5.27 PICOXYSTROBIN (258)

TOXICOLOGY

Picoxystrobin is the ISO-approved name for methyl (*E*)-3-methoxy-2-[2-(6-trifluoromethyl-2-pyridyloxymethyl)phenyl]acrylate (IUPAC) (CAS No. 117428-22-5). Picoxystrobin is a broad-spectrum, systemic cereal fungicide from the strobilurin group. Picoxystrobin's mode of fungicidal activity is to block mitochondrial electron transport at the Q_o site of complex III, reducing ATP production and inhibiting cellular respiration.

Picoxystrobin has not been evaluated previously by JMPR and was reviewed at the present meeting at the request of CCPR.

All critical studies contained statements of compliance with GLP and met the minimum requirements of the applicable OECD or national test guidelines.

Biochemical aspects

Radiolabelled picoxystrobin administered by oral gavage is rapidly absorbed, with peak plasma ^{14}C levels seen at approximately 2 or 12 hours in rats administered 10 or 100 mg/kg bw, respectively. Picoxystrobin is well absorbed, with approximately 70% of the radioactivity from an oral dose of 100 mg/kg bw detected in bile and urine. Distribution is extensive, with peak radioactivity levels being detected in liver, pancreas, kidney and blood plasma. Excretion is predominantly via the bile and thence into faeces and is essentially complete within 120 hours for a dose of 100 mg/kg bw. Excretion in urine was greater in females (approximately 30%) than in males (approximately 20%). Picoxystrobin is extensively metabolized, with over 30 identified metabolites. Significant biotransformation reactions include ester hydrolysis, oxidation, *O*-demethylation and glucuronide conjugation.

Toxicological data

In the rat, picoxystrobin is of low acute oral and dermal toxicity (LD_{50}s > 2000 mg/kg bw), but is of high acute toxicity by inhalation (LC_{50} = 0.11 mg/L). In the rabbit, picoxystrobin is slightly irritating to the skin and moderately irritating to the eye, and it was not a skin sensitizer in a maximization test in guinea-pigs.

A consistent finding in animals exposed to picoxystrobin is reduced body weight gain, frequently associated with reduced feed consumption. Given the mode of pesticidal action on ATP production, the body weight effects might not be entirely secondary to the reduced feed consumption. Another common finding is increased liver weights.

In a 90-day dietary toxicity study in mice, the NOAEL was 800 ppm (equal to 137 mg/kg bw per day), based on increased relative liver weight (> 10%) and reduced body weight gains at 1600 ppm (equal to 291 mg/kg bw per day).

In a 90-day dietary toxicity study in rats, body weight gain was reduced from the first observation period (week 1), and terminal body weights were approximately 10% lower in the 1250 ppm (equal to 105 mg/kg bw per day) groups than in controls. Liver weight corrected for body weight was increased by more than 10% at 1250 ppm and by 5–8% at 500 ppm, but there were no associated pathological findings. The NOAEL was 500 ppm (equal to 42 mg/kg bw per day), based on the reductions in body weight gain and increased liver weights (> 10%) at 1250 ppm.

In a 90-day dietary toxicity study in dogs, reductions in body weights and feed consumption were seen from the first observation period (week 1) at 500 ppm (equal to 17 mg/kg bw per day), with a NOAEL of 250 ppm (equal to 8.5 mg/kg bw per day). In a 1-year dietary toxicity study in dogs, reddened gums, fluid faeces and thin appearance were seen, together with reductions in body weight and feed consumption, at 500 ppm (equal to 16 mg/kg bw per day). The NOAEL was 150 ppm (equal to 4.6 mg/kg bw per day). The Meeting concluded that an overall NOAEL for the dog studies was 8.5 mg/kg bw per day.

The chronic toxicity and carcinogenicity of picoxystrobin have been investigated in two studies in mice at dose levels up to 800 ppm or 4800 ppm and in two studies in rats at dose levels up to 750 ppm or 3500 ppm. In the first mouse carcinogenicity study, slight, but not adverse, reductions in body weight (approximately 5%) and increases in liver weights (approximately 10%) were seen at 800 ppm (equal to 109 mg/kg bw per day), the highest dose tested. In the second mouse carcinogenicity study, survival was significantly increased in males receiving 2400 or 4800 ppm. Pathological changes seen in the liver in the 4800 ppm groups were macroscopic nodules, microscopic foci of alteration and a significant increase in total hepatocellular tumours in males and centrilobular hepatocyte hypertrophy in females. The tumours were seen predominantly in males surviving to the end of the study, and additional statistical analyses indicated that the increases were related to the increased survival in these mice. The NOAEL for toxicity in mice was 600 ppm (equal to 71 mg/kg bw per day), based on increased liver weights (> 10%) in both sexes at 2400 ppm (equal to 293 mg/kg bw per day). The NOAEL for carcinogenicity was 4800 ppm (equal to 585 mg/kg bw per day), the highest dose tested, as the increase in liver tumours in males at 2400 and 4800 ppm is considered to be secondary to increased survival in these groups and therefore not relevant to the risk assessment of picoxystrobin.

In the first rat chronic toxicity and carcinogenicity study, Alpk (Wistar-derived) male rats receiving 750 ppm had increased survival and increased incidences of large granular lymphocyte leukaemia. The incidence of leukaemia was outside the test facility's historical control range and was still statistically significant when corrected for the increased survival. The leukaemia incidence was of marginal statistical significance, it is a spontaneous finding in this strain of rat, there were no associated pathological changes in other organs (e.g. the spleen) and the finding was not duplicated in a second study that employed higher dose levels; therefore, the Meeting concluded that these leukaemias were incidental findings. In the first study, the NOAEL for toxicity was 200 ppm (equal to 12 mg/kg bw per day), based on reduced body weight gain and kidney weights. In the second rat chronic toxicity and carcinogenicity study, in Crl:CD(SD) rats (Sprague-Dawley derived), survival was increased in the picoxystrobin groups, with over twice as many rats from the 3500 ppm groups surviving to the end of the study. Reductions in body weight gain, feed consumption and feed conversion efficiency were seen during the first year of the study in the 3500 ppm groups. Liver weight relative to body weight was increased by more than 10% at both interim and terminal kills in the 3500 ppm groups. Testes weights were increased in top-dose rats at the interim kill. Statistically significant increases in the incidences of interstitial cell hyperplasia and benign adenoma in the testes were observed in male rats at 3500 ppm. Although the majority of adenomas and hyperplasia occurred in terminal or near-terminal animals, the results were still statistically significant when corrected for the increased survival, and the Meeting considered it likely that the increases in testicular interstitial cell adenoma and hyperplasia in the 3500 ppm males were related to exposure to the test substance. The NOAEL for toxicity in rats was 1000 ppm (equal to 45 mg/kg bw per day), based on testicular interstitial cell hyperplasia and benign adenoma, reduced body weights and increased relative liver weights at 3500 ppm (equal to 162 mg/kg bw per day).

The Meeting concluded that picoxystrobin is not carcinogenic to mice or rats.

Picoxystrobin has been tested in an adequate range of genotoxicity studies. No evidence of genotoxicity was seen, other than a weak response in a mouse lymphoma mammalian cell gene mutation assay with metabolic activation.

The Meeting concluded that picoxystrobin is unlikely to be genotoxic.

Based on the lack of genotoxicity and the absence of carcinogenicity in rats and mice, the Meeting concluded that picoxystrobin is unlikely to pose a carcinogenic risk to humans.

Two multigeneration reproductive toxicity studies in rats have been performed with picoxystrobin at dose levels up to 750 ppm or 2500 ppm. In the first study, the NOAEL for reproduction was 750 ppm (equal to 78 mg/kg bw per day), the highest dose tested. The NOAEL for parental toxicity and offspring toxicity was 200 ppm (equal to 21 mg/kg bw per day), based on reductions in body weight gain at 750 ppm. In the second study, the NOAEL for reproduction was 2500 ppm (equal to 130 mg/kg bw per day), the highest dose tested. The NOAEL for parental and

offspring toxicity was 1000 ppm (equal to 52 mg/kg bw per day), based on body weight deficits and thymic atrophy at 2500 ppm in parental animals and pups.

The developmental toxicity of picoxystrobin has been assessed in rats and rabbits. In rats, misaligned fifth sternebrae were present in 1.5% of fetuses in the 100 mg/kg bw per day group, above the cited historical control range of 0–1.4%. The NOAEL for developmental toxicity was 30 mg/kg bw per day, based on an increased incidence of misaligned fifth sternebrae at 100 mg/kg bw per day. The NOAEL for maternal toxicity was 30 mg/kg bw per day, based on body weight deficits and reduced feed consumption during the dosing period at 100 mg/kg bw per day.

