

5.6 CHLORFENAPYR (254)

TOXICOLOGY

Chlorfenapyr is the ISO-approved name for 4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-trifluoromethyl-1H-pyrrole-3-carbonitrile (IUPAC) (CAS No. 122453-73-0). Chlorfenapyr is a contact and stomach insecticide that acts, following metabolic activation, as an uncoupler of oxidative phosphorylation in mitochondria. It has limited systemic activity.

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

All critical studies with chlorfenapyr were certified to be compliant with GLP, unless otherwise specified.

Biochemical aspects

In two metabolism studies, one of which was not certified to be compliant with GLP, chlorfenapyr labelled with ^{14}C in either the pyrrole or the phenyl ring was administered by oral gavage to intact and bile duct-cannulated rats. The radiolabel was relatively slowly absorbed, the extent varying from 80% at 2 mg/kg bw to 65% at 20 mg/kg bw. The maximum concentration of radiolabel in plasma was achieved after about 8–12 hours, was dose proportional (at 2–20 mg/kg bw) and did not differ between males and females. Absorbed radiolabel was slowly distributed throughout the body, with concentrations in fat, liver and adrenals being greater than those in plasma. In general, tissue radiolabel concentration increased with dose. Blood and tissue concentrations of radiolabel were 2- to 3-fold higher in female rats than in male rats. Excretion was relatively rapid, mainly via the faeces, ranging from 80% to 106% of the administered dose in 7 days. There was little or no potential for accumulation, with 70% of the dose excreted in 24 hours and approximately 90% within 48 hours. The elimination half-life for plasma radiolabel was approximately 56 hours. Most of the chlorfenapyr in faeces was present as the unchanged compound, comprising material that was not absorbed together with material excreted via the bile, which was the main route of elimination. Faeces also contained minor amounts of *N*-dealkylated, debrominated and hydroxylated oxidation products of chlorfenapyr. Excretion via the urine was minor, representing only 5–11% of the administered dose over 7 days. There was no elimination of chlorfenapyr-related radioactivity via respiration.

The major routes of metabolism are *N*-dealkylation, dehalogenation, hydroxylation and conjugation, but not with sulfate or glucuronide. There is no cleavage of the bond between the pyrrole and phenyl rings of chlorfenapyr during its biotransformation.

Toxicological data

Chlorfenapyr technical is moderately toxic via the oral route, with LD_{50} s of 441 mg/kg bw in rats and 45 mg/kg bw in mice, and via the inhalation route, with an LC_{50} of 0.83 mg/L in rats. Chlorfenapyr was of low toxicity after dermal exposure in rabbits ($\text{LD}_{50} > 2000$ mg/kg bw). It is not irritating to the skin or eye of rabbits and is not a dermal sensitizer in the guinea-pig maximization test.

Following repeated administration of chlorfenapyr to mice, rats and dogs, decreased feed consumption and body weight gains were observed in all three species. Increased liver weights, associated with hepatocellular hypertrophy, and vacuolation in the brain and spinal cord were also noted in rats and mice.

In a 28-day study in mice, the NOAEL was 160 ppm (equal to 30.1 mg/kg bw per day), based on decreased body weight gain, mortality and increased relative liver weight at 240 ppm (equal to 43.6 mg/kg bw per day). In a 90-day study in mice, the NOAEL was 80 ppm (equal to 14.8 mg/kg bw per day), based on increased relative spleen weight and myelopathy in brain and spinal cord in males at 160 ppm (equal to 27.6 mg/kg bw per day).

In a 28-day study in rats, the NOAEL was 600 ppm (equal to 68.3 mg/kg bw per day), based on increases in relative liver weights and alanine aminotransferase activity at 900 ppm (equal to 106.3 mg/kg bw per day). In a 90-day study in rats, the NOAEL was 300 ppm (equal to 22 mg/kg bw per day), based on increases in relative liver weight, alkaline phosphatase activity and blood urea nitrogen and, in females, changes in red cell parameters (haemoglobin) at 600 ppm (equal to 44.9 mg/kg bw per day). Vacuolation of the brain and spinal cord was seen at higher doses (900 ppm, equal to 106.3 mg/kg bw per day, and above).

In a 90-day dietary study in dogs, the NOAEL was 120 ppm (equal to 4.0 mg/kg bw per day), based on decreased body weight gain at 200 ppm (equal to 7.1 mg/kg bw per day). In a 1-year dietary study in dogs, the NOAEL was 120 ppm (equal to 4.0 mg/kg bw per day), based on reduced body weight and body weight gain at 240 ppm (equal to 8.7 mg/kg bw per day). The overall NOAEL for these two studies in the dog was 4 mg/kg bw per day.

Long-term studies of toxicity and carcinogenicity were performed in mice and rats, with similar NOAELs in the two species. In an 18-month dietary study in mice, the NOAEL for non-neoplastic effects was 20 ppm (equal to 2.8 mg/kg bw per day), based on decreases in body weight gain and vacuolation of the white matter of the brain at 120 ppm (equal to 16.6 mg/kg bw per day). No evidence of carcinogenicity was found.

In a 24-month dietary study in rats, the NOAEL for non-neoplastic effects was 60 ppm (equal to 2.9 mg/kg bw per day), based on reduced body weight and body weight gain and increased liver weight associated with hepatocellular hypertrophy at 300 ppm (equal to 15 mg/kg bw per day). No evidence of carcinogenicity was found.

The Meeting concluded that chlorfenapyr was not carcinogenic in rats and mice.

The potential genotoxicity of chlorfenapyr was tested in an adequate range of in vitro and in vivo studies. Chlorfenapyr showed no evidence of genotoxicity.

