per day, whereas a dinocap dose of 25 mg/kg bw per day produced cleft palate in nearly all fetuses and had marked effects on otoconia formation. Additional studies showed that the teratogenicity of dinocap in mice was associated with the 4-propylpentyl analogue and not the methylheptyl analogue present in meptyldinocap. In a developmental study in rats, marked maternal toxicity and marked reductions (approximately 50%) in food consumption were seen with a meptyldinocap dose of 500 mg/kg bw per day, such that this dose level had to be terminated by gestation day 11. At the next highest dose level of 150 mg/kg bw per day, there were reductions from gestation days 6 to 9 in food consumption (approximately 18 g per rat) and maternal body weight gain (approximately 14 g per rat) at the start of the dosing period. The body weight deficit and increased absolute liver weights (23%) were evident at the end of the study, but there were no indications of fetotoxicity. The NOAEL for maternal toxicity was 50 mg/kg bw per day, with the NOAEL for fetotoxicity being 150 mg/kg bw per day. In a rabbit developmental toxicity study with meptyldinocap, maternal body weight loss was

seen in several dams before dosing commenced and in half the dams exposed at 48 mg/kg bw per day early in the dosing period. From gestation days 7 to 10, dams in the top dose group had a mean deficit of 44 g in body weight gain relative to controls; although this was similar in magnitude to the decrease in food consumption over the same period, there was no apparent consistency in individual body weight gains or food consumption. Over the remainder of the study, the body weight gain in the top dose group was similar to that in controls, and from gestation days 20 to 28 (during which dosing continued), the body weight gain was greater than that in controls. There were no effects on the fetuses at any dose level. The maternal NOAEL was 12 mg/kg bw per day, and the NOAEL for fetotoxicity was 48 mg/kg bw per day.

The Meeting concluded that meptyldinocap did not induce developmental toxicity and that it was not teratogenic.

There are no specific neurotoxicity studies on meptyldinocap, but there were no indications of neurotoxicity in routine studies, including a 90-day study in rats that included a functional observational battery.

No information on medical surveillance or poisoning incidents was available.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.02 mg/kg bw on the basis of the NOAEL of 1.6 mg/kg bw per day in the 90-day dietary study in dogs, based on reduced body weight gain in males at 3.9 mg/kg bw per day. A safety factor of 100 was applied.

The Meeting concluded that an ARfD was unnecessary, as there were no effects that could be attributed to a single exposure. Meptyldinocap did not produce neurotoxicity, fetotoxicity or reproductive effects and has an oral LD_{50} of greater than 2000 mg/kg bw. The Meeting reviewed in depth the reduced body weight gains and food consumption seen in the early stages of the 90-day study in dogs and the developmental toxicity studies in rats and rabbits. In the rat developmental toxicity study, the body weight deficits were considered secondary to reduced food consumption, which was probably associated with palatability issues. The Meeting concluded that the body weight and food consumption patterns seen in the early stages of the dog and rabbit studies were not consistent between individual animals. The findings in these three studies did not provide an appropriate basis for establishing an ARfD for meptyldinocap.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Twenty-eight-day study of toxicity with meptyldinocap[a]	Toxicity	200 ppm, equal to 33 mg/kg bw per day	750 ppm, equal to 126 mg/kg bw per day
	Seventy-eight-week study of toxicity and carcinogenicity with dinocap[a]	Toxicity	15 ppm, equal to 2.8 mg/kg bw per day	100 ppm, equal to 18 mg/kg bw per day
		Carcinogenicity	150 ppm, equal to 23 mg/kg bw per day[b]	—
Rat	Ninety-day study of toxicity with meptyldinocap[a]	Toxicity	650 ppm, equal to 40 mg/kg bw per day	2000 ppm, equal to 122 mg/kg bw per day
	Thirty-month study of toxicity and carcinogenicity	Toxicity	200 ppm, equal to 6.4 mg/kg bw per day	2000 ppm, equal to 71 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
	with dinocap[a]	Carcinogenicity	2000 ppm, equal to 71 mg/kg bw per day[b]	—
	Multigeneration study of reproductive toxicity with dinocap[a]	Reproductive toxicity	400 ppm, equal to 27 mg/kg bw per day[b]	—
		Parental toxicity	200 ppm, equal to 13 mg/kg bw per day	400 ppm, equal to 27 mg/kg bw per day
		Offspring toxicity	200 ppm, equal to 13 mg/kg bw per day	400 ppm, equal to 27 mg/kg bw per day
	Developmental toxicity study with meptyldinocap[c]	Maternal toxicity	50 mg/kg bw per day	150 mg/kg bw per day
		Embryo and fetal toxicity	150 mg/kg bw per day[b]	—
Rabbit	Developmental toxicity study with meptyldinocap[c]	Maternal toxicity	12 mg/kg bw per day	48 mg/kg bw per day
		Embryo and fetal toxicity	48 mg/kg bw per day[b]	—
Dog	Ninety-day study of toxicity with meptyldinocap[a]	Toxicity	60 ppm, equal to 1.6 mg/kg bw per day	120 ppm, equal to 3.9 mg/kg bw per day[b]

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

Estimate of acceptable daily intake for humans

0–0.02 mg/kg bw

Estimate of acute reference dose

Unnecessary

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

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

Critical end-points for setting guidance values for exposure to meptyldinocap

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid; moderately well absorbed (60–70%)
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	Relatively rapid
Metabolism in animals	Extensively metabolized, initially hydrolysis to remove the crotonate side-chain and then via oxidation of the methylheptyl chain
Toxicologically significant compounds (animals, plants and the environment)	Meptyldinocap
Acute toxicity	
Rat, LD_{50}, oral	> 2000 mg/kg bw

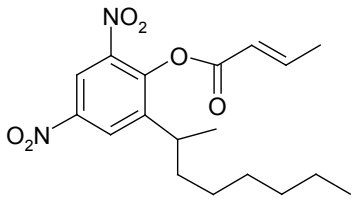
Rat, LD_{50}, dermal	> 5000 mg/kg bw
Rat, LC_{50}, inhalation	1.2 mg/L (4 h, nose only)
Rabbit, dermal irritation	Slight
Rabbit, ocular irritation	Moderate
Mouse, dermal sensitization	Sensitizer (local lymph node assay)
Short-term studies of toxicity	
Target/critical effect	Body weight gain (males)
Lowest relevant oral NOAEL	Dog: 1.6 mg/kg bw per day (meptyldinocap)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Body weight
Lowest relevant NOAEL	Mouse: 2.8 mg/kg bw per day (dinocap)
Carcinogenicity	Not carcinogenic in rats or mice
Genotoxicity	
	Not genotoxic in vitro or in vivo
Reproductive toxicity	
Reproduction target/critical effect	Pup survival
Lowest relevant reproductive NOAEL	Rat: 13 mg/kg bw per day (dinocap)
Developmental target/critical effect	None
Lowest relevant developmental NOAEL	Rabbit: 48 mg/kg bw per day (meptyldinocap)
Neurotoxicity/delayed neurotoxicity	
	No indications in routine studies
Other toxicological studies	
	No data
Medical data	
	No data