In rabbits, the mean number of fetuses per litter was reduced at 100 mg/kg bw per day, but this appeared to be related to increased pre-implantation losses, which occur before the start of administration of picoxystrobin. Increased incidences of skeletal anomalies were seen in the 100 mg/kg bw per day group. The NOAEL for developmental toxicity was 25 mg/kg bw per day, based on an increase in skeletal anomalies at 100 mg/kg bw per day. The NOAEL for maternal toxicity was 25 mg/kg bw per day, based on body weight deficits and reduced feed consumption during the dosing period at 100 mg/kg bw per day.

The Meeting concluded that picoxystrobin is not teratogenic in rats or rabbits.

In an acute neurotoxicity study in rats, there was no evidence of neuropathy at 2000 mg/kg bw, the highest dose tested. The NOAEL for toxicity was less than 200 mg/kg bw, based on dose-related, transient decreases in motor activity and in body weight at all dose levels. A benchmark dose evaluation indicated that a derived NOAEL in the acute neurotoxicity study was likely to be much lower than 200 mg/kg bw. There was no evidence of neurotoxicity in a 90-day neurotoxicity study in rats at dose levels up to 3500 ppm (equal to 207 mg/kg bw per day), the highest dose tested.

In a 28-day dietary immunotoxicity study in rats and mice, no effects on immunoglobulin M response to sheep red blood cells were observed at the highest doses tested, 4800 ppm (equal to 727 mg/kg bw per day) in mice or 3500 ppm (equal to 229 mg/kg bw per day) in rats.

The plant metabolite IN-H8612 (1,3-dihydro-3-oxoisobenzofuran-1-carboxylic acid) was of low acute oral toxicity to rats (LD_{50} > 2000 mg/kg bw). In a 28-day toxicity study in rats, the NOAEL was 1600 ppm (equal to 182 mg/kg bw per day), the highest dose tested. IN-H8612 was negative in an Ames test for bacterial gene mutation and produced equivocal results at high concentrations in a chromosomal aberration assay in human lymphocytes. On the basis of the limited in vivo data available, the toxicological potency of IN-H8612 is similar to or lower than that of picoxystrobin, but additional data are required to resolve its potential to induce chromosomal aberrations in vivo. The Meeting was unable to conclude on the genotoxic potential of IN-H8612. The international estimated daily intake (IEDI) was above 0.15 µg/person per day, the threshold of toxicological concern (TTC) for a compound with evidence of genotoxicity. The Meeting was unable to conclude on the toxicological relevance of estimated intakes of IN-H8612.

The soil metabolite IN-QDY63 (2-[2-(6-trifluoromethyl-2-pyridyloxymethyl)] benzoic acid) was of moderate acute oral toxicity to rats (LD_{50} = 387 mg/kg bw). IN-QDY63 was negative in an Ames test for bacterial gene mutation. In a 90-day dietary toxicity study in rats, the NOAEL was 180 ppm (equal to 14 mg/kg bw per day), based on increased kidney weights and renal tubule pathological changes at 600 ppm (equal to 48 mg/kg bw per day). The limited data available indicate that the toxicity of IN-QDY63 is quantitatively similar to or greater than that of picoxystrobin. The estimated IEDI for IN-QDY63 was 9.7 µg/person per day, below the applicable TTC of 90 µg/person per day. The Meeting concluded that IN-QDY63 was not of toxicological concern at the estimated dietary intake levels.

Three other plant metabolites of picoxystrobin were considered:

- Phthalic acid is a widely used industrial chemical. It is not genotoxic and is not a developmental toxicant in rats (NOAEL = 1763 mg/kg bw per day). Phthalic anhydride, which hydrolyses to phthalic acid, is not carcinogenic in mice or rats, with NOAELs above

748 mg/kg bw per day. The Meeting concluded that phthalic acid is not a toxicologically relevant metabolite of picoxystrobin.

- 2-(2-Formylphenyl)-2-oxoacetic acid is not supported by any toxicological studies, but a structural alert for genotoxicity was identified. The IEDI was above 0.15 µg/person per day, the TTC for a compound with a structural alert for genotoxicity. The Meeting was unable to conclude on the toxicological relevance of estimated intakes of 2-(2-formylphenyl)-2-oxoacetic acid.
- 2-(2-Hydroxymethylphenyl)-2-oxoacetic acid (PAG3) is not supported by any toxicological studies, and no structural alerts for genotoxicity were identified. The estimated IEDI for PAG3 was 16.4 µg/person per day, below the applicable TTC of 90 µg/person per day. The Meeting concluded that PAG3 was not of toxicological concern at the estimated dietary intake levels.

Medical surveillance of production plant workers has not identified any cases of occupational illness related to picoxystrobin. There are no reports of poisoning cases with picoxystrobin.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.09 mg/kg bw on the basis of the overall NOAEL of 8.5 mg/kg bw per day in the 90-day and 1-year dog studies, based on body weight loss, reduced feed consumption and clinical signs at 16 mg/kg bw per day. A safety factor of 100 was applied.

The Meeting established an ARfD of 0.09 mg/kg bw on the basis of the overall NOAEL of 8.5 mg/kg bw per day in the 90-day and 1-year dog studies, based on body weight loss and reduced feed consumption at the beginning of the study at 16 mg/kg bw per day. A safety factor of 100 was applied. This value is supported by a benchmark dose analysis of the motor activity changes seen at the lowest dose in the acute neurotoxicity study. The Meeting noted that this ARfD is possibly conservative and that it might be possible to refine it.

Picoxystrobin's mode of fungicidal activity is to block mitochondrial electron transport, reducing ATP production and inhibiting cellular respiration; this could result in impaired body weight gains. In the absence of any information on the mode of toxicological action for reductions in body weight and body weight gain, these effects were considered as adverse and relevant for the setting of guidance values.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month studies of toxicity and carcinogenicity[a,b]	Toxicity	600 ppm, equal to 71 mg/kg bw per day	2400 ppm, equal to 293 mg/kg bw per day
		Carcinogenicity	4800 ppm, equal to 585 mg/kg bw per day[c]	—
Rat	Acute neurotoxicity study[d]	Toxicity	—	200 mg/kg bw per day[e]
	Ninety-day study of toxicity[a]	Toxicity	500 ppm, equal to 42 mg/kg bw per day	1250 ppm, equal to 105 mg/kg bw per day
	Two-year studies of toxicity and carcinogenicity[a,b]	Toxicity	1000 ppm, equal to 45 mg/kg bw per day	3500 ppm, equal to 162 mg/kg bw per day
		Carcinogenicity	3500 ppm, equal to 162 mg/kg bw per day[c]	—
	Multigeneration study of reproductive toxicity[a,b]	Reproductive toxicity	2500 ppm, equal to 130 mg/kg bw per day[c]	—

Species	Study	Effect	NOAEL	LOAEL
		Parental toxicity	1000 ppm, equal to 52 mg/kg bw per day	2500 ppm, equal to 130 mg/kg bw per day
		Offspring toxicity	1000 ppm, equal to 52 mg/kg bw per day	2500 ppm, equal to 130 mg/kg bw per day
	Developmental toxicity study[d]	Maternal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
		Embryo and fetal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
Rabbit	Developmental toxicity study[d]	Maternal toxicity	25 mg/kg bw per day	100 mg/kg bw per day
		Embryo and fetal toxicity	25 mg/kg bw per day	100 mg/kg bw per day
Dog	Ninety-day and 1-year studies of toxicity[a,b]	Toxicity	250 ppm, equal to 8.5 mg/kg bw per day	500 ppm, equal to 16 mg/kg bw per day

[a] Dietary administration.

[b] Two or more studies combined.

[c] Highest dose tested.

[d] Gavage administration.

[e] Lowest dose tested.