The Meeting concluded that chlorfenapyr was unlikely to be genotoxic in vivo.

On the basis of the lack of genotoxicity and the absence of carcinogenicity in the rat and the mouse, the Meeting concluded that chlorfenapyr is unlikely to be carcinogenic in humans.

In a two-generation reproductive toxicity study in rats, the NOAEL for effects on fertility was 600 ppm (equal to 44 mg/kg bw per day), the highest dose tested. The NOAEL for parental toxicity was 60 ppm (equal to 5 mg/kg bw per day), based on decreased body weight and body weight gain at 300 ppm (equal to 22 mg/kg bw per day). The NOAEL for offspring toxicity was 60 ppm (equal to 5 mg/kg bw per day), based on decreased body weight of pups at 300 ppm (equal to 22 mg/kg bw per day).

In a developmental toxicity study in rats, the NOAEL for maternal toxicity was 75 mg/kg bw per day, based on decreased body weight at 225 mg/kg bw per day. The NOAEL for developmental toxicity was 225 mg/kg bw per day, the highest dose tested.

In a developmental toxicity study in rabbits, the NOAEL for maternal toxicity was 5 mg/kg bw per day, based on decreased body weight gain at 15 mg/kg bw per day. The NOAEL for developmental toxicity was 30 mg/kg bw per day, the highest dose tested.

The Meeting concluded that chlorfenapyr was not teratogenic.

In an acute neurotoxicity study in rats, the NOAEL for systemic toxicity was 45 mg/kg bw, based on clinical signs of toxicity (2 lethargic animals out of 20) at 90 mg/kg bw and above. Lethality (20%) was observed at 180 mg/kg bw. There was no evidence for neuropathological effects or neurotoxicity up to the highest dose tested (180 mg/kg bw).

In a 1-year neurotoxicity study in rats, the NOAEL for neurotoxicity was 60 ppm (equal to 2.6 mg/kg bw per day), based on vacuolar myelinopathy, vacuolation and/or myelin sheath swelling of the brain and spinal cord in males at 300 ppm (equal to 13.6 mg/kg bw per day). There was no change in motor activity or other behavioural activity. The effects observed were reversible within 16 weeks.

In a developmental neurotoxicity study in rats, the NOAEL for maternal toxicity was 15 mg/kg bw per day, the highest dose tested. The NOAEL for developmental neurotoxicity was 10 mg/kg bw per day, based on an increased incidence of multifocal vacuolation (minimal to moderate severity) of the white matter of the brain on postnatal day 22 at 15 mg/kg bw per day. This effect appears to be reversible (i.e. 38 days after end of treatment), as no adverse effects on either behaviour or neuropathology were evident in rats on postnatal day 60.

Single-dose studies on the pharmacological action of MK-242 were performed in mice, rats and rabbits to evaluate effects on the central nervous system, autonomic nervous system, respiratory and cardiovascular systems, gastrointestinal system, skeletal muscle and blood coagulation. The only relevant pharmacological effects were observed on the central nervous system, such as changes in general behaviour and an increase in body temperature. Convulsions due to stimulation of the central nervous system were thought to be the cause of death observed in rats and mice after acute intoxication. No changes in the electroencephalogram were observed at non-lethal doses in rabbits. NOAELs were 3 mg/kg bw in mice, 10 mg/kg bw in rats and 30 mg/kg bw (the highest dose tested) in rabbits, based on depression of grooming behaviour and reactivity, a decrease in spontaneous motor activity and prone position in mice and rats.

The acute oral toxicity of four chlorfenapyr animal metabolites (AC 312,094, AC 303,268, AC 322,250 and AC 325,195) was tested in Sprague-Dawley rats.

AC 312,094 was of low acute oral toxicity in rats ($LD_{50} > 5000$ mg/kg bw) and showed no mutagenic potential in microbial test systems.

AC 303,268 was of high acute oral toxicity in rats ($LD_{50} = 27$ mg/kg bw). This metabolite showed no mutagenic potential in microbial test systems. It is present at significant levels in livestock.

AC 322,250 was of slight acute oral toxicity in rats ($LD_{50} = 2500$ mg/kg bw) and showed no mutagenic potential in microbial test systems.

AC 325,195 was of moderate acute oral toxicity in rats ($LD_{50} = 776$ mg/kg bw) and showed no mutagenic potential in microbial test systems.

There were no reports of adverse health effects of chlorfenapyr in manufacturing plant personnel.

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

Toxicological evaluation

The Meeting established an ADI for chlorfenapyr of 0–0.03 mg/kg bw, based on a NOAEL of 2.8 mg/kg bw per day for decreases in body weight gain and vacuolation of the white matter of the brain at 16.6 mg/kg bw per day in an 18-month mouse study and a NOAEL of 2.9 mg/kg bw per day for reduced body weight and body weight gain and increased liver weight associated with hepatocellular enlargement at 15 mg/kg bw per day in a 2-year rat study. This was supported by a NOAEL of 2.6 mg/kg bw per day for reversible vacuolar myelinopathy, vacuolation and/or myelin sheath swelling of the brain and spinal cord in males at 13.6 mg/kg bw per day in a 1-year study of neurotoxicity in rats. A safety factor of 100 was applied.

The Meeting established an ARfD for chlorfenapyr of 0.03 mg/kg bw, based on the NOAEL of 3 mg/kg bw for depression of grooming and reactivity and decreased spontaneous motor activity observed at 10 mg/kg bw in a pharmacological study in mice. A 100-fold safety factor was applied.