Summary

	Value	**Study**	**Safety factor**
ADI	0–0.02 mg/kg bw	Ninety-day study of toxicity in dogs	100
ARfD	Unnecessary		

RESIDUE AND ANALYTICAL ASPECTS

Meptyldinocap is a protectant and curative fungicide for the control of powdery mildew diseases. As a new compound it is evaluated at the first time by the JMPR. The meptyldinocap is the single isomer [2,4-dinitro-6-(1-methylheptyl)phenyl crotonate] of the existing active substance dinocap.



The 2,4-dinitro-6-(1-ethylhexyl)phenyl crotonate, present in the technical meptyldinocap in 1.5% concentration, is considered as impurity. The dinocap is a mixture of 2,4-dinitro-6-octylphenyl crotonates and 2,6-dinitro-4-octylphenyl crotonates. The 'octyl' being a mixture of 1-methylheptyl, 1-ethylhexyl and 1-propylpentyl groups. Approximately 22% of dinocap is meptyldinocap. Dinocap was last evaluated as new compound by the 1998 (R) and for some additional commodities by the 2001 Meetings of the JMPR. Presently both dinocap and meptyldinocap are marketed, but the manufacturers intend to gradually replace dinocap with meptyldinocap.

The manufacturer submitted information on metabolism in plants, analytical methods and residues in/on pome fruits, stone fruits, grapes, strawberries, cucurbits with edible and inedible peel which were evaluated by the present Meeting.

The studies evaluated by the present Meeting were conducted either with meptyldinocap or dinocap. The typical composition of the test substances are given below:

Isomers	Meptyldinocap	Dinocap
Meptyldinocap, 2,4-dinitro-6-(1-methylheptyl)phenyl crotonate	98.5 %	22 %
2,6-dinitro-4-(1-methylheptyl)phenyl crotonate	0 %	11 %
2,4-dinitro-6-(1-ethylhexyl)phenyl crotonate[1]	1.5 %	22 %
2,6-dinitro-4-(1-ethylhexyl)phenyl crotonate	0 %	11 %
2,4-dinitro-6-(1-propylpentyl)phenyl crotonate	0 %	22 %
2,6-dinitro-4-(1-propylpentyl)phenyl crotonate	0 %	11 %

Animal metabolism

The intended use for meptyldinocap is on vines, cucurbits and strawberries, which are not fed to animals. Therefore, no animal metabolism studies were provided for evaluation.

Farm animal metabolism studies evaluated by previous Meetings of the JMPR indicated that no radioactive residues were detectable in milk or tissues when lactating caws were fed with dinocap at 0.1, 0.3 and 1 ppm dose levels.

Plant metabolism

The plant metabolism studies on apples, cucumber and squash submitted to the current meeting had already been evaluated by the 1998 JMPR, and they were a re-evaluated by the present Meeting. The metabolism studies were carried out with meptyldinocap. A single major metabolite [2, 4-dinitro-6-(1-methylheptyl) phenol] was identified and it is referred to as 2,4-DNOP.

An apple tree was treated with a single foliar application of an EC formulation containing 45.6% ai at a rate equivalent to 1.96 kg ai/ha, four times the normal maximum application rate (0.49 kg ai/ha). Apple and leaf samples were taken on the day of application, both before and after treatment, and after 7, 14, and 21 days. Half of each fruit sample was analysed as whole fruit, and the other half peeled and the peel and pulp analysed separately.

The samples were extracted with methanol which recovered more than 90% of the radioactivity from the day 0 samples and 40–60 % from the aged samples. More than 92% of the radioactivity at each PHI was associated with the peel. The total radioactivity recovered in the neutral and alkaline methanolic extracts was more than 80% in all cases.

Two compounds present in the apple fruit have been identified by coelution with standards in both normal phase TLC and reversed phase HPLC. These are the parent meptyldinocap and its corresponding phenol, 2,4-DNOP. The parent compound was present in all of the treated samples, On the day of treatment, meptyldinocap was present at 2.12 mg/kg. After seven days the level had fallen to 0.52 mg/kg, representing 23% of the total radioactivity. After 14 days, the concentration of meptyldinocap had decreased to 0.25 mg/kg (11% of the total radioactivity), and after 21 days it was present at 0.12 mg/kg (8% of the total radioactivity). The half-life of meptyldinocap was calculated to be 5.2 days, The single major metabolite, 2,4-DNOP, was present at lower levels: it comprised roughly 24% of the total radioactivity in the aged samples (0.03–0.08 mg/kg, expressed as parent equivalent).

Five minor metabolites could be identified by gas chromatography with mass spectrometric detection: [2-methyl-5-nitro-7-(2-octyl) benzoxazole, 2-(hydroxymethyl)-5-nitro-7-(2-octyl) benzoxazole, 4-(1-propenyl)-5-nitro-7-(2-octyl)benzoxazole, 5-nitro-7-(octyl) benzoxazole and 2-hydroxymethyl-5-nitro-(2-octyl)-phenyl crotonamide]. The corresponding concentrations ranged from 0.001–0.007 mg/kg.

In cucumber, the distribution and rate of decrease of residues after a single treatment with ^{14}C-meptyldinocap at 0.56 kg ai/ha were studied. The residues of ^{14}C-meptyldinocap dissipated rapidly from the cucumber leaves and stems. The half lives of radioactive residues on leaves and stems were 11.8 days and 18.8 days, respectively. The ^{14}C residues on the leaves decreased from 38.2 mg/kg immediately after application to 1.4 mg/kg at final harvest. The ^{14}C residues in the stems decreased from 3.6 mg/kg immediately after application to 0.5 mg/kg at final harvest, 65 days after last application.