Estimate of acceptable daily intake for humans

0–0.09 mg/kg bw

Estimate of acute reference dose

0.09 mg/kg bw

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

Additional data on the genotoxicity of the plant metabolites IN-H8612 and 2-(2-formylphenyl)-2-oxoacetic acid

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	75% in 48 h, based on urinary and biliary excretion
Distribution	Extensive; highest levels in liver and kidneys
Potential for accumulation	No evidence for accumulation
Rate and extent of excretion	> 95% within 5 days (low dose); mainly bile and faeces
Metabolism in animals	Extensive, with over 30 identified metabolites
Toxicologically significant compounds in animals, plants and the environment	Picoxystrobin, IN-H8612 and 2-(2-formylphenyl)-2-oxoacetic acid (plant metabolites) and IN-QDY63 (soil metabolite)
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	0.11 mg/L (4 h, nose-only)
Rabbit, dermal irritation	Slightly irritating
Rabbit, ocular irritation	Moderately irritating
Dermal sensitization	Not a sensitizer (Magnusson & Kligman test in guinea-pigs)
Short-term studies of toxicity	
Target/critical effect	Reduced body weight and feed consumption; clinical signs (dog)
Lowest relevant oral NOAEL	8.5 mg/kg bw per day (90-day and 1-year dog combined)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (28-day rat)

Lowest relevant inhalation NOAEC	0.025 mg/L (28-day rat)
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Reduced body weight and feed consumption; liver (mouse); testes, interstitial cell hyperplasia and adenoma (rat)
Lowest relevant NOAEL	45 mg/kg bw per day (2-year rat)
Carcinogenicity	Not carcinogenic
Genotoxicity	
	Unlikely to be genotoxic
Reproductive toxicity	
Target/critical effect	Reduced body weight gain in parents and pups
Lowest relevant reproductive NOAEL	130 mg/kg bw per day (highest dose tested)
Lowest relevant parental NOAEL	70 mg/kg bw per day
Lowest relevant offspring NOAEL	70 mg/kg bw per day
Developmental toxicity	
Target/critical effect	Reduced maternal and fetal body weight; skeletal anomalies
Lowest relevant maternal NOAEL	25 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	25 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity	Reduced motor activity, reduced body weight: LOAEL 200 mg/kg bw (rat)
Subchronic (90-day) neurotoxicity	Not neurotoxic: NOAEL 207 mg/kg bw per day (highest dose tested) (rat)
Immunotoxicity	
Twenty-eight-day study	Not immunotoxic in mice or rats: NOAEL 229 mg/kg bw per day (highest dose tested) (rats)
Other toxicological studies	
Metabolite IN-H8612	Oral LD_{50} > 2000 mg/kg bw (rat) 28-day toxicity study in rats: NOAEL 182 mg/kg bw per day Not mutagenic in bacteria; equivocal results for chromosomal aberrations in vitro
Metabolite IN-QDY63	Oral LD_{50} 387 mg/kg bw (rat) 90-day toxicity study in rats: NOAEL 14 mg/kg bw per day Not mutagenic in bacteria
Medical data	
	No reports of poisonings or adverse effects in production plant workers

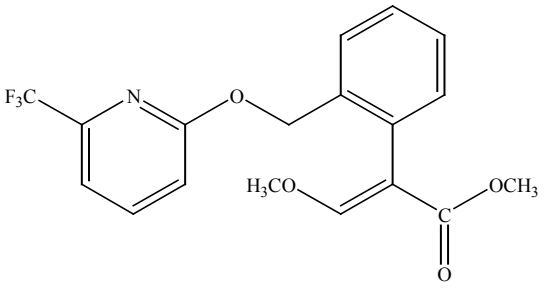
Summary

	Value	Study	Safety factor
ADI	0–0.09 mg/kg bw	90-day and 1-year studies (dog)	100
ARfD	0.09 mg/kg bw	90-day and 1-year studies (dog)	100

RESIDUE AND ANALYTICAL ASPECTS

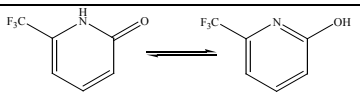
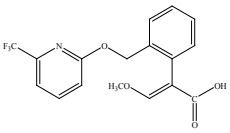
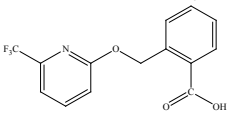
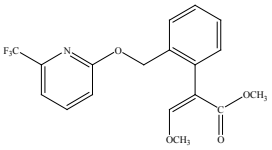
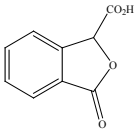
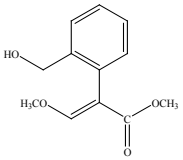
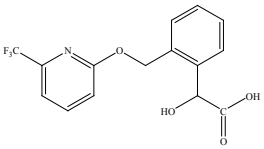
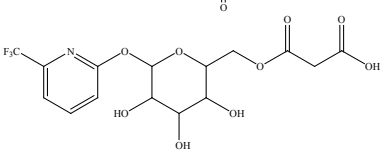
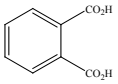
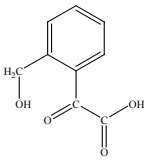
Picoxystrobin (ISO common name) is a strobilurin type fungicide for use by foliar application in a range of broadacre crops including cereals, sweet corn, soya bean, rape and pulses. At the Forty-third Session of the CCPR, picoxystrobin was scheduled for evaluation as a new compound by the 2012 JMPR. Data was provided on the metabolism of picoxystrobin in food producing animals and plants, methods of analysis, stability of residues in stored analytical samples, GAP information, supervised residue trials, processing and animal feeding studies.

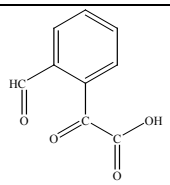
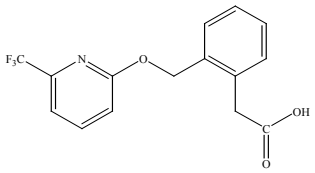
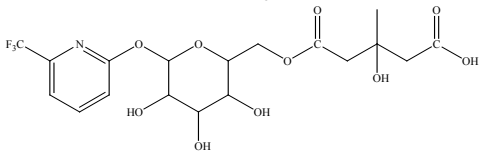
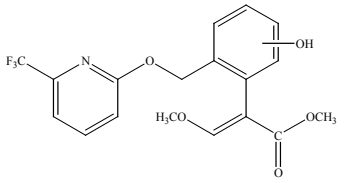
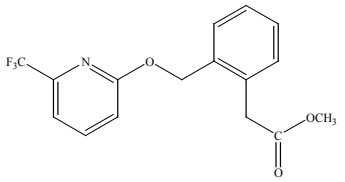
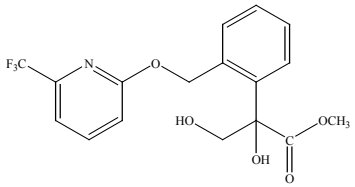
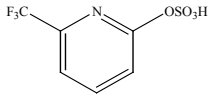
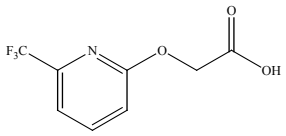
The IUPAC name for picoxystrobin is methyl (*E*)-3-methoxy-2-[2-(6-trifluoromethyl-2-pyridyloxymethyl)phenyl]acrylate



The 2012 JMPR established an ADI of 0–0.09 mg/kg bw for picoxystrobin and an ARfD of 0.09 mg/kg bw.

The following abbreviations are used for the metabolites discussed below:

Code	Chemical name	Structure
IN-QDK50	6-(Trifluoromethyl)-1*H*-pyridin-2-one	
IN-QDY62	(*E*)-3-Methoxy-2-[2-(6-trifluoromethyl-2-pyridyloxymethyl)-phenyl]acrylic acid	
IN-QDY63	2-[2-(6-Trifluoromethyl-2-pyridyloxymethyl)] benzoic acid	
IN-QCD12	Methyl (*Z*)-3-methoxy-2-[2-(6-trifluoromethyl-2-pyridyloxymethyl)-phenyl]acrylate	
IN-H8612	1,3-Dihydro-3-oxoisobenzofuran-1-carboxylic acid	
IN-QDY60	Methyl (*E*)-3-methoxy-2-(2-hydroxymethylphenyl)acrylate	
IN-QGS46	2-Hydroxy-2-[2-(6-trifluoromethyl-2-pyridyloxymethyl)phenyl] acetic acid	
IN-QGU72	2-Malonylglucosyl-6-trifluoromethylpyridine	
IN-K2122	Phthalic acid	
PAG3	2-(2-Hydroxymethylphenyl)-2-oxoacetic acid	

Code	Chemical name	Structure
-	2-(2-Formylphenyl)-2-oxoacetic acid	
IN-QFA35	2-[2-(6-Trifluoromethyl-2-pyridyloxymethyl)phenyl] acetic acid	
IN-QGU73	Mixture of isomers, where n=3, 4 or 6 2-{n-(3-Hydroxy-3-methylglutaryl)glucosyl}-6-trifluoromethylpyridine	
R290447	Methyl (*E*)-3-methoxy-2-[n-hydroxy-2-(6-trifluoromethyl-2-pyridyloxymethyl)-phenyl]acrylate	
IN-QCD09	Methyl 2-[2-(6-trifluoromethyl-2-pyridyloxymethyl)-phenyl]acetate	
R290461	Methyl 2,3-dihydroxy-2-[2-(6-trifluoromethyl-2-pyridyloxymethyl)-phenyl]propionate	
PYST2	6-Trifluoromethyl-2-pyridylsulfuric acid	
R409665, metabolite 30	2-(6-Trifluoromethyl-2-pyridyloxy)acetic acid	

Animal metabolism

The Meeting received information on the metabolism of radio-labelled picoxystrobin (separately ^{14}C-labelled at the pyridinyl and phenacrylate rings) in rats, lactating goats and laying hens.