Based on available information, it was not possible for the Meeting to determine whether the ADI and ARfD would also cover the metabolite AC 303,268.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity ^a	Toxicity	20 ppm, equal to 2.8 mg/kg bw per day	120 ppm, equal to 16.6 mg/kg bw per day
		Carcinogenicity	240 ppm, equal to 34.5 mg/kg bw per day ^b	—
	Pharmacological study ^c	Toxicity	3 mg/kg bw	10 mg/kg bw
Rat	Two-year study of toxicity and carcinogenicity ^a	Toxicity	60 ppm, equal to 2.9 mg/kg bw per day	300 ppm, equal to 15 mg/kg bw per day
		Carcinogenicity	600 ppm, equal to 30.8 mg/kg bw per day ^b	—
	Two-generation study of reproductive toxicity ^a	Reproductive toxicity	600 ppm, equal to 44 mg/kg bw per day ^b	—
		Parental toxicity	60 ppm, equal to 5 mg/kg bw per day	300 ppm, equal to 22 mg/kg bw per day
		Offspring toxicity	60 ppm, equal to 5 mg/kg bw per day	300 ppm, equal to 22 mg/kg bw per day
	Developmental toxicity study ^c	Maternal toxicity	75 mg/kg bw per day	225 mg/kg bw per day
		Embryo and fetal toxicity	225 mg/kg bw per day ^b	—
	Acute neurotoxicity study ^c	Toxicity	45 mg/kg bw	90 mg/kg bw
		Neurotoxicity	180 mg/kg bw ^b	—
	One-year neurotoxicity study ^a	Neurotoxicity	60 ppm, equal to 2.6 mg/kg bw per day	300 ppm, equal to 13.6 mg/kg bw per day
Developmental neurotoxicity study ^c	Maternal toxicity	15 mg/kg bw per day ^b	—	
	Offspring neurotoxicity	10 mg/kg bw per day	15 mg/kg bw per day	
Rabbit	Developmental toxicity study ^c	Maternal toxicity	5 mg/kg bw per day	15 mg/kg bw per day
		Embryo and fetal toxicity	30 mg/kg bw per day ^b	—
Dog	Thirteen-week and 1-year studies of toxicity ^{a,d}	Toxicity	120 ppm, equal to 4 mg/kg bw per day	240 ppm, equal to 8.7 mg/kg bw per day

^a Dietary administration.

^b Highest dose tested.

^c Gavage administration.

^d Two or more studies combined.

Estimate of acceptable daily intake for humans

0–0.03 mg/kg bw

Estimate of acute reference dose

0.03 mg/kg bw

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

Additional studies on the toxicity of AC 303,268 to enable adequate characterization of the dietary risk from this metabolite. The Meeting was aware that additional studies on the compound have been performed but did not have access to sufficiently detailed reports to enable their evaluation.

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

Critical end-points for setting guidance values for exposure to chlorfenapyr*Absorption, distribution, excretion and metabolism in mammals*

Rate and extent of oral absorption	Slow, approximately 80% and 65% in the low-dose and high-dose groups, respectively
Dermal absorption	No data
Distribution	Extensive
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid and almost complete in 168 h in urine and faeces
Metabolism in animals	Absorbed dose metabolized by <i>N</i> -dealkylation, debromination, ring hydroxylation and conjugation
Toxicologically significant compounds in animals, plants and the environment	Chlorfenapyr , AC 303,268

Acute toxicity

Rat, LD ₅₀ , oral	441 mg/kg bw
Rabbit, LD ₅₀ , dermal	> 2000 mg/kg bw
Rat, LC ₅₀ , inhalation	0.83 mg/L (4 h aerosol, whole-body exposure)
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Not irritating
Dermal sensitization	Not sensitizing (Magnusson & Kligman)

Short-term studies of toxicity

Target/critical effect	Decreased body weights and weight gain, increased liver weights, vacuolation of the white matter (rat and mouse)
Lowest relevant oral NOAEL	4 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	100 mg/kg bw per day (rabbit)
Lowest relevant inhalation NOAEC	20 mg/m ³ (rat)

Long-term studies of toxicity and carcinogenicity

Target/critical effect	Reduced growth rate and feed intake, vacuolation of the white matter (mice), haematological changes (rat)
Lowest relevant NOAEL	2.8 mg/kg bw per day (mouse carcinogenicity study)
Carcinogenicity	Not carcinogenic

Genotoxicity

Not genotoxic

Reproductive toxicity

Target/critical effect	Reductions in pup body weights at parentally toxic doses
Lowest relevant parental NOAEL	5 mg/kg bw per day
Lowest relevant reproductive NOAEL	44 mg/kg bw per day (highest dose tested)
Lowest relevant offspring NOAEL	5 mg/kg bw per day

Developmental toxicity

Target/critical effect	Not teratogenic, no developmental toxicity
Lowest relevant maternal NOAEL	5 mg/kg bw per day (rabbit)
Lowest relevant developmental NOAEL	30 mg/kg bw per day (highest dose tested) (rabbit)

Neurotoxicity

Acute neurotoxicity target/critical effect	Not acutely neurotoxic
One-year neurotoxicity target/critical effect	Vacuolation of the white matter (reversible) (rat)
Lowest relevant NOAEL	2.6 mg/kg bw per day (rat)
Neurodevelopmental toxicity target/critical effect	Vacuolation of white matter of the brain (reversible) (rat)
Lowest relevant NOAEL	10 mg/kg bw per day

