

5.26 PYMETROZINE (279)

TOXICOLOGY

Pymetrozine is the ISO-approved common name for (*E*)-4,5-dihydro-6-methyl-4-(3-pyridylmethyleneamino)-1,2,4-triazin-3(2*H*)-one (IUPAC), with CAS number 123312-89-0. Pymetrozine, which was developed under the code CGA 215944, is an insecticide that acts by inhibiting feeding, but the precise molecular targets are uncertain.

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

All critical studies contained statements of compliance with GLP.

Biochemical aspects

Absorption of pymetrozine (labelled with 6-¹⁴C-triazine or 5-¹⁴C-pyridine) administered to rats by gavage at 0.5 or 100 mg/kg bw was rapid, with maximal blood concentrations achieved at 15 minutes and 4 hours, respectively. The extent of oral absorption was high (> 80%) at both doses, based on urinary and biliary data. Pymetrozine was widely distributed in the body. High concentrations of both triazine- and pyridine-labelled material were found in the liver and kidney. The labelled material was rapidly excreted via urine (50–75% in 24 hours). There was a disproportionate increase in the AUC at 100 mg/kg bw, indicating a saturation of elimination.

Absorbed pymetrozine was extensively metabolized, with unmetabolized parent compound representing approximately 10% of the excreted radiolabel. Compounds containing both ring structures represented over 50% of the identified metabolites. The kinetics, excretion pattern, tissue distribution of radioactivity and metabolite profile were similar for both radiolabelled sites and both administered dose levels as well as when the administration of radiolabelled pymetrozine was preceded by 14 days of administration of the unlabelled material. A comparative study showed no notable differences in the metabolite profile in rats and mice.

Toxicological data

Pymetrozine was of low acute toxicity in rats via the oral route (LD₅₀ = 5820 mg/kg bw) and dermal route (LD₅₀ > 2000 mg/kg bw) and by inhalation exposure (LC₅₀ > 1.8 mg/L air). Pymetrozine was not irritating to the skin of rabbits, but was transiently, mildly irritating to the eyes of rabbits. It was weakly sensitizing in the guinea-pig maximization test.

In all species, the liver was a target organ, with increases in weight, hepatocellular hypertrophy and necrosis. Investigations on liver enzyme activities in mice and rats revealed that pymetrozine administration resulted in significant reversible induction of the activities of some P450 enzymes and increased hepatocellular proliferation. Reduced thymus weight and thymic atrophy were also seen in all species, as were spleen and testicular effects. Reduced body weight gain, often associated with reductions in feed consumption, was also a consistent finding.

In a 90-day study of toxicity in mice, dietary pymetrozine concentrations were 0, 1000, 3000 and 7000 ppm (equal to 0, 143, 429 and 1000 mg/kg bw per day for males and 0, 252, 589 and 1240 mg/kg bw per day for females, respectively). No NOAEL was identified, as hepatocellular necrosis was observed at 1000 ppm (equal to 252 mg/kg bw per day) in female mice.

In a 28-day study of toxicity in rats, pymetrozine was administered by gavage at a dose of 0, 10, 100 or 600 mg/kg bw per day. The NOAEL was 10 mg/kg bw per day, based on thymic atrophy and hyperplasia of the splenic white pulp at 100 mg/kg bw per day.

In a 28-day study of toxicity in rats, dietary pymetrozine concentrations were 0, 100, 500, 2000 and 10 000 ppm (equal to 0, 10, 55, 203 and 691 mg/kg bw per day for males and 0, 10, 55, 212 and 699 mg/kg bw per day for females, respectively). The NOAEL was 2000 ppm (equal to

203 mg/kg bw per day), based on a range of effects on the liver, spleen, thymus, adrenals and testes at 10 000 ppm (equal to 691 mg/kg bw per day).

In a 90-day study of toxicity in rats, dietary pymetrozine concentrations were 0, 50, 500 and 5000 ppm (equal to 0, 3.4, 33 and 360 mg/kg bw per day for males and 0, 3.6, 34 and 370 mg/kg bw per day for females, respectively). The NOAEL was 500 ppm (equal to 33 mg/kg bw per day), on the basis of thymic atrophy, hepatocellular hypertrophy and renal calcification at 5000 ppm (equal to 360 mg/kg bw per day).

In a 28-day study in which dogs were administered pymetrozine in the diet at a concentration of 0, 100, 500 or 2500 ppm (equal to 0, 3.2, 15 and 55 mg/kg bw per day for males and 0, 2.8, 16 and 50 mg/kg bw per day for females, respectively), the NOAEL was 100 ppm (equal to 2.8 mg/kg bw per day), based on decreased thymus weights in females at 500 ppm (equal to 16 mg/kg bw per day).

