The maximum dietary burden for poultry is 1.3 ppm. No residues above the LOQ of the analytical method used were observed in the feeding study for laying hens at the lowest dose level equivalent to 2 ppm in the diet. Maximum residues expected are: muscle, fat, liver, kidney and eggs are all < 0.01 mg/kg.

The Meeting estimated maximum residue levels for poultry meat 0.01(*) mg/kg (fat); poultry offal 0.01(*) and eggs 0.01 (*) mg/kg.

As no residues are observed at the maximum feeding level for poultry, the STMRs for poultry meat, edible offal and eggs are the same as the maximum residue levels.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of cyfluthrin has resulted in recommendations for MRLs and STMRs for raw and processed commodities. Consumption data were available for 22 food commodities and were used in the dietary intake calculation. The results are shown in Annex 3.

The International Estimated Daily Intakes for the 13 GEMS/Food regional diets, based on estimated STMRs were in the range 0–2% of the maximum ADI of 0.04 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of cyfluthrin from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The international estimated short-term intake (IESTI) for cyfluthrin was calculated for the food commodities (and their processing fractions) for which maximum residue levels and HRs were estimated and for which consumption data were available. The results are shown in Annex 4.

For the general population the IESTI varied from 0–120% of the ARfD (0.04 mg/kg bw) while for children the IESTI varied from 0–240% of the ARfD. The IESTI (as a% of the ARfD) for broccoli for children was 120% and 70% for the general population, 240% for head cabbage for children and 100% for the general population.

The Meeting concluded that the short-term intake of residues of cyfluthrin resulting from uses that have been considered by the JMPR, except the uses on broccoli and head cabbage, is unlikely to present a public health concern.

The Meeting noted that no residue data relating to alternative GAP were submitted for broccoli and head cabbage. The information provided to the JMPR precludes an estimate that the dietary intake would be below the ARfD for consumption for broccoli and head cabbage by children.

5.8 LAMBDA-CYHALOTHRIN (146)

TOXICOLOGY

Lambda-cyhalothrin, the ISO approved common name for (*R*)-cyano(3-phenoxyphenyl)methyl (1*S*,3*S*)-rel-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate is a synthetic cyano-containing type II pyrethroid insecticide (CAS No. 91465-08-6).

Cyhalothrin (CAS No. 68085-85-8) was evaluated by JMPR in 1984, when an ADI of 0–0.02 mg/kg bw was established based on a NOAEL of 20 ppm, equal to 2 mg/kg bw per day, identified on the basis of clinical signs in a 2-year study in mice; a NOAEL of 30 ppm, equal to

1.5 mg/kg bw per day, identified on the basis of decreased body-weight gain in a three-generation study in rats; and a NOAEL of 2.5 mg/kg bw per day, identified on the basis of neurotoxicity in a 6-month study in dogs, and using a safety factor of 100.

At its meeting in 2000, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a temporary ADI of 0–0.002 mg/kg bw based on a LOEL of 1 mg/kg bw per day for induction of liquid faeces in dogs in a 26-week study, and using a safety factor of 500. The high safety factor was used to compensate for the absence of a no-observed-effect level (NOEL) in this study.

At its meeting in 2004, JECFA concluded that the toxicity of cyhalothrin is similar in rats and dogs. The Committee decided that the temporary ADI could be replaced by an ADI of 0–0.005 mg/kg bw, which was determined by dividing the LOEL of 1 mg/kg bw per day in dogs (also the NOEL for rats) by a safety factor of 200. The safety factor incorporated a factor of 2 to compensate for the absence of a NOEL in dogs.

Lambda-cyhalothrin consists of two of the four enantiomers (i.e., the *cis* 1*R*α*S* and *cis* 1*S*α*S* enantiomeric pair) of cyhalothrin. One of the two enantiomers of lambda-cyhalothrin is the insecticidally active gamma-cyhalothrin (CAS No. 76703-62-3). Cyhalothrin comprises about 50% lambda-cyhalothrin.

Lambda-cyhalothrin was evaluated by the present Meeting within the Periodic Re-evaluation Programme of the CCPR. For the present re-evaluation, studies with cyhalothrin and lambda-cyhalothrin were available.