<i>Other toxicological studies</i>	
Acute toxicity of metabolites	AC 312,094: rat LD ₅₀ > 5000 mg/kg bw AC 303,268: rat LD ₅₀ = 27 mg/kg bw AC 322,250: rat LD ₅₀ = 2500 mg/kg bw AC 325,195: rat LD ₅₀ = 776 mg/kg bw
Genotoxicity of metabolites	Not genotoxic
<i>Medical data</i>	
	No data available

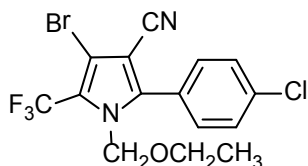
Summary

	Value	Study	Safety factor
ADI	0–0.03 mg/kg bw	Eighteen-month (mouse) and 2-year (rat) studies of toxicity; 1-year neurotoxicity study (rat)	100
ARfD	0.03 mg/kg bw	Pharmacological study (mouse)	100

RESIDUE AND ANALYTICAL ASPECTS

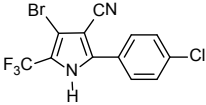
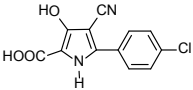
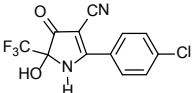
The chlorfenapyr is a pro-insecticide-miticide. Its biological activity depends upon its activation to another chemical (CL303268). Oxidative removal of the N-ethoxymethyl group of chlorfenapyr by mixed function oxidases forms CL303268. This compound uncouples oxidative phosphorylation at the mitochondria, resulting in the disruption of ATP production, cellular death, and ultimately organism mortality. It is considered for the first time by the 2012 JMPR.

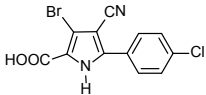
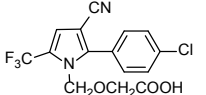
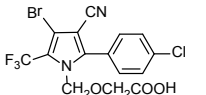
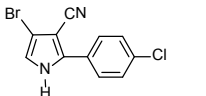
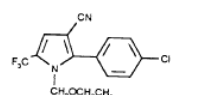
The chemical name of chlorfenapyr is: 4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile. Its structural formula is shown in the following figure:



The Meeting received information on identity, metabolism, storage stability, residue analysis, use patterns, residues (resulting from supervised trials on citrus fruit, papaya, bulb vegetable, fruiting vegetables (melon, squash, cucumber), tomato, eggplant, pepper, potato, carrot and tea, and fates of residues during processing, and livestock feeding studies.

Metabolites codes and names used in the discussion that follows are detailed below:

	Chlorfenapyr	4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile
	CL303268	4-bromo-2-(p-chlorophenyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile
	CL152837	4-hydroxy-2-(p-chlorophenyl)-5-(carboxylic)-pyrrole-3-carbonitrile a hydroxylated CL303268 metabolite
	CL325195	2-(4-chlorophenyl)-5-hydroxyl-4-oxo-5-(trifluoromethyl)-3-pyrrole-3-carbonitrile

	CL322250	4-bromo-2-(p-chlorophenyl)-5-(carboxylic)-pyrrole-3-carbonitrile
	CL152835	desbromo-N-carboxymethylmethoxy BAS 306 I
	CL325157	{[3-bromo-5-(p-chlorophenyl)-4-cyano-2-(trifluoromethyl)pyrrol-1-yl]methyl}-acetic acid
	CL152832	destrifluoromethyl CL303268
	CL312094	2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile

Animal metabolism

The Meeting received information on the fate of orally dosed chlorfenapyr in laying hens and lactating goats. Studies were carried out with ^{14}C -chlorfenapyr, labelled at the phenyl (U) and pyrrole ring. The bond between the pyrrole ring and the phenyl ring was not cleaved in metabolism studies.

Metabolism in laboratory animals (rat) was summarized and evaluated by the WHO panel of the JMPR in the present meeting.

Lactating goats, were dosed via capsules with ^{14}C -chlorfenapyr for seven consecutive days at low dose diets (3.0–3.2 ppm feed) and high dose diets (16–25 ppm feed) to determine the fate of chlorfenapyr in milk and tissues.

The major route of elimination of the radioactivity was via the faeces which accounted for 67 to 76% of the administered dose; urine accounted for 6.3 to 15% of the administered dose. The distribution of the TRR in milk and tissues from both labels was similar. In the high dose group, the TRR in milk increased from 0.03 to 0.07 mg eq/kg by day 7 while ^{14}C residues in tissues ranged from 0.03–0.05 mg eq/kg in muscle to 1.4–1.5 mg eq/kg in liver.

Chlorfenapyr was the major component of the ^{14}C residues in milk (25–68% TRR), fat (47–78% TRR) and muscle (29–52% TRR). Other major ^{14}C residue components were CL303268 in fat (4.5–19% TRR) Metabolism was more extensive in liver and kidney and in these tissues chlorfenapyr represented less than 7 and 10% TRR respectively. The major components of the ^{14}C residue in liver and kidney released following pepsin hydrolysis were CL325195 and its conjugates which accounted for somewhere between 12 and 48% of TRR as well as CL152837 and its conjugates which accounted for 7 to 24% TRR. Lack of separation of some of the components made it difficult to estimate proportions of the different components.

Chlorfenapyr undergoes extensive metabolism in the goat involving modification of the phenyl ring and the substituents of the pyrrole ring. The metabolic pathways of chlorfenapyr include N-dealkylation, dehalogenation and hydroxylation of both the phenyl and the pyrrole ring, hydroxylation and oxidation of the N-alkyl group and conjugation to endogenous components.