The metabolism of picoxystrobin in rats was evaluated by the WHO panel of the JMPR at the present Meeting. It was concluded that picoxystrobin is extensively metabolized with over 30 identified metabolites. Significant biotransformation reactions include ester hydrolysis, oxidation, O-demethylation and glucuronide conjugation.

Picoxystrobin was administered to lactating goats by capsule twice daily immediately after milking for 7 days at 10 and 13.5 ppm in feed for the pyridinyl and phenacrylate labels respectively (0.244 and 0.296 mg/kg bw/day).

The majority of the dose was excreted in urine (46–49%), and faeces (27–36%).

Residues in milk reached a plateau by day 4 (maximum TRR of 0.010–0.012 mg parent equivalents/kg (mg eq./kg)). A total of 0.06–0.20 % of the administered dose was recovered in milk.

Total residues in muscle were 0.006–0.010 mg eq./kg. In fat, total residues were 0.021–0.034 mg eq./kg. In liver, total residues were 0.12–0.34 mg eq./kg, and kidney residues were 0.057–0.15 mg eq./kg. A total of 0.11–0.20% of the administered dose was recovered in liver, with 0.01–0.02% recovered in kidney.

Residues in milk and muscle were not characterised due to the low total residues.

Parent was present in fat, liver and kidney. In fat, parent was the only significant residue, at 55–81% of TRR and 0.012–0.024 mg eq./kg. Other compounds (unidentified) ranged from 0.002–0.004 mg eq./kg (5.2–20% TRR) in fat.

In liver, parent was only present at 0.003 mg eq./kg (1.0–2.7% TRR). A number of components were found; only IN-QDY62 and IN-QFA35, at 0.017 and 0.013 mg eq./kg respectively, exceeded 0.01 mg eq./kg, and no component exceeded 10% TRR.

Parent was found in kidney at 0.002–0.004 mg eq./kg (2.5–3.8% TRR). The only significant component was IN-QFA35, at 14–15% TRR (0.008–0.020 mg eq./kg).

IN-QDY62, a rat metabolite, was found in the faeces, urine and bile. IN-QFA35, another rat metabolite, was found in bile.

Hens were dosed for 10 days, at a mean dose of 11.3 and 10.9 ppm in feed for the pyridinyl and phenacrylate labels respectively (0.947 and 0.883 mg/kg bw/day).

The majority (65–94%) of the administered dose was excreted.

Residues in egg yolks and whites reached a plateau at 8–10 days, at 0.19–0.21 mg eq./kg for yolks and 0.006–0.015 mg eq./kg for whites. Total residues in muscle, fat and liver were 0.019–0.023, 0.027–0.070 and 0.16–0.31 mg eq./kg respectively. In yolks, 0.08–0.10% of the administered dose was recovered, compared with 0.01–0.02% in white, 0.04–0.05% in muscle, 0.01–0.02% in fat, and 0.07–0.14% in liver.

Only day 10 yolks were extracted and characterised. Parent was found in yolk (0.003–0.005 mg eq./kg, or 1.3–2.2% of TRR), along with three metabolites IN-QDK50, IN-QFA35 and IN-QCD09, none of which exceeded 0.01 mg eq./kg or 10% of the TRR.

All three of these metabolites, IN-QDK50 (urine), IN-QFA35 (bile), and IN-QCD09 (bile), are metabolites found in rats.

The metabolism of picoxystrobin was similar in lactating goats and laying hens. Important metabolic pathways were:

- Oxidative cleavage of the molecule at the ether bridge to yield IN-QDK50 and IN-QDY60. Only IN-QDK50 was found in hens, while both metabolites were found in goats.
- Hydrolysis of the methyl ester to IN-QDY62.
- Loss of the methoxy methyl group, with subsequent hydroxylation of the carbon side chain, hydrolysis of the methyl ester, and further cleavage of the side chain yielding IN-QDY63 as a terminal metabolite.
- Cleavage of the acrylate side chain at the 2 position to yield phenyl acetate metabolites, with or without subsequent hydrolysis of the methyl ester, and/or hydroxylation at the 2 position, yielding IN–QGS46 and IN-QFA35.
- Hydroxylation of the phenyl ring (R290447).

Plant metabolism

Metabolism of ^{14}C-pyridinyl- and ^{14}C-phenacrylate-picoxystrobin was investigated in wheat, rape seed and soya bean.

Wheat (field grown) was treated twice by foliar application at Zadok's stages 32 and 65–69 at 405–437 g ai/ha, giving a total seasonal rate of 842 and 817 g ai/ha for the pyridinyl and phenacrylate labels respectively. Forage was harvested 14 days after the second application, with straw and grain being collected at normal harvest.

Parent was identified in grain (3.5–7.6% of TRR, 0.006–0.011 mg eq./kg). The only other components identified in grain were phthalic acid, IN-H8612 and PAG3 at 7.4%, 15%, and 7.9% (0.023, 0.046, and 0.024 mg eq./kg) respectively. Parent was the largest residue in forage (50–56% of TRR, 2.0–3.3 mg eq./kg) and straw (20–21% and 2.0–2.4 mg eq./kg). No other residue components exceeded 10% TRR in forage or straw, although a number of metabolites exceeded 0.01 mg eq./kg.

Phthalic acid, IN-H8612, and PAG3 were not found in rats.

Rape (greenhouse grown) was treated with two late season foliar applications at BBCH growth stages 80 and 85 with either the pyridinyl or the phenacrylate label at individual rates of 403–483 g ai/ha. Forage was sampled 7 days after the first application and 14 days after the second application, with remaining plant material and seed collected at normal harvest 21 days after the second application.

In all cases, parent was the most significant residue, at 80–96% of the TRR (5.6–9.9 mg eq./kg) in forage, 70–72% of TRR (8.3–9.4 mg eq./kg) in foliage at harvest, and 89–94% of TRR (1.5–2.3 mg eq./kg) in seed. All metabolites were < 10% of the TRR. The only other component identified in seed was Z-isomer (IN-QC12), at 0.6% TRR (0.02 mg eq./kg). In forage and dry plant material at harvest, Z-isomer, IN-QDY62, IN-QDY63, IN-QDK50 and its glucose conjugate were identified (maximum 7.4% TRR or 0.96 mg eq./kg). The small extent of metabolism of picoxystrobin in rape compared with wheat and soya bean is likely the result of the late application and the fact that the experiment was conducted in a greenhouse rather than in the field.

IN-QDY62 (faeces, urine and bile), IN-QDY63 (bile) and IN-QDK50 (urine) are all rat metabolites.

Soya beans (field grown) was treated with ^{14}C-pyridinyl or ^{14}C-phenacrylate-labelled picoxystrobin. Two foliar applications were made at BBCH 69 and 73–75 to give target seasonal rates of 200 g ai/ha. Foliage (hay) samples were collected 14 days after the second application, with dry stalks and seed collected at normal harvest.

Parent was found in seed (1.5–5.9% TRR, or 0.002–0.004 mg eq./kg). In forage, parent was significant at 7.4–10% TRR (0.13–0.18 mg eq./kg). In seed, only phthalic acid (INK2122) and 2-(2-formylphenyl)-2-oxoacetic acid (R730529) were found at levels above 10% TRR and 0.01 mg eq./kg (21% TRR/0.030 mg eq./kg and 26% TRR/0.036 mg eq./kg respectively). Other significant residues in forage included the glucose conjugate of IN-QGS46 (8.4–14%, or 0.14–0.26 mg eq./kg, mixed glucose conjugates of R290461 (total 26–31%/0.44–0.55 mg eq./kg and malonyl glucose conjugate of R290461 (10%/0.18 mg eq./kg).

Phthalic acid and 2-(2-formylphenyl)-2-oxoacetic acid are not rat metabolites. IN-QGS46 (bile and urine) and R290461 (urine) are rat metabolites.

The major metabolic pathways for picoxystrobin in plants were:

- Oxidative cleavage of the molecule at the ether bridge to yield IN-QDK50 and IN-QDY60. IN-QDK50 was subsequently conjugated with glucose and malonic or glutaric acid, while the phenacrylate cleavage product was subject to further oxidation and cleavage giving phthalic acid or IN-H8612;
- Loss of the methoxy methyl group followed by reduction of the enol, further hydroxylation of the side chain, and conjugation of the hydroxyl groups with glucose and malonic acid (R290461 and conjugates); and
- Hydrolysis of the ester, followed by oxidation and cleavage of the acrylate moiety ultimately yielding the benzoic acid metabolite IN-QDY63 or a phenyl-acetic acid metabolite (IN-QFA35), with or without glucose conjugation of the hydroxyl or carboxylic acid functionalities.