For lambda-cyhalothrin, specifications were established by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) and published as *WHO specifications and evaluations for public health pesticides: lambda-cyhalothrin* [27] (technical material, 2003). For other formulations, specifications also exist.

All pivotal studies with cyhalothrin and lambda-cyhalothrin were certified as being compliant with GLP.

Biochemical aspects

Oral doses of cyhalothrin were readily but incompletely absorbed (30–40% of radiolabel was recovered in urine) in rats and dogs. Peak blood concentrations were reached after 4–7 h. In male rats treated with replacement bile obtained from treatment-naive rats, biliary excretion was about 11%. At a low dose, most (70%) of the administered material was excreted in the faeces and urine within 24 h. After 7 days, 2–3% of the cyhalothrin administered persisted as unchanged residue in fat. Metabolism in rats and dogs was similar, involving initial cleavage of the molecule at the ester bond. In rats dosed with cyhalothrin, major metabolites identified in urine were the sulfate conjugate of 3-(4'-hydroxyphenoxy) benzoic acid (compound XXIII) glucuronide conjugate of (1*RS*)-*cis*-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanoic acid (i.e., the compound 1a glucuronide). Minor metabolites identified were unconjugated compound XXIII and 3-phenoxybenzoic acid (compound V).

In volunteers given a single dose of lambda-cyhalothrin in capsules, serum and urine contained the metabolites compound XXIII, compound V and compound 1a ((1*RS*)-*cis*-3-(*Z*-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanoic acid, TMFVCA). Their presence suggests that the initial metabolism of this compound in humans is similar to that in rats and dogs.

[27] Available from: http://www.who.int/whopes/quality/en/Lambda-cyhalothrin_eval_specs_WHO_2003.pdf

Toxicological data

The acute oral LD_{50} of lambda-cyhalothrin in rats was 79 mg/kg bw in males and 56 mg/kg bw in females. The observed clinical signs (ataxia, decreased activity, tiptoe gait, splayed gait, loss of stability, dehydration, urinary incontinence, hunched posture, piloerection, salivation, ungroomed appearance and pinched-in sides) were typical of this class of pyrethroids.

In studies with lambda-cyhalothrin in rats, the inhalation LC_{50} value was 60 mg/m^3 (0.06 mg/L), and the dermal LD_{50} was 632 mg/kg bw in males and 696 mg/kg bw in females. Lambda-cyhalothrin was not irritating to the skin and only slightly irritating to the eyes. With respect to dermal sensitization, the results of a maximization test with lambda-cyhalothrin in guinea-pigs were inconclusive. Technical-grade cyhalothrin has been reported to cause skin sensitization in a Buehler test and a maximization test in guinea-pigs.

In a 90-day feeding study in rats given cyhalothrin, the NOAEL was 50 ppm, equal to 2.6 mg/kg bw per day, on the basis of reduced body-weight gain and food consumption. In a 90-day feeding study in rats given lambda-cyhalothrin, the NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw per day, on the basis of reduced body-weight gain and food consumption. In a 26-week study in dogs fed capsules containing cyhalothrin and a 1-year study in dogs fed capsules containing lambda-cyhalothrin, increased incidences of liquid faeces was observed, with an overall NOAEL of 0.1 mg/kg bw per day. The increased incidences of liquid faeces were observed from the first week of treatment. Other pyrethroids produce this effect, which may be the consequence of the local gastrointestinal equivalent of paraesthesia in the skin. In the two studies in dogs, signs of systemic neurotoxicity (ataxia, tremors, and occasionally convulsions) were observed, with an overall NOAEL of 0.5 mg/kg bw per day. Signs of systemic neurotoxicity were observed from the first week and generally occurred within a few hours after treatment.

In a 2-year dietary study with cyhalothrin in mice, the NOAEL was 20 ppm, equal to 1.8 mg/kg bw per day, on the basis of clinical signs (piloerection and hunched posture) in males. An increase in the incidence of mammary adenocarcinomas in the groups receiving the intermediate or highest dose was at the upper limit of the range for historical controls and was not dose-related. The Meeting therefore considered that it was unlikely that these tumours were caused by treatment with cyhalothrin.