Laying hens were orally treated with ^{14}C -chlorfenapyr once daily for 7 consecutive days via capsule, at nominal doses of 3.0 or 15 ppm feed of [phenyl (U)- ^{14}C] chlorfenapyr and 3.1 or 14 ppm of (pyrrole- ^{14}C) chlorfenapyr. Analyses of the excreta of dosed animals over the 7-day testing period

showed that 78 to 94% of the administered doses were excreted. Radioactive residues were highest in liver followed by kidney, skin/fat, eggs and lowest in muscle.

The ^{14}C residues in skin with fat were predominantly parent chlorfenapyr (71–84% TRR), whereas in eggs the ^{14}C residues were mainly chlorfenapyr (33–42% TRR) and the N-dealkylation product (CL303268, 28–34% TRR). The ^{14}C residues in muscle comprised mainly chlorfenapyr (25–31% TRR) and CL152832 (11–23% TRR). In liver and kidney major ^{14}C residue components were chlorfenapyr (liver 2–3% TRR, kidney 7–17% TRR) and CL303268 (liver 3–17% TRR; kidney 14–25% TRR), however extractability of ^{14}C with the solvent system used was low at 14–32% for liver and 69–79% for kidney. When liver and kidneys from additional groups of birds dosed at the equivalent of 16–17 ppm were subjected to a more extreme extraction scheme, major metabolites were CL152835 (23–28% TRR in liver; 25–26% TRR in kidney) and CL325157 (23–35% TRR in liver; 44–51% in kidney). Chlorfenapyr was present at 5.6–8.2% TRR in liver and 5.7–7.9% TRR in kidney. Other components were CL303268 (6.9–8.9% liver; 3.8–3.9% kidney), CL152837 (3.8–6.3% liver; 1.7–2.3% kidney) and CL312094 (1.6–3.2% liver).

Metabolism of chlorfenapyr in the hen takes place at the phenyl ring and the substituents of the pyrrole ring. Fragmentation between the two rings is not evident. The metabolic processes comprised of N-dealkylation, dehalogenation, ring hydroxylation, and oxidation of the terminal N-alkyl group

The metabolism of chlorfenapyr in goats and hens is qualitatively the same as for rats.

Plant metabolism

The Meeting received plant metabolism studies for chlorfenapyr on cotton, citrus fruit, tomato, head lettuce and potato. Studies were made with ^{14}C -chlorfenapyr labelled at either the phenyl (U) or pyrrole ring.

Orange trees were sprayed with ^{14}C -chlorfenapyr at 3×0.74 kg ai/ha. The TRR in fruit harvested one week before the third treatment and 7 to 28 days after the last ranged from 0.10 to 0.35 mg eq/kg. TRR in oranges was nearly all located in the peel (91–96%). Chlorfenapyr was the major component of ^{14}C residues accounting for 55–77% of the TRR in fruit. Other metabolites identified were CL303268 (1.4–3.3% TRR), CL222250 (0.9–1.1% TRR) and CL325195 (1.0–2.3% TRR). Numerous unidentified compounds were present but at levels that individually did not exceed 0.01 mg eq/kg.

Tomato plants were treated with 5×0.22 kg ai/ha sprays of ^{14}C -chlorfenapyr. TRR in fruits harvested at 7 to 14 days after the last application ranged from 0.03 to 0.05 mg eq/kg. Chlorfenapyr was the major ^{14}C residue component and accounted for 38–50% of the TRR in tomato fruit. Numerous unidentified components were individually present at level that did not exceed 0.01 mg eq/kg.

Head lettuce was treated with ^{14}C -chlorfenapyr as five sprays at 0.22 kg ai/ha. Solvent extracted ^{14}C accounted for 90–98% of the TRR in head lettuce. Chlorfenapyr was the predominant ^{14}C residue component and accounted for 75–77% of the TRR in lettuce. Other metabolites identified were CL303268 (1.1–1.3% TRR), CL312094 (0.8–1.4% TRR) and CL325194 (1.2–1.8% TRR). Numerous unidentified compounds were present but at levels that individually did not exceed 0.01 mg eq/kg.

Potato plants were sprayed with ^{14}C -chlorfenapyr a rate of 0.22 kg ai/ha once a week for four weeks. TRR in the potato tubers was below the detection limit. There was no translocation of ^{14}C -chlorfenapyr from foliage to tubers.

Cotton plants were sprayed with ^{14}C -chlorfenapyr at a rate of 0.45 kg ai/ha as 5 applications at 7 day intervals. The cotton was harvested near 28 days after the last application. TRR in cottonseed (seed meal plus linters) was 0.27–31 mg eq/kg. Chlorfenapyr was the major ^{14}C residue and accounted for 59% to 68% of the TRR in cottonseed.

The metabolism of chlorfenapyr in the various plants studies is qualitatively similar. Generally chlorfenapyr is the major portion of the residue. There were a large number of unidentified metabolites; however, each accounted for equal to or less than 0.01 mg eq/kg.

Environmental fate in soil

The Meeting received information on the fate of chlorfenapyr on confined rotational crops, field crop rotation, aerobic degradation in soil, photo-degradation on soil, aqueous hydrolysis and photolysis. Studies were carried out with ^{14}C -chlorfenapyr, labelled at the phenyl (U) and pyrrole ring.

Chlorfenapyr was persistent in studies on aerobic soil degradation with DT_{50} values in a range of soils ranging from 241 to over 1000 days in laboratory studies and 157 to 418 days in field studies.

In a confined rotational crop study, the ^{14}C -chlorfenapyr was sprayed on the bare sandy loam soil in the treatment plot at weekly intervals for five consecutive weeks at a rate of 0.45 kg ai/ha. Rotational crops of leaf lettuce, carrot, barley and soya bean were planted at 31, 60, 119 and 364 days after treatment.