Hydroxylation of the phenyl ring was also observed in wheat, while small amounts of the *Z*-isomer of picoxystrobin (IN-QCD12) were found in rape and wheat.

Environmental fate

The Meeting received information on the aerobic degradation of picoxystrobin in soil, photolysis on the soil surface, field dissipation in soil, hydrolysis, aqueous photolysis, and metabolism in rotational cropping (both field and confined).

Aerobic metabolism of picoxystrobin in the dark was studied in various soil types at 20 °C. The DT_{50} values were 16–38 days, with DT_{90} values of 76–337 days. The major degradation pathways were ester hydrolysis, cleavage of the ether bridge to give IN-QDK50 (subsequently methylated), and mineralisation to carbon dioxide.

Picoxystrobin applied to thin layers of soil and irradiated for a period equivalent to 30 summer days at 50 ° latitude degraded rapidly with a DT_{50} of 7 days. The major degradation pathways were cleavage of the ether bridge and methyl acrylate moiety, yielding IN-QDK50 and phthalic acid, and finally mineralisation to carbon dioxide.

Microbial and photolytic degradation are both significant for picoxystrobin in/on soil.

Field dissipation studies for picoxystrobin were conducted in France, Germany, the UK, Canada and the USA. Degradation was relatively rapid (DT_{50} = 1.3–35 days, DT_{90} = 42–437 days). Metabolite levels were low, often below the limit of quantification, and less than parent. There was no evidence of accumulation of parent or metabolites.

Residues on succeeding crops

Rotational crop metabolism studies were conducted for ^{14}C-pyridinyl- and ^{14}C-phenacrylate-labelled picoxystrobin.

In one field rotation study, spring wheat, lettuce and carrot were sown 304–308 days after final application of radiolabelled compound at seasonal rates of 820–888 g ai/ha. The second field study involved winter wheat sown 107 days after the second of two foliar applications of labelled compound at a seasonal rate of 817–842 g ai/ha.

Picoxystrobin breaks down relatively rapidly in soil, and does not accumulate to a significant extent in following crops. Total residues did not exceed 0.01 mg eq./kg in wheat grain, lettuce and carrot roots from the field rotational studies. In wheat forage and straw and carrot leaves in the field studies, the most significant component was IN-QDK50 and conjugates, with a maximum total of 0.058 mg eq./kg (35–63% TRR), with free IN-QDK50 comprising only 0.002–0.006 mg eq./kg, or 2.0–6.9% TRR. No other components exceeded 0.01 mg eq./kg, or 10% TRR in any of the field rotational crop matrices. IN-QDK50 is a rat metabolite, found in urine.

Residues of picoxystrobin or its metabolites in following crops are therefore unlikely to be significant.

Methods of analysis

The Meeting received details of analytical methods for picoxystrobin residues in plant and animal matrices.

Analysis of picoxystrobin and the metabolites IN-QDK50, IN-QDY62 and IN-QDY63 in plant matrices involved extraction with acetonitrile/water, solid phase extraction clean-up, and GC/MS or LC/MS/MS analysis. LOQs are 0.01 mg/kg.

Methods were developed for analysis of parent in animal matrices. Samples were extracted with acetonitrile and in some cases cleaned up by solid phase extraction clean-up, with analysis by GC/MS or LC/MS/MS. LOQs are 0.01 mg/kg.

The suitability of the US FDA Pesticide Analytical Manual, Volume I (PAM I 3rd edition) protocols was assessed, with the GC method being found suitable for analysis of parent only in fatty and non-fatty plant matrices (apple and soya bean).

Suitable single residue analytical methods therefore exist for parent and the metabolites IN-QDK50, IN-QDY62 and IN-QDY63 in plant matrices, and for parent in animal matrices. A multi-residue method has been validated for the determination of parent only in plant matrices.

Stability of residues in stored analytical samples

Storage stability of picoxystrobin and the metabolites IN-QDK50, IN-QDY62 and IN-QDY63 in a range of plant commodities including high (apples, apple juice and lettuce), medium (wheat forage and apple pomace) and low (wheat straw and soya bean meal) water content, high acid (grapes), high protein (dry pea), high starch (potato), and high oil (soya bean seed and refined oil) content was assessed for samples stored frozen for 24 months. With the exception of the metabolites IN-QDY62 and IN-QDY63 in soya bean oil, which were stable for 18 and 6 months respectively, all analyte/sample combinations were stable for 24 months frozen storage.

The stability of residues of picoxystrobin in animal commodity samples over the period of storage in the feeding studies was acceptable.

Definition of the residue

Total residues in milk and muscle were very low (≤ 0.012 mg eq./kg). In goat fat, parent was the only identified component, at 55–81% of the TRR and 0.012–0.024 mg/kg. In liver and kidney, parent was present at low levels (1.0–3.8% TRR; 0.002–0.004 mg eq./kg). The only components in liver > 0.01 mg eq./kg were IN-QDY62 and IN-QFA35 at 0.017 and 0.035 mg/kg respectively. No components exceeded 10% of the TRR in liver. In kidney, only IN-QFA35 (14–15% TRR, or 0.008–0.020 mg/kg) was significant. In egg yolks, no components were found at > 10% of TRR or 0.01 mg eq./kg. Both IN-QFA35 and IN-QDY62 are also metabolites found in rats.

As parent was the only identified residue in fat, and was found in all analysed animal tissues, it is a suitable marker compound for analysis. A residue definition of parent compound only is proposed for picoxystrobin in animal commodities for both compliance and risk assessment purposes.

The octanol-water partition coefficient ($\log_{10}K_{OW}$) for picoxystrobin is 3.7. In the cattle feeding study at the highest feeding level, mean residues of picoxystrobin were < 0.01 mg/kg in muscle, compared with 0.028 mg/kg in subcutaneous fat. Residues were undetectable in skim milk, with a mean level of 0.026 mg/kg in cream. The Meeting concluded that picoxystrobin residues are fat-soluble.

In oilseed rape, the major component was parent at 89–94% of the TRR (1.5–2.3 mg eq./kg) in seed, and 70–96% of the TRR (5.6–9.9 mg eq./kg) in foliage. In wheat, parent was the only significant component in forage and straw (20–55% TRR, 2.0–3.3 mg eq./kg), and was found in grain (3.5–7.6% TRR, 0.006–0.011 mg eq./kg). In soya bean, parent was found at low levels in seed (1.5–5.9% TRR, 0.002–0.004 mg eq./kg). Parent was present at 0.13–0.18 mg eq./kg (7.4–10% TRR) in soya bean forage.

Other identified components in wheat grain were phthalic acid (IN-K2122) at 7.4% TRR, 0.023 mg eq./kg, PAG3 (7.9% of TRR, 0.024 mg eq./kg), and IN-H8612 (15% TRR, 0.046 mg eq./kg). In soya bean, only phthalic acid (21% TRR, 0.030 mg eq./kg) and 2-(2-formylphenyl)-2-oxoacetic acid (26% TRR, 0.036 mg eq./kg) were significant for seed. In soya bean forage, residue profiles were qualitatively similar to those for seed. IN-QGS46-glucoside was present at 0.26 mg eq./kg (14% TRR), with R290461-glucosides at 31% (0.55 mg eq./kg), and R290461 malonyl glucoside at 10% TRR (0.18 mg eq./kg).

Total residues did not exceed 0.01 mg eq./kg in wheat grain, lettuce and carrots from the field rotation studies. In wheat forage and straw and carrot leaves, the only significant (> 0.01 mg eq./kg, > 10% TRR) residue was IN-QDK50 and conjugates, which reached a total of 0.058 mg eq./kg (35–63% of TRR), with free IN-QDK50 comprising only 0.002–0.006 mg eq./kg, or 2.0–6.9% TRR. Picoxystrobin breaks down relatively rapidly in soil, and does not accumulate significantly in following crops. Residues of picoxystrobin or its metabolites in following crops are therefore unlikely

to be significant, and inclusion of metabolites in the residue definition for rotational crops is not necessary, especially as IN-QDK50 is a metabolite found in rats.

The Meeting concluded that phthalic acid is not a toxicologically relevant metabolite, while PAG3 and IN-QDY63 were not of toxicological concern at the estimated dietary intake levels.