In a 2-year dietary study with cyhalothrin in rats, the NOAEL was 50 ppm, equal to 2.3 mg/kg bw per day, on the basis of a reduction in body-weight gain. No treatment-related changes in tumour incidence were observed in this study.

The Meeting concluded that cyhalothrin is not carcinogenic in rodents.

Lambda-cyhalothrin was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence for genotoxicity was observed in any test. A number of published studies, largely from the same laboratory, have reported significant increases in DNA damage in vitro (Comet assay) and chromosomal aberrations in vitro and in vivo. The materials tested in these studies were either commercial formulations of unknown composition or were inadequately described. In view of the uniform finding of a lack of genotoxicity in those studies in which lambda-cyhalothrin was adequately characterized, the Meeting concluded that lambda-cyhalothrin is unlikely to be genotoxic.

In view of the lack of genotoxicity of lambda-cyhalothrin and the absence of carcinogenicity shown by cyhalothrin in mice and rats, the Meeting concluded that lambda-cyhalothrin is unlikely to pose a carcinogenic risk to humans.

In a multigeneration dietary study with cyhalothrin in rats, the NOAEL for parental toxicity was 30 ppm, equivalent to 2.0 mg/kg bw per day, on the basis of a reduction in body-weight gain. The NOAEL for offspring toxicity was 30 ppm, equivalent to 2 mg/kg bw per day, on the basis of reduced body-weight gain during lactation. The NOAEL for reproductive toxicity was 100 ppm, equivalent to 6.7 mg/kg bw per day, i.e., the highest dose tested.

The effect of oral exposure to cyhalothrin on prenatal development was investigated in rats and rabbits. In a study of developmental toxicity in rats treated by gavage, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of a reduction in body weight and loss of limb coordination. The NOAEL for foetal toxicity was 15 mg/kg bw per day, i.e., the highest dose tested. In a study of developmental toxicity in rabbits treated by gavage, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of reduced body-weight gain and food consumption. The NOAEL for fetotoxicity was 30 mg/kg bw per day, i.e., the highest dose tested.

In a study of acute neurotoxicity in rats given lambda-cyhalothrin by gavage, the NOAEL was 2.5 mg/kg bw per day on the basis of signs of neurotoxicity (increased breathing rate, urinary incontinence, salivation, reduced response to sound).

In a comparative study on the acute effects of pyrethroids in rats treated by oral gavage, in which the data were analysed using a nonlinear exponential threshold model, lambda-cyhalothrin showed decreased motor activity with a benchmark threshold dose (estimate of the highest no-effect level at which the rats would not display any decrease in motor activity) of 0.5 mg/kg bw. In a 90-day dietary study, the NOAEL was 150 ppm (equal to 11 mg/kg bw per day), i.e., the highest dose tested.

In a study of developmental neurotoxicity in rats, the NOAEL for maternal toxicity was 60 ppm, equal to 4.9 mg/kg bw per day, on the basis of reduced body-weight gain during gestation. The NOAEL for offspring toxicity was 60 ppm, equal to 10.7 mg/kg bw per day, based on maternal lambda-cyhalothrin intake, on the basis of reduced body-weight gain during lactation. No evidence for developmental neurotoxicity was observed.

In case reports in humans, no systemic effects were reported. In most cases exposure was by the dermal and inhalation routes. Predominant signs were skin paraesthesia, numbness, irritation of the skin, red eyes, coughing and sneezing.

No toxicological studies on metabolites of cyhalothrin were available. However, the Meeting considered it likely that the metabolites would be less neurotoxic than cyhalothrin, as none contains an intact pyrethroid structure.

The Meeting concluded that the existing database on lambda-cyhalothrin was adequate to characterize the potential hazards to foetuses, infants and children.