The whole mature fruit harvested 48 days after application contained ^{14}C residues of 0.16 mg/kg and whole mature fruit harvested 63 days after application contained 0.09 mg/kg. Of the whole mature fruit harvested 48 days after application, the peels contained 0.15 mg/kg and the flesh contained 0.11 mg/kg. The proportion of parent compound and 2, 4-DNOP was about the same in cucumber fruits at days 48 and 63.

Of the residues extracted from the leaves by acetone, only one metabolite (2,4-DNOP) occurred in significant (> 10%) quantity. The metabolism of ^{l4}C-meptyldinocap in cucumber leaves was extensive, leading to 18 minor metabolites. Only 2,4-DNOP could be identified amounting to 2.4% of TRR at day 8, while the unextractable residues accounted for 58% of TRR.

The half-life of the radioactivity was 8 days in the squash leaves treated with ^{14}C-meptyldinocap two times at a rate of 0.56 kg ai/ha. 2,4-DNOP was the main metabolite in the leaves and was also found in the fruit. About 6 unidentified metabolites were found in the fruit and 10 in the leaves, none of which individually accounted for more than 10% of the TRR. The 2,4-DNOP, meptyldinocap, organic soluble metabolites and water soluble polar metabolites and unextractable ^{14}C-residues amounted to 1.3%, 5.9%, 5.5%, 21% and 57.6% of TRR, respectively.

Photolysis, under natural daylight conditions, played a major role in the rapid dissipation of meptyldinocap from plant foliage. The concentration of meptyldinocap did not change on covered leaves over 27 hours following the foliar treatment with ^{14}C-meptyldinocap, while it decreased to 39% on leaves exposed to natural light. The extract of 27-hour uncovered leaves contained 53% polar photoproducts.

In summary, the metabolism of meptyldinocap is complex resulting in a large number of metabolites present at low concentrations. The metabolism of 2, 4- meptyldinocap appears to proceed by relatively rapid hydrolysis of the crotonate ester (half lives are about 5, 8 and 11.8 days on apple fruits, quash and cucumber leaves, respectively) to the corresponding phenol (2,4-DNOP). The

phenol is then further metabolised rapidly to a large number of more polar compounds, none of which is present in a significant amount. The proposed pathway for the formation of minor metabolites involves reduction of a nitro group to the amine. Metabolites are then formed by reaction of the amine with formic or acetic acid to form amides, or by intramolecular transfer of the crotonyl group to form the crotonamide. Ring closure of the amides then forms benzoxazoles. Individual metabolites could not be isolated. The amines could readily form conjugates with acids to form amides. Further degradation led to small carbon units which were subsequently incorporated into a number of natural products including cutin, lignin and other constituents that make up the acid detergent fibre.

Environmental fate in soil

Soil metabolism, degradation, leaching, rotational crop studies are not requires for compounds with intended use of foliar application only on permanent crops with no crops planted in rotation.

As part of the plant metabolism studies soil samples were also taken and analysed for meptyldinocap residues.

The ^{14}C residues in the top 2.5 cm of soil of cucumber plot decreased from 0.45 mg/kg immediately after application to 0.31 mg/kg after 63 days. The ^{14}C residues in the 2.5–7.6 cm soil depth never exceeded 0.02 mg/kg and the 7.6–15.2 cm soil depth residues never exceeded 0.007 mg/kg.

The ^{14}C residues in the top section of the soil (0–2.5 cm) of quash plot decreased from 0.43 mg/kg after the last treatment to 0.40 mg/kg 63 days later. The ^{14}C residues in the other soil sections were low.

The residues of [^{14}C]meptyldinocap in the soil in which the cucumber or squash were grown dissipate at a much slower rate than from the plants. There appeared to be no significant leaching of [^{14}C]-meptyldinocap residues into the lower depths of the soil.

Metabolism in rotational crops

The studies evaluated by the 1998 JMPR indicated that when beans, oats and turnips were grown in soil in which cucumber and squash were treated with [^{14}C]meptyldinocap 250 days earlier, the radioactive residues in samples taken until maturity of crops were at or below 0.02 mg/kg. Consequently, residues in follow up crops are unlikely to occur in measurable concentration.

Methods of analysis

The analytical methods used for determination of meptyldinocap residues in supervised trials were principally the same as those evaluated by the 1998 JMPR. Following the solvent extraction, the residues are converted to the corresponding phenols and determined by GC after methylation or analysed directly by HPLC-MS/MS. The validated limit of quantification for the meptyldinocap was 0.025 mg/kg and for combined residues 0.05 mg/kg. The average recoveries ranged from 80 to 104% with relative standard deviation of 7–14%. The concurrent recoveries obtained during the analysis of samples were in the same range.

The DFG S-19 multi residue method was found to be suitable for the determination of meptyldinocap residues in apples, barley grain, grapes and soya bean flour over in the concentration range from 0.05 mg/kg to 1.0 mg/kg with a validated limit of quantitation (LOQ) of 0.025 mg/kg for parent compound. The meptyldinocap peak was well separated from the dinocap isomers under the gas chromatographic conditions applied. The independent laboratory validation trials were conducted to satisfy the relevant requirements of the European Commission and the US EPA Guidelines.

Stability of residues in stored analytical samples

The stability of residues were tested in apples and grapes using 97.5% pure 2,4-dinitro-6-octylphenyl crotonates (2,4-DNOPC isomers) and 2,6-dinitro-4-octylphenyl crotonate isomer mixtures. The 'octyl' being a mixture of 1-methylheptyl, 1-ethylhexyl and 1-propylpentyl groups. In separate set of experiments the untreated samples were spiked at 1 mg/kg level. The overall mean procedural recoveries for 2,4-dinitro-6-octylphenyl crotonates in grapes and apples were 94.5% (RSD: 5.25%) and 88.6% (RSD: 10.3%) the average of residues remained over the period of 24 months were 89.8% (RSD: 10.13%) 71.5% (RSD: 10.5%), respectively. The results indicate that residues of the 2,4-DNOPC isomers are stable in apples, grapes, tomatoes, peaches and strawberries stored frozen up to 24 months. The stability of the meptyldinocap alone during deep-frozen storage could not be determined from these studies. However, it may be assumed to be similar to the other isomers.

Definition of the residue

Results of metabolism studies on fruits and fruiting vegetables indicate that the parent compound, meptyldinocap, forms the main residue remaining in the plant tissues at harvest. The major metabolite, the corresponding phenol, 2,4-DNOP, showed concentrations of 2–10% of total radioactivity only. The concentration of the major metabolite, the corresponding phenol (2, 4-DNOP) had not changed with time after application of the pesticide, indicating that that further metabolism to a number of minor compounds occurred relatively quickly. Initially the meptyldinocap amounted to the major portion of the TRR. The proportion of 2, 4-DNOP gradually increased with time and it was present in about the same concentration as meptyldinocap 48–63 days after the treatment of cucumber. The parent/2, 4-DNOP ratio was about 4 in apples 21 days after application.