The International Estimate Daily Intake (IEDI) of IN-H8612 was 0.15 µg/person/day, above the Threshold of Toxicological Concern (TTC) for a compound with evidence of genotoxicity. The Meeting was unable to conclude on the toxicological relevance of the estimated intakes of IN-H8612.

2-(2-Formylphenyl)-2-oxoacetic acid is not supported by any toxicological studies but a structural alert for genotoxicity was identified. The IEDI was above 0.15 µg/person/day, the TTC for a compound with a structural alert for genotoxicity. The Meeting was unable to conclude on the toxicological relevance of the estimated intakes of 2-(2-formylphenyl)-2-oxoacetic acid.

Conjugated compounds (such as those of IN-QDK50, IN-QGS46 or R290461) are not suitable for inclusion in the residue definition, as their analysis requires specialised analytical methods incorporating enzymatic digestion or hydrolysis steps. IN-QDK50 is a metabolite in the rat.

Given that parent is the major component of the residue in many plant matrices (rape seed and forage, and wheat forage and straw), and was found in all other plant matrices tested, it is the most suitable marker compound for analysis of picoxystrobin residues. A residue definition of parent compound is proposed for plant matrices for the purposes of compliance.

Because the Meeting was unable to conclude on the toxicological relevance of the metabolites IN-H8612 and 2-(2-formylphenyl)-2-oxoacetic acid, the Meeting could not reach a conclusion on a residue definition for dietary risk assessment.

Residue definition for picoxystrobin in plant and animal commodities (for compliance with maximum residue levels): *picoxystrobin.*

Residue definition for picoxystrobin in plant and animal commodities (for dietary risk assessment): *a conclusion could not be reached*.

Picoxystrobin residue is fat-soluble.

Residues of supervised residue trials on crops

The Meeting received supervised trial data for application of picoxystrobin on sweet corn, peas (dry), beans (dry), soya bean (dry), wheat, barley and rape seed conducted in the USA and Canada. The OECD MRL calculator was used as a tool to assist in the estimation of maximum residue levels from the selected residue data set obtained from the supervised residue trials. 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 using expert judgement. Then the OECD MRL calculator was employed. If the statistical calculation spreadsheet suggested a different value from that estimated by the Meeting, a brief explanation of the deviation was supplied.

In all trials, duplicate field samples were collected at each sampling interval and separately analysed. The mean result of the duplicate analyses was taken as the best estimate of the residue.

Labels were available from Canada, describing the registered uses of picoxystrobin.

Sweet corn

Picoxystrobin is registered in Canada for use in sweet corn at a GAP of 4 × 0.22 kg ai/ha and a 7 day PHI. The Canadian use pattern constitutes the critical GAP for sweet corn.

Eleven trials were conducted in sweet corn at GAP in the USA and Canada. Residues in sweet corn cobs at the 7 day PHI were < 0.01 (11) mg/kg.

The meeting estimated a maximum residue level of 0.01* mg/kg for picoxystrobin in sweet corn (corn-on-the-cob), together with a median residue and a highest residue both at 0.01 mg/kg.

Pulses

Picoxystrobin is registered in pulses except soya bean (chickpea, lentil, guar bean, lablab bean, broad bean (dry), pigeon, pea, lupin, field bean, kidney bean, lima bean, navy bean, pinto bean, tepary bean, adzuki bean, black-eyed pea, catjang, cowpea, cowpea, crowder pea, moth bean, mung bean, rice bean, southern pea, urd bean, and field pea) in Canada, at a maximum rate of 2 × 0.22 kg ai/ha with a 14 day PHI for harvest for human consumption.

Eleven trials were conducted in peas (dry) and eleven in beans (dry) in the USA and Canada and were evaluated against the Canadian GAP.

Residues in pea seed at the Canadian GAP were: < 0.01 (4), 0.010, 0.012, 0.013, 0.016 (2), 0.025 and 0.033 mg/kg. Residues in bean seed at the 14 day PHI were: < 0.01 (6), 0.011 (2), 0.016 and 0.038 (2) mg/kg.

Given the similarity of the data sets (confirmed by the Mann-Whitney U test), and the identical GAPs, the Meeting decided to combine the data sets for peas (dry) and beans (dry) for the purposes of determining a group maximum residue level. Residues were: < 0.01 (10), 0.010, 0.011 (2), 0.012, 0.013, 0.016 (3), 0.025, 0.033, and 0.038 (2) mg/kg.

The Meeting estimated a maximum residue level of 0.06 mg/kg for pulses (except soya bean), along with a median residue of 0.0105 mg/kg.

Picoxystrobin is registered in soya bean in Canada at a GAP of 3 × 0.22 kg ai/ha and a 14 day PHI. The Canadian use pattern represents the critical GAP for picoxystrobin in soya bean.

Twenty trials were conducted in soya bean in the USA and Canada and were assessed against the Canadian GAP. Residues in soya bean (dry) at the 14 day PHI were: < 0.01 (13), 0.010, 0.011, 0.012, 0.019, 0.031, 0.035, and 0.039 mg/kg.

The Meeting estimated a maximum residue level of 0.06 mg/kg for soya bean (dry), with a median residue of 0.01 mg/kg.

Cereal grains

In Canada, picoxystrobin is registered in cereal grains: wheat, barley, oats, rye, and triticale at a GAP of 3 × 0.22 kg ai/ha, with a PHI of 45 days.

Twenty-three trials were conducted in wheat in the USA and Canada and were assessed against the GAP of Canada. Residues in wheat grain from trials matching Canadian GAP were: < 0.01 (15), 0.010 (2), 0.013, 0.014, 0.019, 0.022, 0.025, and 0.028 mg/kg.

Seventeen trials were conducted in the USA and Canada in barley and were assessed against the Canadian GAP. Residues in barley grain from trials matching the Canadian GAP were: < 0.01 (4), 0.011, 0.014, 0.016 (2), 0.017, 0.022, 0.028 (2), 0.029, 0.047, 0.087, 0.12, and 0.22 mg/kg.

The Meeting decided that the residue data sets for wheat and barley were not sufficiently similar to combine for the purposes of establishing a group maximum residue level for cereal grains.

The Meeting estimated a maximum residue level of 0.04 mg/kg for picoxystrobin in wheat, with a median residue of 0.01 mg/kg.

Given the GAPs in Canada are the same for wheat, rye and triticale and the similarity of the crops, the Meeting decided to extrapolate from the wheat residue data to estimate maximum residue levels of 0.04 mg/kg for picoxystrobin in rye and triticale, with median residues of 0.01 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg for picoxystrobin in barley, with a median residue of 0.017 mg/kg.

Given the GAPs are the same for barley and oats and the similarity of the crops, the Meeting decided to extrapolate from the barley residue data to estimate a maximum residue level of 0.3 mg/kg for picoxystrobin in oats, with a median residue of 0.017 mg/kg.

Picoxystrobin is registered in Canada for use in maize (field, seed and popcorn), with a GAP of 3 × 0.22 kg ai/ha, and a 7 day PHI.

Fifteen trials were conducted in maize at GAP in the USA and Canada. Residues in maize grain matching the Canadian GAP were: < 0.01 (13), 0.011, and 0.012 mg/kg.

The Meeting estimated a maximum residue level of 0.02 mg/kg for picoxystrobin in maize, together with a median residue of 0.01 mg/kg. The OECD MRL calculator yielded a value of 0.015 mg/kg. A higher limit than that generated by the calculator was chosen, noting the high level of censoring in the data set.

Rape seed

Seventeen trials were conducted in oilseed rape in the USA and Canada but were not according to a registered GAP. As a result the Meeting was unable to make a maximum residue level recommendation.

Animal feeds

Sweet corn forage

The GAP for sweet corn in Canada is 4 × 0.22 kg ai/ha, with a 0 day grazing interval. Residue data for sweet corn forage was collected for the USA and Canadian sweet corn trials. However, most samples were collected 7 days after treatment, which is not consistent with Canadian GAP.

Residues in sweet corn forage at 0 days after treatment (DAT) were 8.4 and 17 mg/kg.

The Meeting concluded that there were insufficient data points to estimate a highest residue and a median residue value for sweet corn forage.

Soya bean forage and hay

The Canadian GAP for soya bean (when forage is to be grazed or hay is to be harvested) is 1 × 0.22 kg ai/ha with a 14 day PHI.

Residue data for soya bean forage and hay were collected for the USA and Canadian soya bean residue trials.

At a 14 day PHI, residues of picoxystrobin in soya bean forage were: < 0.01, 0.25, 0.46, 0.57 (2), 0.80, 0.84, 0.88, 0.93, 1.4, 1.6 (3), 1.9, 2.0 (2), 2.1, 2.9, and 3.5 mg/kg (dry weight basis).