Toxicological evaluation

Although increased incidences of liquid faeces were observed in dogs given lambda-cyhalothrin/cyhalothrin, which may represent a consequence of a local gastrointestinal equivalent of paraesthesia in the skin, the Meeting considered that it was not appropriate to base the ADI and ARfD on local effects on the gastrointestinal tract, observed after bolus administration.

The most sensitive systemic effect of lambda-cyhalothrin/cyhalothrin was neurotoxicity (decreased motor activity), which was observed in a study of acute toxicity in rats given lambda-cyhalothrin orally, with a threshold dose of 0.5 mg/kg bw, and in repeat-dose studies with cyhalothrin and lambda-cyhalothrin in dogs treated orally (ataxia, tremors, occasionally convulsions) with a NOAEL of 0.5 mg/kg bw per day. On the basis of these effects, the Meeting established a group ADI for cyhalothrin and lambda cyhalothrin of 0–0.02 mg/kg bw, using a safety factor of 25. Because lambda-cyhalothrin is relatively rapidly absorbed and excreted and the neurotoxic effects are rapidly reversible and dependent on C_{max}, the Meeting considered it appropriate to adjust the safety factor for the reduced variability in C_{max} compared with AUC. The Meeting considered that the ADI of 0.02 mg/kg bw is adequately protective against the other, non-neurotoxic effects of lambda-cyhalothrin/cyhalothrin observed in short- and long-term studies with repeated doses, and in studies of reproductive and developmental toxicity, where the use of a safety factor of 100 would be appropriate.

The Meeting established a group ARfD for cyhalothrin and lambda-cyhalothrin of 0.02 mg/kg bw on the basis of systemic neurotoxicity (decreased motor activity) observed in a study of acute toxicity in rats given lambda-cyhalothrin orally with a threshold dose of 0.5 mg/kg bw per day, and in repeat-dose studies with cyhalothrin and lambda-cyhalothrin in dogs treated orally, in which neurotoxic effects (ataxia, tremors, occasionally convulsions) occurred during the first week, within a few hours after treatment, with an overall NOAEL of 0.5 mg/kg bw per day, and using a safety factor of 25. For the same reasons as described above, the Meeting considered it appropriate to adjust the safety factor for the reduced variability in C_{max} compared with AUC.

A toxicological monograph was prepared.

Levels relevant for risk assessment

(a) Cyhalothrin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity [a]	Toxicity	20 ppm, equal to 1.8 mg/kg bw per day	100 ppm, equal to 9.2 mg/kg bw per day
		Carcinogenicity	500 ppm, equal to 51 mg/kg bw per day[c]	—
Rat	Ninety-day study of toxicity[a]	Toxicity	50 ppm, equal to 2.6 mg/kg bw per day	250 ppm, equal to 14 mg/kg bw per day
	Two-year study of toxicity and carcinogenicity [a]	Toxicity	50 ppm, equal to 2.3 mg/kg bw per day	250 ppm, equal to 12 mg/kg bw per day
		Carcinogenicity	250 ppm, equal to 12 mg/kg bw per day[c]	—
	Two-generation study of reproductive toxicity[a]	Parental toxicity	30 ppm, equivalent to 2.0 mg/kg bw per day	100 ppm, equivalent to 6.7 mg/kg bw per day [d]
		Offspring toxicity	30 ppm, equivalent to 2.0 mg/kg bw per day	100 ppm, equivalent to 6.7 mg/kg bw per day [d]
		Reproductive toxicity	100 ppm, equivalent to 6.7 mg/kg bw per day[c]	—
	Developmental toxicity[b]	Maternal toxicity	10 mg/kg bw per day	15 mg/kg bw per day
		Fetotoxicity	15 mg/kg bw per day [c]	—
Rabbit	Developmental toxicity[b]	Maternal toxicity	10 mg/kg bw per day	30 mg/kg bw per day
		Fetotoxicity	30 mg/kg bw per day [c]	—
Dog	Twenty-six-week study[b]	Toxicity	2.5 mg/kg bw per day	10 mg/kg bw per day

[a] Dietary administration.

[b] Gavage administration.

[c] Highest dose tested.