The analytical method, which is used in the residue trials, determined meptyldinocap residues as a sum of the parent and the corresponding phenol. Multi residue methods, based on gas chromatographic and HPLC-MS/MS detection are available for the determination of meptyldinocap alone and have been validated for four representative commodities. Residues deriving from the use of dinocap could be identified based on the presence of 2,6-DNOP isomers provided that the chromatographic system used has sufficient resolution.

The current residue definition of dinocap is dinocap. As meptyldinocap is one isomer of dinocap, it is covered by the current residue definition. Non-selective methods cannot distinguish meptyldinocap from dinocap, but selective methods are available. While meptyldinocap and dinocap are both registered for crop uses, it is preferable, for enforcement purposes, to maintain a single residue definition.

It follows that, at least while dinocap MRLs are maintained, the residue definition for meptyldinocap as "dinocap, sum of all isomers" would be a practical solution.

The present Meeting established an ADI of 0–0.02 mg/kg/bw day. The new ADI is applicable for the sum of meptyldinocap and its corresponding phenol, when only they are present in the commodities analysed.

The Meeting recommended that while dinocap MRLs are maintained, the residue definition for meptyldinocap enforcement purposes should be dinocap, sum of all isomers.

Definition of the residue for dietary exposure assessment: the sum of meptyldinocap and the corresponding phenol, 2,4-DNOP, expressed as the parent meptyldinocap.

A residue definition for animal products is not required as no residue is expected to occur in animal products from the targeted use of meptyldinocap.

Results of supervised trials on crops

All trials were conducted according to GAP and the samples were analysed within the tested deep-frozen storage period. The methods applied for the analyses of samples determine meptyldinocap

residues as a sum of the parent and the corresponding phenol. The validity of the results was confirmed with concurrent recovery tests performed in the same analytical batch.

Cucumber and courgettes

GAP in France, Italy and Slovenia permits maximum 3 applications at 10 days with maximum dosage of 0.21 kg ai/ha and a PHI of 3 days. A total of eight supervised field trials on cucumbers/courgette were conducted according to maximum GAP in greenhouses located in the North and South European zones. Samples collected 3 days after the last application contained residues of < 0.005 (2), 0.01, 0.02 (4) and 0.04 mg/kg.

The Meeting estimated a maximum residue level, STMR value and HP value for Fruiting vegetables, Cucurbits, except melons of 0.07, 0.02 and 0.04 mg/kg.

Melons

GAP in France, Italy and Slovenia permits a maximum of 3 applications at 10 days with a maximum rate of 0.21 kg ai/ha and PHI of 3 days. A total of eight supervised field trials on melons were conducted according to maximum GAP in the North and South European zones. Whole fruit samples collected 3 days after the last application contained residues: < 0.005, 0.008, 0.02 (4), 0.05 and 0.28 mg/kg. No detectable residues were found in pulp samples.

The Meeting estimated a maximum residue level, STMR value and HP value for melons of 0.5, 0.005 and 0.28 mg/kg, respectively. Note: there is no information on pulp residues at high whole fruit residue.

The Meeting recommended to re-evaluate the current CXL of 0.05* for dinocap in fruiting vegetables cucurbits.

Grapes

GAP in France, Greece, Hungary and the UK permits a maximum of 4 applications with a maximum rate of 0.21 kg ai/ha and a PHI of 21 days. A total of eighteen trials were conducted on Grapes in Europe between 2005 and 2007. Eight trials with two formulations side by side containing meptyldinocap alone and the mixture of 2,4-DNPOC and 2,6-DOPOC (three isomers of each compound). In addition, eight trials were conducted in 2006 with a formulation containing meptyldinocap. All trials were performed with the permitted maximum application rate and frequency.

Samples collected at day 21 following the last application of meptyldinocap contained residues: < 0.01 (5), < 0.025 (6), 0.03 (3), 0.06 (2), 0.08, and 0.12 mg/kg.

The Meeting estimated a maximum residue level, STMR value and HP value for grapes 0.2, 0.025 and 0.12 mg/kg, respectively.

The Meeting noted that the current CXL of 0.5 mg/kg for dinocap in grapes covers the residues deriving from the use of meptyldinocap.

Strawberry

The GAP of France, Italy and Slovenia permits a maximum of 3 applications at 10 day intervals with a maximum rate of 0.21 kg ai/ha and a PHI of 3 days. A total of eight supervised field trials on strawberries were conducted according to the maximum GAP in greenhouses located in Northern and Southern Europe. The pesticide treatment was made with a formulation containing meptyldinocap.

Residues in samples collected 3 days after the final application of meptyldinocap, in ranked order, were: 0.03, 0.06, 0.07, 0.08, 0.09, 0.11, 0.12, 0.13 mg/kg.

The Meeting estimated a maximum residue level, STMR value and HP value for grapes 0.3, 0.085 and 0.13 mg/kg, respectively

The Meeting noted that the current CXL of 0.5 mg/kg for dinocap in strawberries covers the residues derived from the use of meptyldinocap.

The Meeting also noted that the current CXL for dinocap in strawberries included a note that it excludes the glasshouse use. The recommended maximum residue level for meptyldinocap is applicable for both uses.

Fate of residues during processing

Grapes

Dinocap was applied 6–8 times to both red and white grape varieties during the growing season at the recommended or 1.5× rate. Samples were collected for processing at intervals of 14–21 days after the final application. A portion of the collected grape bunches were subjected to vinification similar to commercial practice. The must from the white grape was divided into two equal portions: one of which was processed further without heating, the other was pasteurized for 2 minutes at approximately 85 °C.

The must of the white wine grapes, both pasteurized and non pasteurized, as well as the must of the red wine grapes was processed into wine following the same processing steps: fermentation; clarification (first racking and second racking); filtration, bottling and maturation. The residues were analysed with methods having LOQs of 0.04 and 0.05 mg/kg and an LOD of 0.01 mg/kg. The average recoveries in grapes, must and wine were in the 70–120% range.