Residues of picoxystrobin in soya bean hay on a dry weight basis at the same interval were: < 0.01, 0.14, 0.39, 0.50, 0.51, 0.52, 0.59, 0.73, 0.81, 1.2, 1.6 (2), 1.7 (2), 1.8, 2.0, 2.1, 2.3 and 2.7 mg/kg.

The Meeting estimated a maximum residue level of 5 mg/kg for picoxystrobin in soya bean fodder, together with a median residue and a highest residue of 1.2 and 2.7 mg/kg respectively. The Meeting estimated a median residue and a highest residue of 1.4 and 3.5 mg/kg respectively for soya bean forage (dry weight).

Pea vines and hay

The GAP for picoxystrobin in pulses (except soya bean) in Canada is 2 × 0.22 kg ai/ha, with a 0 day PHI for vines (forage) and hay.

Data for pea vines and pea hay were collected for selected sites in the USA and Canadian pulse residue trials.

At a 0 day PHI, residues of picoxystrobin in pea vines were: 9.5, 14, 19, 22, 35 and 55 mg/kg (dry weight basis).

Residues of picoxystrobin in pea hay on a dry weight basis at the same interval were: 4.1, 7.1, 11, 14, 18, and 64 mg/kg.

The Meeting estimated a maximum residue level of 100 mg/kg for picoxystrobin in pea hay or pea fodder (dry), noting the value of 150 mg/kg estimated by the OECD MRL calculator. However, the Meeting agreed that 100 mg/kg represented a more realistic estimate of the maximum residue expected in pea fodder treated in accordance with GAP.

The highest residue and median residue values for pea hay are 64 and 12.5 mg/kg respectively (dry weight basis). The Meeting estimated a highest residue and a median residue value for pea vines of 55 and 20.5 mg/kg respectively (dry weight basis).

Wheat, barley, oat, rye and triticale forage, hay and straw

The Canadian GAP for wheat, barley, oat, rye and triticale forage is 1 × 0.22 kg ai/ha, with a 7 day grazing interval. The Canadian GAP for wheat, barley, oat, rye and triticale hay is 3 × 0.22 kg ai/ha, with a 14 day PHI. The Canadian GAP for wheat, barley, rye, oat and triticale straw is 3 × 0.22 kg ai/ha, with a 45 day PHI.

Residue data for wheat forage, hay and straw, and barley hay and straw were generated in the USA and Canada in accordance with the Canadian GAP.

Residues of picoxystrobin in wheat forage at a 7 day PHI were: 1.1, 1.3, 1.6, 1.7, 1.9, 2.2, 2.3, 3.6 (2), 3.7, 3.8, 3.9, 4.5, 4.6, 4.8, 6.3, 6.4, 7.0, 7.4, 8.9, 9.7, 11 (2), 12, and 31 mg/kg (dry weight basis).

Residues of picoxystrobin in wheat hay at a 14 day PHI were: 0.18, 0.19, 0.24, 0.41, 0.48, 0.51, 0.61, 0.68, 0.72, 0.78, 0.81, 0.90, 1.0, 1.1 (2), 1.4, 1.5, 1.7, 1.8, 2.4, 2.5, 2.8, 3.4, 3.6, and 4.0 mg/kg (dry weight basis).

Residues of picoxystrobin wheat straw at a 45 day PHI were: < 0.01, 0.016, 0.022 (2), 0.029, 0.033, 0.043, 0.079, 0.10 (2), 0.11, 0.15, 0.28, 0.29, 0.32, 0.36, 0.49, 0.50, 0.52, 0.62, 0.86, 1.2 (2), and 1.7 mg/kg (dry weight basis).

Residues of picoxystrobin in barley hay at a 14 day PHI were: 0.20, 0.32, 0.34, 0.38, 0.39, 0.46, 0.55, 0.66, 0.77, 0.78, 0.86, 1.3, 1.4, 1.7 (2), 2.3, 2.4, 3.5, and 5.5 mg/kg (dry weight basis).

Residues of picoxystrobin in barley straw at a 45 day PHI were: 0.049, 0.050, 0.066, 0.069, 0.082, 0.087, 0.13, 0.22, 0.23, 0.24, 0.28, 0.35, 0.40, 0.41, 0.80, and 1.2 mg/kg (dry weight basis).

A median residue value and a highest residue value of 4.5, and 31 mg/kg respectively were estimated for wheat forage for use in livestock dietary burden calculations. The Meeting agreed that these values could be extrapolated to barley, oat, rye and triticale forage for the purposes of the livestock dietary burden calculations.

Hay and straw of different cereal grains are generally indistinguishable in trade.

The Meeting determined that the residue data sets for wheat and barley hay and for wheat and barley straw were similar (Mann-Whitney U-test).

The Meeting agreed to combine the data sets for wheat and barley hay for the purposes of estimating maximum residue levels for cereal fodders. The combined data set for wheat and barley hay were: 0.18, 0.19, 0.20, 0.24, 0.32, 0.34, 0.38, 0.39, 0.41, 0.46, 0.48, 0.51, 0.55, 0.61, 0.66, 0.68, 0.72, 0.77, 0.78 (2), 0.81, 0.86, 0.90, 1.0, 1.1 (2), 1.3, 1.4 (2), 1.5, 1.7 (3), 1.8, 2.3, 2.4 (2), 2.5, 2.8, 3.4, 3.5, 3.6, 4.0, and 5.5 mg/kg.

The Meeting agreed to combine the data sets for wheat and barley straw for the purposes of estimating median and highest residue values for cereal straws. The combined data set for wheat and barley straw were: < 0.01, 0.016, 0.022 (2), 0.029, 0.033, 0.043, 0.049, 0.050, 0.066, 0.069, 0.079, 0.082, 0.087, 0.10 (2), 0.11, 0.13, 0.15, 0.22, 0.23, 0.24, 0.28 (2), 0.29, 0.32, 0.35, 0.36, 0.40, 0.41, 0.49, 0.50, 0.52, 0.62, 0.80, 0.86, 1.2 (3), and 1.7 mg/kg.

Using the combined wheat and barley hay data set, the Meeting estimated maximum residue levels of 7 mg/kg for barley straw and fodder, dry and for wheat straw and fodder, dry, with median

and highest residue values of 0.88 and 5.5 mg/kg (dry weight basis) respectively, for wheat and barley hay.

The Meeting agreed that the combined data set for barley and wheat hay could be extrapolated to the other cereal crops with the same GAP in Canada and estimated maximum residue levels of 7 mg/kg for oat straw and fodder, dry, for rye straw and fodder, dry, and for triticale straw and fodder, dry.

The Meeting estimated median and highest residue values of 0.88 mg/kg and 5.5 mg/kg (dry weight basis) respectively for oat hay, rye hay and triticale hay, using the barley and wheat hay data set.

Using the combined wheat and barley straw data set, the Meeting estimated median and highest residue values of 0.225 and 1.7 mg/kg (dry weight basis) respectively, for wheat and barley straw.

The Meeting estimated median and highest residue values of 0.225 and 1.7 mg/kg (dry weight basis) for oat straw, rye straw and triticale straw, using the barley and wheat straw data set.

Maize forage and stover

The GAP for picoxystrobin in maize in Canada is 3 × 0.22 kg ai/ha, with a 0 day PHI for grazing of forage, and a 7 day PHI for grain and stover.

Residue data for maize forage and maize stover were collected for the USA and Canadian trials.

Residues in maize forage in accordance with the Canadian GAP were: 3.5, 4.6, 5.0, 5.7, 6.2, 6.3, 6.7, 7.1, 8.0, 8.5, 9.7, 11, 12, 13, and 14 mg/kg (dry weight basis).

Residues in maize stover in accordance with the Canadian GAP were: 0.023, 0.94, 1.0, 2.1, 2.2, 3.2, 3.5, 3.8, 5.7, 6.0, 6.6, 7.4, 8.2, 8.5 and 8.6 mg/kg (dry weight basis).

A median and a highest residue value of 7.1, and 14 mg/kg (dry weight) respectively were estimated for maize forage for use in livestock dietary burden calculations.

The Meeting determined a maximum residue level of 20 mg/kg for picoxystrobin in maize fodder, together with a median and a highest residue of 3.8 and 8.6 mg/kg (dry weight) respectively.

Processing studies

Processing studies were conducted in wheat, barley, soya bean, and maize. Processing factors are tabulated below.