The radioactivity in rotational crops was attributed to chlorfenapyr and metabolites CL325195 and CL312094. At the 31-day plant back interval, the concentration of chlorfenapyr, in rotational crops ranged from ≤ 0.01 (crops other than carrots) to 0.13 (carrot, immature roots) mg eq/kg, CL325195 was present at ≤ 0.01 mg eq/kg and CL312094 at < 0.01 to 0.03 mg eq/kg. At a plant back interval of 60 days or later, all residue components were ≤ 0.01 mg eq/kg. There were many minor unidentified metabolites in each rotational crop that were individually present at less than or equal to 0.01 mg eq/kg. The metabolite profile in rotational crops was similar for both labels.

The Meeting concluded that residues of chlorfenapyr in rotational crop with minimum plant back interval of 31 days may be possible, but residues would be at or near the limit of quantification of the analytical method, 0.01 mg/kg.

Methods of analysis

Adequate analytical methods exist for the determination of chlorfenapyr residues in both plant and animal matrices. The basic approach for plant matrices employs extraction by homogenisation with methanol:water, and column clean-up using SPE. The extraction solvent system used for animal matrices depends on the tissue and is typically acetone for milk, methanol for muscle and acetonitrile for fat, liver and kidney. Residues are determined by gas chromatography (GC) with an electron capture detector (ECD), nitrogen phosphorous detector (NPD) or mass spectra detection (MS) or by liquid chromatography with mass spectra detection (MS). The limit of quantification was usually 0.01–0.05 mg/kg.

Stability of residues in stored analytical samples

The Meeting received information on the stability of chlorfenapyr in plant commodities during two years freezer storage and milk stored frozen for three months. The chlorfenapyr residues were stable in all the crop matrices (orange, tomato, tomato process fractions, cabbage, lettuce, potato, peach, pear, strawberry and grape) for at least two years. The chlorfenapyr residues in milk were stable for at least three months.

Definition of the residue

Parent chlorfenapyr was a major component of ^{14}C residues in goat's milk (25–68%), fat (47–78%) and muscle (9–52%) and in hens eggs (40%), muscles (31%) and skin/fat (84%). Other major ^{14}C residue components were CL303268 in eggs (31%) and goat fat (4.5–19%) and CL152832 in chicken muscle (11–23% TRR) and chicken kidney (2–11% TRR). Parent chlorfenapyr was extensively metabolised in livestock liver and kidney. CL152835 and CL325157 were major components of the ^{14}C residue in hen liver (23% and 35%) and kidney (28% and 51%). Major components of the ^{14}C residue in goat liver and kidney were CL325195 and its conjugates (about 12–48% TRR) and CL152837 and its conjugates (about 7 to 24% TRR). Chlorfenapyr was present in goat and chicken

liver and kidney at 0.5–17% TRR. As chlorfenapyr is a major component of the residue in most tissues and is present in all tissues, milk and eggs, chlorfenapyr is an adequate residue definition for compliance purposes.

Negligible residues of chlorfenapyr and metabolites are expected in poultry tissues and eggs as the dietary burden for chickens is about 600 times less than the dosing level used in the poultry metabolism studies. It is not necessary to include CL152832, CL152835 and CL325157 in the residue definition for dietary risk assessment for animal commodities.

Available analytical methods only measure parent chlorfenapyr.

The major metabolites found in animal commodities are considered to have comparable or lower toxicity compared to the parent compound. The exception to this is CL303268 which is more acutely toxic than the parent compound (20–30×). As there was no other information on the toxicological properties of this compound it was not possible to determine whether the parent and this metabolite should be evaluated individually or together in assessing risk associated with dietary exposure. The Meeting could not reach a conclusion on a residue definition for dietary risk assessment associated with exposure to residues in animal commodities.

In the lactating cow feeding study residues of chlorfenapyr in fat were at least 16× higher than in muscle. The log Kow for chlorfenapyr 5.28 suggested fat solubility. Residues of chlorfenapyr are fat-soluble.

For plants, chlorfenapyr was the major component of the ¹⁴C residue in oranges (55–77%), tomatoes (38–50%), lettuce (75–77%) and cottonseed (59–68%), and often the only compound present in plants at levels above 0.01 mg/kg. CL303268 was sometimes present but at low levels, <5% TRR. The residue definition for plant commodities for compliance purposes should be chlorfenapyr. As the toxicological database available to the Meeting did not allow for conclusions to be made regarding an appropriate health-based guidance values for CL303268 the Meeting could not reach a conclusion on a residue definition for dietary risk assessment associated with exposure to residues in plant commodities.

The Meeting recommended the following residue definition for chlorfenapyr.

Definition of the residue for compliance with the MRL for animal and plant commodities: *chlorfenapyr*.

Definition of the residue for estimation of dietary intake for animal and plant commodities: *a conclusion could not be reached*

The residue is fat soluble.

Results of supervised residue trials on crops

The Meeting received supervised trials data for chlorfenapyr on citrus fruit, papaya, garlic, bulb onion, melons, peppers, eggplants, tomatoes, potatoes and tea. Where the available data permit, the Meeting decided to estimate maximum residue levels. However, as the Meeting could not determine a residue definition for estimation of dietary intake, STMR and HR values are not estimated.

The OECD calculator was used as a tool in the estimation of the maximum residue level from the selected residue dataset obtained from trials conducted according to GAP. First, the Meeting reviewed all relevant factors related to each data set in arriving at a best estimate of the maximum residue level using expert judgment. Then, the OECD calculator was employed. If the statistical calculation spreadsheet suggested a different value from that recommended by the JMPR, a brief explanation of the deviation was provided.