Six grape samples taken 20–21 days or at shorter intervals after the last treatment did not contain residues above the LOQ. These trials could not be used for estimation of the processing factor. Other trials on red and white grapes resulted in measurable residues in grapes harvested 14–21 days after last pesticide treatment. The results of processing studies are summarised below:

PHI (days)	14	21	21	21[a]	21[a]
Grape	0.1	0.59	0.33	0.347	0.67
Must	< 0.04	< 0.05	< 0.01	< 0.05	< 0.05
Wine	< 0.04	< 0.01	< 0.01	< 0.01	< 0.01
Pf must/juice	< 0.4	< 0.085	< 0.030	< 0.144	< 0.075
Pf wine	< 0.4	< 0.017	< 0.030	< 0.029	< 0.015

[a] White grapes

The median processing factors for must and wine are < 0.08 and < 0.023 based on samples collected at the recommended PHI. The Meeting estimated STMR values of 0.0020 mg/kg and 0.00072 mg/kg for must and wine, respectively.

Raisins were prepared from the harvested grapes in two trials. However, the results are contradictory (the calculated processing factors were 2.26 and 0.417) and a processing factor could not be calculated.

Strawberry

Strawberry samples, taken 3 days after last pesticide treatment with dinocap, were processed to jam and preserve with a procedure resembling commercial practice. The residues measured in RAC and processed products are summarised below.

Dosage kg ai/ha & appl. No	0.4–0.41 × 6	0.39–0.42 × 6	0.21–0.22 × 3	0.20–0.21 ×3
Strawberry fruits (unwashed)	0.23	0.31	0.07	0.13
Jam	0.079	0.07	< 0.01	0.06
Preserve	< 0.05	0.11	< 0.01	0.11
Pf for jam	0.34	0.23	< 0.14	0.46
Pf for preserve	< 0.22	0.35	< 0.14	0.85

The calculated median processing factor for both jam and preserve is 0.285. The Meeting estimated an STMR value of 0.024 for strawberry jam and preserve.

Residues in animal commodities

Animal metabolism studies performed with dinocap evaluated by previous Meetings of the JMPR revealed that no radioactive residues were detectable in milk or tissues at any dose level (0.1-1 ppm). Consequently animal feeding studies are not required.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of meptyldinocap resulted in recommendations for MRLs and STMR values for raw and processed commodities. Where data on consumption were available for the listed food commodities, dietary intakes were calculated for the 13 GEMS/Food Consumption Cluster Diets. The results are shown in Annex 3.

The IEDIs in the thirteen Cluster Diets, based on estimated STMRs were 0 % of the maximum ADI (0.02 mg/kg bw). The Meeting concluded that the long-term intake of residues of difenoconazole from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

As the establishment of an ARfD was previously considered unnecessary, the Meeting concluded that the short-term intake of meptyldinocap residues is unlikely to present a public health concern.

5.19 NOVALURON (217)

RESIDUE AND ANALYTICAL ASPECTS

Novaluron is an insecticide of the class diflubenzoylureas. It was evaluated for the first time by JMPR in 2005 (T, R). The compound was listed for additional MRLs by 2010 JMPR at the Forty-first Session of the CCPR.

The manufacturer has submitted supervised crop field trial studies to support additional MRLs for the following commodities: broccoli, cabbage, mustard greens, Swiss chard, tomato (increase MRL), cherry, peach, plum, blueberry, snap bean (common bean), dry bean, and sugar cane. The supervised crop field trials are supplemented by the relevant GAPs, analytical methods, storage stability data, processing studies, and a poultry feeding study.

Methods of analysis

The analytical methods used in the supervised trials are based on the two methods previously included in the JMPR Evaluation in 2005: GC/ECD or HPLC with UV detection. A variation of the GC method uses a mass selective detector (MSD). A variation of the HPLC method uses LC/MS/MS. Adequate method validation at 0.05 mg/kg was reported with each crop field trial study. Average method and concurrent recoveries were all within the range of 70–120%, with relative standard deviations (RSD) at or below 20%.

Stability of residues in stored analytical samples

From the JMPR Report (2005) it can be concluded that minimum storage stability intervals of 12 months for high water content samples, 5 months for high oil content samples, 8 months for acidic commodities, and 12 months for high starch commodities are indicated. Additionally, in some of the crop field trial studies reported a control sample was fortified and stored frozen with the treated field samples. The fortified control was analysed at the time of analysis of the field samples. The percentages remaining were in the 71–118% range. All crop field trial samples were analysed within periods of demonstrated frozen storage stability.

Results of supervised trials on crops

Stone fruits

In all trials, determinations were made on the fruit without pit and no data on pit weights were available to express results on a fruit with pit basis. The absence of pit would be anticipated to yield slightly exaggerated residue values.

Peaches

A report on peach supervised field trials from the US was available. The US GAP is 3 applications at 0.36 kg ai/ha of an EC formulation with an 8 day PHI. The ranked order of residues on peaches (without pit) (n = 15) at the maximum GAP were: 0.20, 0.25, 0.41, 0.42 (2), 0.49, <u>0.58</u> (2), 0.66, 0.70, 0.90, 0.92, 1.0 (2), 2.1 mg/kg

Plums

A report on plum supervised field trials form the US was available. The US GAP is 3 applications at 0.36 kg ai/ha with an EC formulation with an 8 day PHI. The ranked order of residues on plums (without pits) (n = 10) at the maximum GAP were: 0.08, 0.16, 0.26, 0.33, <u>0.35, 0.47,</u> 0.48, 0.62, 0.79, 0.80 mg/kg.

Cherries

A report on cherry supervised field trials form the US was available. The US GAP is 3 applications at 0.36 kg ai/ha with an EC formulation with an 8 day PHI. The ranked order of residues on cherries (without pits) (n = 7) at the maximum GAP were: 0.76, 0.97, 2.0, 2.2, 3.0, 3.9, 4.1 mg/kg.

The Meeting noted that the GAPs are identical for cherry, peach, and nectarine and that the US label specifies use on stone fruit. The Meeting decided to use the cherry supervised field trial data to estimate a maximum residue level of 7 mg/kg for stone fruit and an STMR of 2.2 mg/kg.

The value derived from use of the NAFTA calculator was 10 mg/kg based on a maximum residue level estimate for cherries (Lognormal 95/99 rule, 99th). However, small data sets may not produce reliable estimates via statistical procedures.

Berries and other small fruits

Blueberries

A report on blueberry supervised field trials in the US was received, where the GAP is 3 applications of an EC formulation at a maximum rate of 0.22 kg ai/ha/application and a PHI of 8 days. Nine trials complied with GAP, and the results in ranked order are: 0.99, 1.0, 1.1, 2.0, 2.1, 2.3, 3.5, 3.6, 3.8 mg/kg.