In a 90-day study in which dogs received pymetrozine in the diet at a concentration of 0, 100, 500 or 2500 ppm (equal to 0, 3.1, 14 and 53 mg/kg bw per day for males and 0, 3.2, 15 and 60 mg/kg bw per day for females, respectively), the NOAEL was 100 ppm (equal to 3.1 mg/kg bw per day), based on thymic atrophy, testicular tubular atrophy, reduced spermatogenesis, hepatocellular necrosis and inflammatory changes in several organs at 500 ppm (equal to 14 mg/kg bw per day).

In a 1-year study in dogs in which pymetrozine was administered in the diet at a concentration of 0, 20, 200 or 1000 ppm (equal to 0, 0.57, 5.3 and 28 mg/kg bw per day for males and 0, 0.57, 5.0 and 27 mg/kg bw per day for females, respectively), the NOAEL was 20 ppm (equal to 0.57 mg/kg bw per day), on the basis of reduced testes weights, increased cholesterol and reduced haemoglobin at 200 ppm (equal to 5.0 mg/kg bw per day).

The pattern of findings in the 90-day and 1-year dog studies was similar, and the effects seen in the 1-year study at 200 and 1000 ppm were marginal. An overall NOAEL for the 90-day and 1-year studies of 100 ppm (equal to 3.1 mg/kg bw per day) was identified, with an overall LOAEL of 200 ppm (equal to 5.0 mg/kg bw per day).

In a 78-week toxicity and carcinogenicity study in mice, dietary concentrations were 0, 10, 100, 2000 and 5000 ppm (equal to 0, 1.2, 12, 254 and 678 mg/kg bw per day for males and 0, 1.2, 11, 243 and 673 mg/kg bw per day for females, respectively). The NOAEL for systemic toxicity was 100 ppm (equal to 11 mg/kg bw per day), based on liver hypertrophy, splenic haemosiderosis and haematopoiesis, and alterations in the weights of the kidneys, spleen and liver at 2000 ppm (equal to 243 mg/kg bw per day). Pymetrozine increased the incidences of hepatocellular adenomas and carcinomas in both sexes at 5000 ppm and in males at 2000 ppm; and of lung adenomas and carcinomas in females at 2000 and 5000 ppm. The NOAEL for carcinogenicity was 100 ppm (equal to 11 mg/kg bw per day), based on increased incidences of hepatocellular carcinomas in males receiving 2000 ppm (equal to 254 mg/kg bw per day) and lung adenomas and carcinomas in females receiving 2000 ppm (equal to 243 mg/kg bw per day).

In a 2-year toxicity and carcinogenicity study in rats, dietary concentrations were 0, 10, 100, 1000 and 3000 ppm (equal to 0, 0.4, 3.7, 39 and 128 mg/kg bw per day for males and 0, 0.4, 4.5, 47 and 154 mg/kg bw per day for females, respectively). The NOAEL for systemic toxicity was 100 ppm (equal to 3.7 mg/kg bw per day), on the basis of effects in both sexes (altered organ weights, foci of cellular change in the liver and thyroid hyperplasia) at 1000 ppm (equal to 39 mg/kg bw per day). Pymetrozine produced an increase in the incidence of hepatocellular adenoma in female rats given 3000 ppm in the diet. The NOAEL for carcinogenicity was 1000 ppm (equal to 47 mg/kg bw per day), based on an increase in the incidence of hepatocellular adenoma in females at 3000 ppm (equal to 154 mg/kg bw per day).

The Meeting concluded that pymetrozine is carcinogenic in male and female mice and in female but not male rats.

Pymetrozine was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence of genotoxicity was found.

The Meeting concluded that pymetrozine is unlikely to be genotoxic.

Mechanistic studies were performed to investigate the mode of action of the liver tumour findings in mice and female rats. Male mice exposed to pymetrozine exhibited moderate increases in proliferation of hepatic smooth endoplasmic reticulum and in activities of P450 enzymes, a sustained stimulation of hepatocyte proliferation and increased hepatocellular hypertrophy. These effects were reversible. A dietary level of 500 ppm was a threshold for these effects in mice. Female rats exposed to pymetrozine at 1000 ppm and above exhibited a weak and reversible induction of hepatic, xenobiotic metabolizing enzymes, most prominently uridine diphosphate–glucuronyl transferase. There were no significant effects at 100 ppm, which is considered to be the threshold. Pymetrozine at up to 1000 ppm in the diet for 18 weeks exhibited no tumour promoting potential in rats initiated with diethylnitrosamine and dihydroxy-di-*N*-propylnitrosamine.