Citrus fruits

Supervised residue trials on orange and lime conducted in Brazil were provided to the Meeting. GAP for citrus in Brazil allows three foliar spray applications at 15 g ai/hL with a PHI 14 days.

In oranges, chlorfenapyr residues in whole fruit from trials in Brazil, matching the GAP in Brazil were (n=7): 0.14, 0.18, 0.39, 0.44, 0.53, 0.54 and 0.87 mg/kg.

In limes, chlorfenapyr residues in whole fruit from trials in Brazil, matching the GAP in Brazil were (n=8): 0.05, 0.08, 0.13, 0.15, 0.17, 0.28, 0.31 and 0.49 mg/kg.

To consider a maximum residue level for a group, residues in individual crops should be similar (e.g., medians should not differ by more than 5×). The Meeting agreed to estimate a maximum residue level for the group Citrus fruit. In deciding whether to combine the datasets for orange and limes for use in the statistical calculator or to only utilize the data from the commodity with the highest residues, the Meeting noted that the populations of residues in oranges and limes are sufficiently different (Mann-Whitney U-test) and decided to use the data from oranges to estimate a maximum residue level of 1.5 mg/kg for citrus fruit.

The median residue in whole orange fruit for use in estimating residues in processed orange commodities was 0.44 mg/kg.

Assorted tropical and sub-tropical fruits – edible peel

Papaya

In five supervised residue trials in papaya conducted in Brazil and matching the Brazilian GAP (3 foliar applications at 12 g ai/hL, PHI 14 days) chlorfenapyr residues were (n=5): < 0.01, 0.03, 0.05, 0.11 and 0.12 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg for papaya.

Bulb vegetables

Garlic

The GAP in Brazil allows for up to 3 foliar applications of 24 g ai/hL with a 14 day PHI. The Meeting noted the instructions for use suggest a spray volume of 800–1000 L/ha. One trial matched GAP with residues of < 0.01 mg/kg. In a further four trials the application rate was expressed in terms of g ai/ha and as the spray volume was not reported the equivalent spray concentration was not available. Using a figure of 800 L/ha the estimated spray concentration would approximate GAP of Brazil with residues of chlorfenapyr in garlic bulbs of < 0.01 (4) mg/kg.

The Meeting estimated a maximum residue level of 0.01 mg/kg (*) for garlic.

Onion, Bulb

In nine supervised residue trials in bulb onion conducted in Brazil and approximating the Brazilian GAP (up to three foliar applications of 180 g ai/ha with a PHI of 14 days), chlorfenapyr residues in onion bulbs were (n=9): < 0.01 mg/kg.

The Meeting estimated a maximum residue level of 0.01 mg/kg (*) for onion, bulb.

Fruiting vegetables, Cucurbits

Melons, except Watermelon

In supervised residue trials in melons, conducted in Brazil and matching the Brazilian GAP (24 g ai/hL, PHI 14 days), chlorfenapyr residues in whole fruit were (n=9): < 0.01, < 0.01, 0.01, 0.02, 0.02, 0.06, 0.06, 0.17 and 0.17 mg/kg. Where residues in pulp were measured they were: < 0.01 (4) and 0.01 mg/kg.

The Meeting estimated a maximum residue level of 0.4 mg/kg melons (except watermelon).

*Fruiting vegetables, other than Cucurbits**Peppers (including pepper, chili and pepper sweet)*

The GAP in the USA is for use on glasshouse grown peppers (up to 3 foliar applications of 224 g ai/ha and a 0-day PHI). Two indoor trials on peppers from the USA were available but these did not match the US GAP.

In field trials on peppers conducted in Brazil and matching the Brazilian GAP of up to three applications of 7.2 g ai/hL with a PHI of 14 days, chlorfenapyr residues were (n=7): < 0.01, 0.01, 0.04, 0.05, 0.06, 0.13 and 0.15 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg for peppers.

Based on the estimated maximum residue level for peppers and a default dehydration factor of 10, the Meeting recommended a maximum residue level of 3 mg/kg for chili peppers (dry).

Egg plant

Four supervised trials were conducted in Mexico according to the Mexico GAP for outdoor crops (up to 96 g ai/ha, PHI 0 days). In trials matching this GAP, chlorfenapyr residues were (n=4): 0.08, 0.09, 0.1 and 0.2 mg/kg.

The Meeting agreed to estimate a maximum residue level of 0.4 mg/kg for eggplant.

Tomato

The GAP in USA is for use on glasshouse grown tomatoes (up to 3 foliar applications of 224 g ai/ha and a 0-day PHI, do not use on varieties with mature fruit of < 2.5 cm diameter). Two indoor tomato trials from the USA were available but these did not match the GAP of the USA.

The GAP in Mexico for field grown tomatoes is for applications at 96 g ai/ha with a 0-day PHI. No trials were available that matched the Mexican GAP.

The residue data from Brazil and Argentina can be assessed against the GAP of Brazil by employing proportionality.

The GAP for field tomatoes in Brazil is for a maximum rate of 12 g ai/hL with a PHI 7 days. While none of the field trials conducted in Brazil and Argentina matched this GAP, chlorfenapyr residues in trials involving a higher (2×) rate of 24 g ai/hL (PHI 7 days) with a spray volume of 1000 L/ha were (n=8): 0.03, 0.09, 0.10, 0.11, 0.14, 0.21, 0.37 and 0.37 mg/kg.

When proportionally adjusted by dividing the residues above by two to reflect the 12 g ai/hL GAP application rate in Brazil, the scaled residues (after rounding) were: 0.02, 0.05, 0.05, 0.06, 0.07, 0.11, 0.19 and 0.19 mg/kg.