The Meeting estimated an STMR and maximum residue level of 2.1 and 7 mg/kg, respectively.

Use of the NAFTA statistical procedure yielded a maximum residue level estimate of 8, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations was 6 mg/kg. The statistical calculation has limited utility with small data sets (n = 9).

Strawberry

A report on strawberry supervised field trials in the US and Canada was received, where the GAP 3 applications of an EC formulation with a maximum application rate of 0.087 kg ai/ha/application and a PHI of 1 day. Using the GAP of the US for both Canadian and US trials, 10 trials complied with GAP, and the results in ranked order are: 0.07, 0.11 (3), 0.12, 0.18 (2), 0.22, 0.26, 0.29 mg/kg. The Meeting estimated an STMR and maximum residue level of 0.l5 and 0.5 mg/kg, respectively.

Use of the NAFTA statistical procedure yielded a maximum residue level estimate of 0.45 mg/kg (0.5 mg/kg rounded up), based on the 99th percentile of a log normal distribution. The mean plus three standard deviations is 0.4 mg/kg.

Brassica vegetables

Broccoli

A report on supervised field trials on broccoli in the US was received. The US GAP is for a maximum of 3 applications of an EC formulation at 0.044–0.087 kg ai/ha/application with a seasonal rate maximum of 0.17 kg ai/ha and a PHI of 7 days. The trials were conducted as 3 applications at 0.056 kg ai/ha, which matches the seasonal maximum rate but is only 64% of the single application rate, i.e., 0.087 mg/kg. The retreatment interval was 5 to 8 days. The broccoli residue decline study indicates a slow loss of residue with a half-life of about 14 days. Therefore, an accumulation effect from the 3 applications can be anticipated and, as the trials match the seasonal maximum application rate, they may be considered as complying with maximum GAP. Six trials complied with GAP, and the residues in ranked order are: < 0.05 (2), 0.10, 0.11, 0.14, 0.38 mg/kg.

Cabbage

A report on supervised field trials on cabbage in the US was received. The US GAP is 3 applications of an EC formulation at 0.087 kg ai/ha/application and a PHI of 7 days. The trials were conducted as

3 applications at 0.056 kg ai/ha, which matches the seasonal maximum rate but is only 64% of the single application rate, i.e., 0.087 mg/kg. The retreatment interval was 5 to 8 days. The cabbage residue decline study indicates residues < LOQ at all time intervals. Based on the broccoli decline study, a slow loss of residue with a half-life of about 14 days might be expected. Therefore, an accumulation effect from the 3 applications can be anticipated and, as the trials match the seasonal maximum application rate, they may be considered as complying with maximum GAP. Six trials complied with GAP, and the residues in ranked order are: < 0.05 (3), 0.08, 0.19, 0.48 mg/kg.

The Meeting used the broccoli and cabbage data as mutual support for a brassica vegetable maximum residue estimate of 0.7 mg/kg (broccoli or cabbage) and an STMR estimate of 0.105 mg/kg (broccoli).

The NAFTA statistical procedure produced for broccoli a maximum residue level estimate of 0.6 mg/kg, based on the 99th percentile of a log normal distribution. The NAFTA statistical procedure produced for cabbage a maximum residue level estimate of 0.6 mg/kg, based on the UCL median 95th. Statistical procedures have limited utility with very small data sets (n = 6 each).

Fruiting vegetables, Cucurbits

Cucumber

A report on supervised field trials on cucumbers in the US was received, where the GAP for all cucurbits is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Six trials complied with GAP, and the results in ranked order are: < 0.05 (6) mg/kg.

Melons

A report on supervised field trials on cantaloupe melons in the US was received, where the GAP for all cucurbits is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Eight trials complied with GAP, and the results in ranked order are: < 0.05 (4), 0.05, 0.07, 0.08, 0.09 mg/kg.

Summer squash (zucchini)

A report on supervised field trials on summer squash in the US was received, where the GAP for all cucurbits is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Seven trials complied with GAP, and the results in ranked order are: < 0.05 (6), 0.07 mg/kg.

The Meeting noted that residue levels from the same GAP are similar on cucumber, cantaloupe, and summer squash and decided to estimate an STMR of 0.05 and a maximum residue level of 0.2 mg/kg, respectively, for fruiting vegetables cucurbits.

The NAFTA statistical calculation procedure is not reliable for highly censored data sets. Using the data set with the lowest percentage of censored data (melons), a maximum residue level estimate of 0.11 mg/kg based on the mean plus 3×SD is suggested.

Fruiting vegetables, other than Cucurbits

Peppers

A report on supervised field trials on peppers in Canada and the US was received. The US GAP for all fruiting vegetables (non-cucurbit) is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Twelve bell pepper trials and 4 non-bell pepper trials complied with the US GAP. The non-bell (< 0.05 (2), 0.20, 0.36 mg/kg) results were not from a different population than the bell pepper results, and the combined results (n = 16) in ranked order are: < 0.05 (5), 0.05 (2), 0.07 (2), 0.14, 0.20, 0.22, 0.28, 0.36, 0.37, 0.38 mg/kg.

Tomato

A report on supervised field trials on tomatoes in Canada and the US was received. The US GAP for all fruiting vegetables (non-cucurbit) is 3 applications of an EC formulation at 0.087 kg ai/ha with a

PHI of 1 day. The use for fruiting vegetables non-cucurbit is for fields (outside) only except tomato, where glasshouse use is also specified.

Four glasshouse trials complied with GAP, and the trial results in ranked order are: < 0.05, 0.06, 0.20, 0.47 mg/kg. Fourteen field trials in Canada and the US complied with the US GAP, and the trial results in ranked order are: < 0.05 (3), 0.06 (2), 0.08 (2), 0.10 (2), 0.13 (2), 0.23, 0.26, 0.28 mg/kg.

The glasshouse and field trial results do not appear to be from different populations and may be combined (n = 18) to yield in ranked order: < 0.05 (4), 0.06 (3), 0.08 (2), 0.10 (2), 0.13 (2), 0.20, 0.23, 0.26, 0.28, 0.47 mg/kg.

The Meeting noted that the GAP is identical for pepper and tomato and that the tomato and pepper residue data sets are not from different populations. The Meeting used the data sets for mutual support and based upon the tomato data set (with the highest residue) estimated an STMR of 0.10 and a maximum residue level of 0.7 mg/kg for fruiting vegetables other than cucurbits to replace the existing Codex MRL of 0.02 (*) mg/kg for tomato.