Raw agricultural commodity (RAC)	Processed commodity	Processing factors	Best estimate processing factor	RAC median residue (mg/kg)	RAC MRL (mg/kg)	Processed commodity median residue (mg/kg)	PF × RAC MRL, where required
Barley	Beer	< 0.05, < 0.25 (2), < 0.5	0.26			< 0.01	–
	Spent grain	0.5, 0.81	0.66			0.011	–
Wheat	Bran	1.9, 2.1, 3.0, 3.8	2.7	0.01	0.04	0.027	0.108
	Germ	2.6, 3.8	3.2			0.032	0.128
	Wholemeal flour	1.1, 1.3	1.2			0.012	–
	Flour	0.21, 0.26	0.24			< 0.01	–
	Type 550 (white) flour	0.83, 1.1	0.97			< 0.01	–
	Patent flour	1.1, 1.2	1.2			0.012	–
	Wholemeal bread	0.45, 1.0	0.73			< 0.01	–
	Type 550 (white) bread	0.64, 0.67	0.66			< 0.01	–

Raw agricultural commodity (RAC)	Processed commodity	Processing factors	Best estimate processing factor	RAC median residue (mg/kg)	RAC MRL (mg/kg)	Processed commodity median residue (mg/kg)	PF × RAC MRL, where required
	Screenings	1.7, 5.1	3.4			0.034	–
Soya bean	Refined oil (solvent extracted)	0.93, 1.0, 1.6, 2.2	1.4	0.01	0.06	0.014	0.084
	Refined oil (mechanically extracted)	3.4, 3.4	3.4			0.034	0.204
	Meal (solvent extracted)	0.03, 0.06, < 0.09, 1.1	0.32			< 0.01	–
	Meal (mechanically extracted)	0.36, 0.60	0.48			< 0.01	–
	Aspirated grain fractions	190, 320	260			2.6	–
	Hulls	2.2, 4.4, 5.1, 5.6	4.3			0.043	–
Maize	Starch	0.025, < 0.068	0.047	0.01	0.02	< 0.01	–
	Grits	0.34, 0.51	0.43			< 0.01	–
	Flour	1.0, 1.2	1.1			0.011	–
	Refined oil (wet milled)	6.4, 7.3	6.9			0.069	0.138
	Refined oil (dry milled)	3.4, 5.4	4.4			0.044	0.088
	Meal	0.77, 0.79	0.78			< 0.01	–
	Aspirated grain fractions	13, 17	15			0.15	

Picoxystrobin concentrated significantly in wheat bran, wheat germ, soya bean refined oil, and maize refined oil.

The Meeting therefore estimated maximum residue levels of 0.15, 0.15, 0.2, and 0.15 mg/kg for wheat bran, processed, wheat germ, soya bean oil, refined, and maize oil, edible, respectively, based on the best estimate processing factors and the raw agricultural commodity maximum residue levels.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of picoxystrobin in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual 2009. Calculation from highest residue, median residue (some bulk commodities), and median processed commodity residue values provides levels in feed suitable for estimating maximum residue levels. The percentage dry matter is taken as 100% when the highest residue levels and median residue levels are already expressed on a dry weight basis.

	US/Canada, maximum	EU, maximum	Australia, maximum	Japan, maximum
Beef cattle	2.29	31.6	64[a]	0.029
Dairy cattle	18.2	32.7	54.1[b]	7.87
Poultry (broiler)	0.028	0.026	0.02	0.004
Poultry (layer)	0.028	9.52[c,d]	0.02	0.02

[a] Maximum calculated dietary burden for beef cattle, used for calculation of mammalian tissue maximum residue levels.

[b] Maximum calculated dietary burden for dairy cattle, used for calculation of the milk maximum residue level.

[c] Maximum calculated dietary burden for laying hens, used for calculation of egg maximum residue level.

[d] Maximum calculated dietary burden for broiler hens, used for calculation of poultry tissue maximum residue levels.

The detailed dietary burden calculations are provided in Annex 6.

Animal feeding studies

Lactating cattle were dosed orally twice daily with picoxystrobin for 29 days at 39.7, 119.5, and 402.8 ppm in feed or 1.35, 4.12 and 12.9 mg/kg bw/day.

Picoxystrobin was not detected in whole milk from the low and mid-dose groups. Low levels (maximum 0.014 mg/kg), were found in some high-dose group samples. Milk residues reached a maximum around day 14. No residues were detected in skim milk, with levels in cream of 0.016–0.048 mg/kg for the high-dose group.

Picoxystrobin was not detected in muscle and kidney for the low or mid-dose groups, was found at < 0.01 mg/kg in muscle and 0.010 mg/kg in kidney for the high-dose group. Residues were detected in liver and fat at all doses. A roughly linear relationship between dose and residue was observed for liver and fat. The maximum residue at the high dose level was 0.10 mg/kg and 0.077 mg/kg for liver and fat (omental) respectively.

Depuration data indicated rapid clearance of residues from milk and tissues. No residues were detected in milk, muscle, perirenal fat or kidney from the depuration animals. Liver residues were undetectable by 8 days after the final dose, and were below the limit of quantification in fat (subcutaneous) by 3 and 15 days.

Laying hens were dosed orally daily with picoxystrobin for 36 days at 15.1, 45.4, 153 (main high-dose group) and 152 (depuration group) ppm in feed, or 0.97, 2.84, 9.49 and 9.53 mg/kg bw/day respectively. No residues were detected in eggs from the low and mid-dose group. In the high-dose group, residues in eggs reached a maximum of 0.014 mg/kg.

In fat, picoxystrobin was below the limit of quantification in the low dose group, while in the mid-dose group residues up to 0.010 mg/kg were found. Fat residues for the high-dose group reached a maximum of 0.016 mg/kg. In muscle, no residues were detected for the low or mid-dose groups, and were below the limit of quantification in the high-dose group. In liver, residues were undetectable in the low and mid-dose groups, and were below the limit of quantification in the high-dose group.

Picoxystrobin cleared rapidly from hen eggs and tissues, with no residues being detected in any samples after depuration day 2.

Animal commodity maximum residue levels

Mammals

The maximum dietary burdens for beef and dairy cattle are 64 and 54 ppm dry weight in feed respectively. Highest residue values calculated by interpolation or using transfer factors for picoxystrobin in mammalian animal matrices are tabulated below.

	Feed level	Residues	Feed level	Residues (mg/kg)			
	(ppm) for milk residues	(mg/kg) in milk	(ppm) for tissue residues	Muscle	Liver	Kidney	Fat
Highest residue determination (beef or dairy cattle)							
Feeding study	120	< 0.01	120	< 0.01	0.017	< 0.01	0.026
	40	< 0.01	40	< 0.01	< 0.01	< 0.01	< 0.01
Dietary burden and estimate of highest residue	54	0	64	0	0.012	0	0.015

Residues of picoxystrobin were not detected in milk from cattle at the two feeding levels bracketing the calculated maximum dietary burden for dairy animals. The Meeting therefore estimated a maximum residue level of 0.01* mg/kg for picoxystrobin in milk.

Residues of picoxystrobin were not detected in muscle or kidney from cattle at the two feeding levels bracketing the calculated maximum dietary burden for beef cattle. Residues were found at low levels above the LOQ in fat and liver of cattle at the next highest feeding level above the maximum dietary burden for beef cattle, and were below the LOQ for the next lowest feeding level.

The Meeting therefore estimated maximum residue levels of 0.02 mg/kg for edible offal (mammalian), meat (from mammals other than marine mammals) (fat), and mammalian fats (except milk fats).

Poultry

The maximum dietary burdens for broiler chickens and laying hens was 9.5 ppm dry weight in feed. Highest residue values calculated by interpolation or using transfer factors for picoxystrobin in poultry animal matrices are tabulated below.

	Feed level	Residues	Feed level	Residues (mg/kg)		
	(ppm) for egg residues	(mg/kg) in egg	(ppm) for tissue residues	Muscle	Liver	Fat
Highest residue determination (broiler or laying hens)						
Feeding study	15	< 0.01	15	< 0.01	< 0.01	< 0.01
Dietary burden and estimate of highest residue	9.5	0	9.5	0	0	< 0.01

Residues of picoxystrobin were not detected in the eggs, muscle or liver of hens fed at the next highest feeding level (15 ppm) above the maximum poultry dietary burden (9.5 ppm). Residues were detectable, but below the LOQ, in the fat of birds fed at 15 ppm.

The Meeting therefore estimated maximum residue levels of 0.01* mg/kg for picoxystrobin in eggs, poultry meat, and poultry, edible offal of. The Meeting estimated a maximum residue level of 0.01 mg/kg for picoxystrobin in poultry fats.

DIETARY RISK ASSESSMENT

Because the Meeting was unable to conclude on the toxicological relevance of the metabolites IN-H8612 and 2-(2-formylphenyl)-2-oxoacetic acid, the Meeting could not reach a conclusion on a residue definition for dietary risk assessment.

As a result, long- and short-term dietary intake assessments could not be conducted.