The Meeting agreed to use the data from Brazil and Argentina, proportionally adjusted to reflect the Brazilian GAP and estimated a maximum residue level of 0.4 mg/kg for tomatoes.

*Root and tuber vegetables**Potato*

In supervised residue trials on potatoes conducted in Brazil and matching the Brazilian GAP (180 g ai/ha, PHI 7 days), chlorfenapyr residues in tubers were (n=9): < 0.01(9).

The Meeting estimated a maximum residue level of 0.01 mg/kg (*) for potato.

Tea, Green

Critical GAP in Japan for chlorfenapyr on tea is for up to 2 foliar spray applications of 5 g ai/hL, 7 days apart, with a PHI of 7 days. In four trials from Japan matching this GAP, chlorfenapyr residues

in green tea were (n=4): 4.2, 4.5, 16 and 28 mg/kg. In two trials involving only one spray application residues were 20 and 29 mg/kg.

The Meeting noted that compared with black tea, green tea is a minor commodity in trade and agreed four trials would be sufficient to estimate a maximum residue level. The Meeting estimated a maximum residue level of 60 mg/kg for green tea.

Fate of residues during processing

Studies were received on the distribution of chlorfenapyr residues in the skin and flesh of citrus and melons and the fate of residues in the processed fractions of citrus (oranges, limes), tomatoes, potatoes, and tea under conditions simulating commercial processing practices.

Estimated processing factors for the commodities considered at this Meeting and used for dietary intake estimation or for estimating livestock dietary burdens are summarized below.

Commodities	Processing factors (PF)	Best estimate PF
Citrus pulp (wet)	1.08, 0.99	1.0 (mean)
Citrus pulp (dry)	0.55, 0.87, 2.3, 2.4	1.6 (median)
Orange oil	3.1, 17, 23, 70	70
Tomato pomace (wet)	63	63
Tomato pomace (dry)	157	157

Processing factors are based on residues of parent chlorfenapyr, processing studies did not measure residues of CL303268

The Meeting estimated a maximum residue level for citrus oil of 30 mg/kg based on a median residue of 0.44 mg/kg in orange fruit (whole) and a processing factor of 70.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of chlorfenapyr in farm animals on the basis of the diets listed in Annex 6 of the 2009 JMPR Report (OECD Feedstuffs Derived from Field Crops), median or highest residue levels estimated at the present Meeting. Dietary burden calculations are provided in Annex 6.

Dietary burden calculations for beef cattle and dairy cattle and poultry are provided below. Potential cattle feed items include: citrus pulp, tomato pomace and potato culls. Potential poultry feed items were: potato culls.

Summary of livestock dietary burden (ppm of dry matter diet)

	US-Canada	EU	Australia	Japan
Beef cattle	0.09	0.05	2.2	-
Dairy cattle	0.08	0.17	2.2 ^{a, b}	-
Poultry Broiler	-	0.005	-	-
Poultry Layer	-	0.005 ^c	-	-

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

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

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

Farm animal feeding studies

The Meeting received a feeding study on lactating dairy cows. Animals were dosed orally for 28 consecutive days equivalent to 0.66, 2.2 and 6.8 ppm dry matter in the feed.

Residues of chlorfenapyr in whole milk of animals in the 0.66, 2.2 and 6.8 ppm groups were < 0.01 mg/kg, < 0.01–0.035 and < 0.01–0.042 mg/kg respectively. In muscle and for the same groups,

residues were < 0.01, < 0.01–0.017 and < 0.01–0.022 mg/kg respectively. Residues of chlorfenapyr in fat were 0.031–0.067, 0.17–0.43 and 0.15–0.60 mg/kg respectively. Residues in liver were < 0.05, < 0.05 and < 0.05–0.054 mg/kg respectively for the 0.66, 2.2 and 6.8 ppm feeding groups. Residues of chlorfenapyr in kidney were < 0.05 mg/kg (LOQ) at all the doses studied.

Animal commodity maximum residue levels

Cattle

For maximum residue estimation, the high residues of chlorfenapyr were obtained for the maximum dietary burden (2.2 ppm) directly using the 2.2 ppm feeding level in the dairy cow feeding study and using the highest tissue concentrations of chlorfenapyr from individual animals within those feeding groups and for milk using the mean residues.

	Feed level (ppm) for milk residues	Residues (mg/kg) in milk	Feed level (ppm) for tissue residues	Residues (mg/kg) in			
				Muscle	Liver	Kidney	Fat
Maximum residue level beef or dairy cattle							
Feeding study ^a	2.2	0.017	2.2	0.017	< 0.05	< 0.05	0.43
Estimated highest chlorfenapyr	2.2	0.017	2.2	0.017	< 0.05	< 0.05	0.43

^a highest residues for tissues and mean residues for milk

The Meeting estimated maximum residue levels of 0.6 (fat) mg/kg for chlorfenapyr in meat (from mammals other than marine mammals), 0.05 (*) mg/kg for edible offal (mammalian) and 0.03 mg/kg for milks.

No feeding study on poultry was available however the estimated dietary burden for poultry is 0.005 ppm, about 600 times less than the level used in the poultry metabolism studies. No residues of chlorfenapyr are expected in poultry tissues and eggs. The Meeting estimated maximum residue levels of 0.01(*) mg/kg for eggs, poultry meat (fat) and poultry edible offal.

DIETARY RISK ASSESSMENT

No maximum residue levels are recommended, nor are levels estimated for use for long- and short-term dietary intake assessments as the Meeting could not reach a conclusion on a residue definition for dietary risk assessment.