The NAFTA statistical procedure estimated a maximum residue level of 0.6 mg/kg for pepper based on the mean plus 3 standard deviations and a maximum residue level of 0.6 mg/kg for tomato, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations was 0.6 mg/kg for pepper and 0.5 mg/kg for tomato. The Meeting considered 0.7 mg/kg a better estimate, given a highest residue of 0.48 mg/kg in a set of 18 values.

Leafy vegetables (including Brassica leafy)

Mustard greens

A report on supervised field trials on mustard greens in Canada and the US was received. The US GAP for all Brassica leafy vegetables is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 7 days. Eleven trials complied with the US GAP, and the results in ranked order are: 2.0, 2.1, 2.6, 3.0, 3.2, 3.6, 4.4, 5.0, 5.2, 10, 19 mg/kg. The Meeting estimates an STMR of 3.6 and a maximum residue level of 25 mg/kg, respectively.

The NAFTA statistical procedure yielded a maximum residue level estimate of 25 mg/kg, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations is also 25 mg/kg.

Swiss chard

A report on supervised field trials on Swiss chard in the US was received. The US GAP for Swiss chard is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Three trials complied with the US GAP, and residues in ranked order are: 2.3, 4.0, and 6.6 mg/kg.

The Meeting estimated an STMR of 4 and a maximum residue level of 15 mg/kg for Swiss chard. The Meeting noted that the number of trials was marginally acceptable, given that Swiss chard is not generally a major crop in production or in consumption.

The NAFTA statistical procedure yields a maximum residue estimate of 14 mg/kg, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations is 11 mg/kg. Statistical procedures have no utility for very small data sets.

Legume vegetables

Common bean

A report on supervised field trials on snap beans (common bean, green bean) in Canada and the US was received. The US GAP for common bean is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Fourteen trials complied with the US GAP, and the results in ranked order are: < 0.05, 0.10, 0.12 (2), 0.14, 0.16 (2), 0.17, 0.18 (3), 0.32, 0.40, 0.46 mg/kg.

The Meeting estimated an STMR of 0.165 and a maximum residue level of 0.7 kg/mg, respectively.

The NAFTA statistical procedure estimated a maximum residue level of 0.7 mg/kg, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations is 0.60 mg/kg.

Pulses

Bean (dry)

A report on supervised field trials on dry beans in the US was received. The US GAP for dry bean is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Thirteen trials complied with the US GAP, and the results in ranked order are: < 0.05 (10), 0.06, 0.08 (2) mg/kg.

The Meeting estimated an STMR and maximum residue level of 0.05 and 0.1 mg/kg, respectively.

Use of the NAFTA statistical procedure yielded a maximum residue level estimate of 0.15 mg/kg, based on the 99th percentile of a log normal distribution. MLE was used to fill-in the < LOQ values. The mean plus 3 standard deviations is also 0.15 mg/kg. Statistical procedures are not reliable for highly censored data sets, and attributing log normal behaviour to the LOQ data may not be appropriate.

Grasses for sugar

Sugar cane

A report on supervised field trials on sugar cane in the US was received. The US GAP for sugar cane is 5 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 14 days. Seven trials comply with the US GAP, and the results in ranked order are: < 0.05, 0.07 (2), 0.08, 0.10, 0.29, 0.31 mg/kg.

The Meeting estimated an STMR of 0.08 and a maximum residue level of 0.5 mg/kg.

The NAFTA statistical procedure yielded a maximum residue level estimate of 0.6 mg/kg, based on the 99th percentile of a log normal distribution. The mean plus 3 standard deviations is 0.5 mg/kg. Statistical procedures are unreliable for small data sets.

Animal feed commodities

Bean forage (green)

A report on supervised field trials on snap beans (common bean, green bean) in Canada and the US was received. The US GAP for common bean is 3 applications of an EC formulation at 0.087 kg ai/ha with a PHI of 1 day. Two types of vine samples were collected at different locations, vine only and vine plus residual pods. Fourteen trials comply with the US GAP, and residue results in ranked order are: 3.1, 5.3, 5.8 (2), 6.6, 6.8, 7.4, 7.8, 8.6, 8.8, 10 (2), 13, 18 mg/kg.

The Meeting estimated an STMR of 8.2 and a highest residue of 18 mg/kg.

Processing studies

Processing studies were provided for plum, tomato, and sugar cane. However, no residues were found in either the sugar cane or processed commodities. The processing factors (transfer factors) and related STMR-Ps are summarized as follows:

Commodity	Number of Studies (n)	Median Novaluron Transfer Factors	Novaluron RAC-STMR (mg/kg)	Novaluron STMR-P (mg/kg)
Plum - dried	2	3.1	0.41	1.27
Tomato - puree	1	< 0.73	0.10	0.073
Tomato - paste	1	1.1	0.10	0.11

The Meeting calculated a maximum residue level of 7 mg/kg for dried plums based on a highest residue of 2.2 mg/kg for stone fruit and a processing factor of 3.1 for plums (2.2 mg/kg × 3.1 = 6.8 mg/kg). This estimate is not needed as the mrl estimate for stone fruit is 7 mg/kg, and 7 mg/kg is equal to or greater than the dried plum estimate.

Farm animal feeding studies

The 2005 JMPR evaluated a ruminant feeding study and derived maximum residue estimates for livestock commodities based on the feeding study, a poultry metabolism study, and the livestock feeding tables then in use. New livestock feeding tables have been adopted, based on the OECD work.

The new uses under consideration by the present JMPR have several livestock feed items: bean vines (green), sugarcane molasses and bagasse, bean seed, and cabbage heads.

The Meeting estimated the dietary burden of novaluron in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual (2009 Edition). Calculation from highest residues, STMR (some bulk blended 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 assumed to be 100% when the highest residue levels and STMRs are expressed on a dry weight basis.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, chicken broilers, and laying poultry are provided in Annex 6 of the 2010 JMPR Report. The calculations were made according to the animal diets from the US/CAN, EU, and Australia in Appendix IX of the FAO Manual (2009 Edition). Bean forage makes a considerable contribution to the diet of cattle in Australia and to a lesser extent in Europe. Preliminary IEDI calculations with bean forage included in the diets of Australian and European cattle indicate that the ADI may be exceeded in at least one region. Therefore a tiered approach was adopted, and bean forage (green) was not included in the livestock diet for Australia or the European Union because novaluron is not registered for use on beans in Australia or in European Union member states, and forages are not generally in international trade (JMPR Report 2009, General Consideration 2.2). Thus, no residue of novaluron is anticipated on bean forage in Australia or in European Union member states.