(b) Lambda-cyhalothrin

Species	Study	Effect	NOAEL	LOAEL
Rat	Ninety-day study of toxicity[a]	Toxicity	50 ppm, equivalent to 2.5 mg/kg bw per day	250 ppm, equivalent to 12.5 mg/kg bw per day
	Acute neurotoxicity[b]	Neurotoxicity	0.5 mg/kg bw [e]	1.3 mg/kg bw [f]

	Ninety-day study of neurotoxicity [a]	Neurotoxicity	150 ppm, equal to 11 mg/kg bw per day [c]	—
	Developmental neurotoxicity [a]	Maternal toxicity	60 ppm, equal to 4.9 mg/kg bw per day	150 ppm, equal to 11.4 mg/kg bw per day
		Offspring toxicity	60 ppm, equivalent to 10.7 mg/kg bw per day [d]	150 ppm, equivalent to 26.3 mg/kg bw per day [d]
		Developmental (neuro)-toxicity	150 ppm, equivalent to 11.4 mg/kg bw per day[c]	—
Dog	One-year study[b]	(Neuro)toxicity	0.5 mg/kg bw per day	3.5 mg/kg bw per day

[a] Dietary administration.

[b] Gavage administration.

[c] Highest dose tested.

[d] Based on maternal intake of lambda-cyhalothrin during lactation.

[e] Threshold dose obtained using a nonlinear exponential threshold model.

[f] ED_{30} (dose associated with a 30% decrease in motor activity) obtained using a nonlinear exponential threshold model.

Estimate of acceptable daily intake for humans

0–0.02 mg/kg bw

Estimate of acute reference dose

0.02 mg/kg bw

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

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

Critical end-points for setting guidance values for exposure to cyhalothrin/lambda-cyhalothrin

Absorption, distribution, excretion and metabolism in animals	
Rate and extent of absorption	Rapid, incomplete absorption (about 40–50% in rats)
Distribution	Highest concentrations in fat, followed by liver and kidney (rats)
Potential for accumulation	Low
Rate and extent of excretion	Rapid (70% in faeces and urine within 24 h in rats)
Metabolism in animals	Sulfate conjugate of 3-(4'-hydroxyphenoxy) benzoic acid (compound XXIII) and glucuronide conjugate of (1RS)-cis-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropane carboxylic acid. Unconjugated compound XXIII and 3-phenoxybenzoic acid (compound V) were minor metabolites.
Toxicologically significant compounds in animals, plants and the environment	Cyhalothrin, lambda-cyhalothrin
Acute toxicity	
Rat, LD_{50}, oral	56 mg/kg bw
Rat, LD_{50}, dermal	632 mg/kg bw
Rat, LC_{50}, inhalation	0.060 mg/L
Rabbit, skin irritation	Not an irritant (cyhalothrin)

Rabbit, eye irritation	Slightly irritating (lambda-cyhalothrin)
Guinea-pig, skin sensitization	Sensitizing (cyhalothrin, Buehler test and Magnusson & Kligman)
Short-term studies of toxicity	
Target/critical effect	Neurotoxicity, i.e., ataxia, tremors, occasionally convulsions (dogs)
Lowest relevant oral NOAEL	0.5 mg/kg bw per day (lambda-cyhalothrin, dogs)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Decreased body weight gain (rats)
Lowest relevant NOAEL	50 ppm, equal to 2.3 mg/kg bw per day (cyhalothrin, rats)
Carcinogenicity	Not carcinogenic (cyhalothrin, mice, rats)
Genotoxicity	
	Not genotoxic (lambda-cyhalothrin)
Reproductive toxicity	
Reproduction target/critical effect	No reproductive effects (rats)
Lowest relevant reproductive NOAEL	100 ppm, equal to 6.7 mg/kg bw per day, i.e., highest dose tested (cyhalothrin, rats)
Developmental target	No developmental effects (rabbits)
Lowest relevant developmental NOAEL	30 mg/kg bw per day (lambda-cyhalothrin, rabbits)
Neurotoxicity/delayed neurotoxicity	
Neurotoxicity	Type II pyrethroid toxicity (choreoathetosis/salivation syndrome)
Lowest relevant oral NOAEL	0.5 mg/kg bw (lambda-cyhalothrin, rats, dogs)
Other toxicological studies	
	No data
Medical data	
	No systemic poisoning reported.
	Skin paraesthesia, numbness, irritation of the skin, red eyes, coughing and sneezing.

Summary for cyhalothrin and lambda-cyhalothrin

	Value	Study	Safety factor
Group ADI	0–0.02 mg/kg bw	Rat, acute neurotoxicity, lambda-cyhalothrin;[a] dog, 1-year, lambda-cyhalothrin	25
Group ARfD	0.02 mg/kg bw	Rat, acute neurotoxicity, lambda-cyhalothrin; dog, 1-year, lambda-cyhalothrin[b]	25

[a] The most sensitive NOAEL for the primary action the chemical and considered protective of other non-neurotoxic effects from studies of repeated doses.

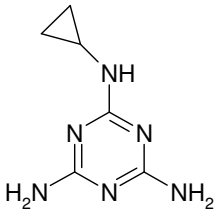
[b] Neurotoxicity occurred a few hours after dosing during the first week of treatment.

5.9 CYROMAZINE (169)

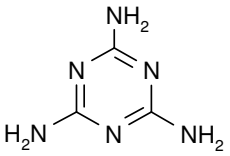
RESIDUE AND ANALYTICAL ASPECTS

Cyromazine was last evaluated by the JMPR in 2006 for toxicology within the Periodic Re-evaluation Programme, where an ADI of 0-0.06 mg/kg bw and an ARfD of 0.1 mg/kg bw were established. The compound was listed at the 38th Session of the CCPR for periodic re-evaluation for residues by the 2007 JMPR. Data submitted by the manufacturer include physical and chemical properties, metabolism in animals and plants, environmental fate in soils, residues in succeeding crops, analytical methods, storage stability, supervised trial on mangos, vegetables and animal commodities and processing studies. Residue and information on good agricultural practices (GAP) was also submitted by the Netherlands.

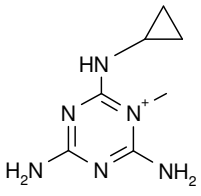
Cyromazine is a selective insecticide that acts by inhibiting the moulting process in insects, particularly in members of the Dipteran family. The figure below shows the compound structure and its main metabolites or degradation products found in animals, plants and/or soils. Metabolism and environmental fate studies submitted to the Meeting were conducted with [triazine-U-^{14}C]cyromazine.



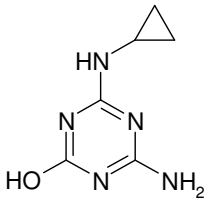
CYROMAZINE



MELAMINE



1-METHYL CYROMAZINE



HYDROXY CYROMAZINE

Animal metabolism

Metabolism studies in rats evaluated by the 2006 JMPR showed that more than 97% of the administered [^{14}C]cyromazine dose was excreted within 24 h, almost exclusively in the urine. Cyromazine was the major compound found in urine (71.5% of the applied radioactivity), with a further 7% attributed to melamine and 8–11% to hydroxy-cyromazine and 1-methyl-cyromazine.

Laying hens that received cyromazine at 5.0 ppm in the feed (equivalent to 0.5 mg/kg body weight/day) for 7 consecutive days had > 99% of the applied radioactivity recovered in the excreta. Egg white and egg yolk had 0.4% and 0.2% of the total applied radioactive dose, respectively; for egg white and egg yolk, an average of 0.15 and 0.12 mg/kg cyromazine equivalents were found in the daily collected eggs of two animals, respectively. Cyromazine represented about 64% TRR in eggs; a metabolite (15.6% TRR) had the same retention volume in an ion exchange column as melamine, but no confirmation of the identity of this compound was performed. Hen tissue residues accounted for 0.1% of the total applied dose, with the highest radioactive levels found in liver, kidney, heart and muscle (0.032, 0.019, 0.10 and 0.09 mg/kg cyromazine equivalents, respectively). The residues in tissues were not characterized. Expired CO_2 and other volatiles accounted for < 0.1% of the applied dose.