Commodity	Level	Animal Dietary Burden, Novaluron, ppm of dry matter diet.			
		US/CAN	EU	Australia	Japan
Beef cattle	Max	1.54	3.03 [a]	2.44	0.0
	Mean	0.44	2.53 [c]	2.44	0.0
Dairy cattle	Max	1.20	1.86 [b]	1.27	0.0
	Mean	1.20	1.36 [d]	1.27	0.0
Poultry – broiler	Max	0.0092	0.174 [e]	0.044	0.0
	Mean	0.0092	0.049 [f]	0.044	0.0
Poultry – layer	Max	0.0092	0.014	0.044 [g]	0.0
	Mean	0.0092	0.014	0.044 [h]	0.0

[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.

A cow feeding study was reviewed by the 2005 JMPR. In the table below, dietary burdens are shown in round brackets (), feeding levels and residue concentrations from the feeding study are shown in square brackets [], and estimated concentrations related to the dietary burdens are shown without brackets.

Cattle Dietary Burden (ppm)						
Feeding Level [ppm]	Cream	Milk	Muscle	Liver	Kidney	Fat
MAXIMUM RESIDUE LEVEL	Mean	Mean	Highest	Highest	Highest	Highest
MAXIMUM RESIDUE LEVEL beef cattle (3.03) [2.6]			0.10 [0.09]	0.16 [0.14]	0.16 [0.14]	2.6 [2.25]
MAXIMUM RESIDUE LEVEL dairy cattle (1.86) [2.6]	2.0 [2.8]	0.093 [0.13]	0.064 [0.09]	0.10 [0.14]	0.10 [0.14]	1.6 [2.25]
STMR	Mean	Mean	Mean	Mean	Mean	Mean
STMR beef cattle (2.53) [2.6]			0.078 [0.08]	0.13 [0.13]	0.13 [0.13]	1.7 [1.73]
STMR dairy Cattle (1.36) [0.35/2.6]	2.6 [0.68/2.80]	0.13 [0.04/0.13]	0.08 [0.04/0.08]	0.13 [0.05/0.13]	0.13 [0.04/0.13]	1.7 [0.45/1.73]

The data from the lactating dairy cow feeding study were used to support mammalian (except marine) milk and meat maximum residue levels.

The Meeting estimated the following STMR values: milk 0.13; cream, 2.6 mg/kg; muscle 0.08; edible offal 0.13; fat 1.7 mg/kg. These levels replace previous estimates.

The Meeting estimated the following maximum residue levels for mammalian commodities (except marine): milk 0.2 mg/kg; milk fat 5 mg/kg; meat (fat) 3 mg/kg; edible offal 0.2 mg/kg. The milk fat estimate assumes that cream contains 50% milk fat. However, as these estimates are lower than previous recommendations, which are now CXLs, the Meeting confirmed the previous recommendations: milk 0.4 mg/kg; milk fat 7 mg/kg; meat (fat) 10 mg/kg; edible offal 0.7 mg/kg. The Meeting noted that the decrease in estimates results from the new OECD animal dietary burden diets adopted by the JMPR. For example consumption of cotton gin trash has dropped from 20% to 5%, and consumption of wet apple pomace has dropped from 40% to 20%.

A poultry feeding study was made available to the Meeting. Groups of laying hens were orally dosed with novaluron at levels of 0, 0.12, 0.36, and 1.2 mg/kg for 56 days. Maximum residues at the 0.12 ppm feeding level were 0.080 mg/kg in eggs (day 47), 0.014 mg/kg in muscle, 0.034 mg/kg in liver, 0.039 mg/kg in kidney, and 0.323 mg/kg in fat (abdominal). Average residues were 0.070 mg/kg in eggs (day 47), 0.012 mg/kg in muscle, 0.033 mg/kg in liver, 0.036 mg/kg in kidney,

and 0.307 mg/kg in fat (abdominal). At the 0.36 ppm feeding level, the maximum and average residues in egg were 0.18 mg/kg and 0.174 mg/kg (day 47), respectively.

In the table below, dietary burdens are shown in round brackets (), feeding levels and residue concentrations from the feeding study are shown in square brackets [], and estimated concentrations related to the dietary burdens are shown without brackets.

Poultry Dietary Burden (ppm)					
Feeding Level [ppm]	Egg	Muscle	Liver	Kidney	Fat
MAXIMUM RESIDUE LEVEL	Mean	Highest	Highest		Highest
MAXIMUM RESIDUE LEVEL Broiler (0.044) [0.12]		0.0044 [0.012]	0.012 [0.033]	0.013 [0.036]	0.11 [0.307]
MAXIMUM RESIDUE LEVEL Laying (0.174) [0.12]	0.10 [0.0703]	0.021 [0.014]	0.049 [0.034]	0.056 [0.039]	0.47 [0.323]
STMR	Mean	Mean	Mean		Mean
STMR Broiler (0.044) [0.12]		0.0044 [0.012]	0.012 [0.033]	0.013 [0.036]	0.11 [0.307]
STMR Laying (0.049) [0.12]	0.029 [0.0703]	0.0048 [0.012]	0.013 [0.033]	0.015 [0.036]	0.13 [0.307]

The data from the laying hen feeding study were used to support poultry egg and meat maximum residue levels.

The Meeting estimated the following STMR values: eggs, 0.029 mg/kg; fat, 0.13 mg/kg; muscle, 0.005 mg/kg ; edible offal, 0.015 mg/kg . These replace previous STMR estimates.

The Meeting estimated the following maximum residue levels for poultry commodities: eggs, 0.1 mg/kg; meat (fat), 0.5 mg/kg; edible offal, 0.1 mg/kg. These estimates replace previous recommendations: eggs 0.01 (*) mg/kg; poultry meat (fat) 0.01 (*) mg/kg; poultry, edible offal of 0.01 (*) mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDIs) of novaluron were calculated for the 13 GEMS/Food Consumption Cluster Diets using STMRs and STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.01mg/kg bw and the calculated IEDIs were 7–50% of the maximum ADI. The Meeting concluded that the long-term intake of residues of novaluron resulting from the uses considered by the current JMPR is unlikely to present a public health concern.

Short-term intake

The2005 JMPR decided that an ARfD was unnecessary. The Meeting therefore concluded that the short-term intake of novaluron residues is unlikely to present a public health concern.