No data were presented relating to the mode of action for the lung tumours observed in female mice exposed to pymetrozine, and it is noted that there are no preneoplastic lesions of the lungs in mice. However, there was no dose–response relationship, lung tumours are a common finding in mice and, generically, species-specific lung tumours in the mouse have been induced by a number of chemicals.

The available information and data do not permit the identification of the modes of action for the lung or liver tumours or the exclusion of their human relevance.

In view of the lack of genotoxicity and on the basis of other available toxicological information, the Meeting concluded that the modes of action for the liver tumours in mice and female rats and for the lung tumours in female mice are likely to involve a threshold. The Meeting concluded that pymetrozine is unlikely to pose a carcinogenic risk to humans from the diet.

In a two-generation study of reproductive toxicity in rats, dietary concentrations were 0, 20, 200 and 2000 ppm (equal to mean intakes of 0, 1.4, 14 and 127 mg/kg bw per day for males and 0, 1.6, 16 and 152 mg/kg bw per day for females, respectively). The NOAEL for reproductive effects was 2000 ppm (equal to 127 mg/kg bw per day), the highest dose tested. The NOAEL for parental toxicity was 200 ppm (equal to 14 mg/kg bw per day), based on reduced body weights and histopathological findings in the liver, spleen and pituitary at 2000 ppm (equal to 127 mg/kg bw per day). The NOAEL for effects on offspring was 200 ppm (equal to 14 mg/kg bw per day), based on reduced pup weight and a delay in eye opening at 2000 ppm (equal to 127 mg/kg bw per day).

In a study of developmental toxicity in rats dosed at 0, 30, 100 or 300 mg/kg bw per day, displaced pubic bones were seen in four fetuses at the top dose level; this malformation has not been recorded in contemporary historical control data. There were also increases in a number of skeletal variations at 300 mg/kg bw per day. The NOAEL for maternal toxicity was 100 mg/kg bw per day, on the basis of decreased body weight gain and initial body weight loss at 300 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 100 mg/kg bw per day, based on increases in skeletal abnormalities (including malformations) at 300 mg/kg bw per day.

In a study of developmental toxicity, rabbits were dosed at 0, 10, 75 or 125 mg/kg bw per day. Viable fetus numbers were reduced at 125 mg/kg bw per day. The NOAEL for maternal toxicity was 10 mg/kg bw per day, based on initial body weight loss with reduced feed consumption at 75 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 10 mg/kg bw per day, based on an increase in 13th ribs and reduced pubis at 75 mg/kg bw per day.

The Meeting concluded that pymetrozine is teratogenic in rats and possibly in rabbits.

The acute neurotoxicity of pymetrozine was investigated in rats at doses of 0, 125, 500 and 2000 mg/kg bw. Three males died at 2000 mg/kg bw. Dose-related reductions in locomotor activity were seen in all dose groups at 4–5 hours post-dosing, but not subsequently. There were no indications of neuropathy. No NOAEL was identified.

In a subchronic (90-day) neurotoxicity study in rats, dietary concentrations were 0, 500, 1000 and 3000 ppm (equal to 0, 35, 68 and 201 mg/kg bw per day for males and 0, 41, 68 and 204 mg/kg

bw per day for females, respectively). The NOAEL for neurotoxicity and systemic toxicity was 1000 ppm (equal to 68 mg/kg bw per day), based on altered behaviours (continuous head movements and abnormal gait) and reduced body weights at 3000 ppm (equal to 201 mg/kg bw per day). There was no evidence of neuropathy.

Pymetrozine showed some evidence of reversible, clinical signs of neurotoxicity, but with no morphological correlates.

Toxicological data on metabolites and/or degradates

The Meeting considered information on 12 metabolites of pymetrozine: 11 found in plants and one (CGA313124) found in milk.¹ No specific toxicological data were submitted on these metabolites, and therefore they were evaluated using the JMPR metabolite assessment scheme.

CGA313124 (6-hydroxymethyl-pymetrozine) is a major urinary metabolite of pymetrozine in rats, equating to approximately 30% (sum of CGA313124 and its acid metabolite) of the administered dose. The Meeting concluded that the toxicity of CGA313124 has been addressed in studies on pymetrozine and that CGA313124 is covered by the reference doses for pymetrozine.

Nicotinic acid (vitamin B₃, niacin) and nicotinamide are natural compounds and are interconverted in the body. The recommended daily intake for vitamin B₃ is approximately 200 µg/kg bw, with approximately 2.5 mg in a serving of some breakfast cereals. Intakes arising from the use of pymetrozine are significantly below these values. Nicotinic acid and nicotinamide are considered not to be relevant metabolites of pymetrozine.

CGA245342 and Ia7 have no alerts for genotoxicity and are in Cramer class III, with a chronic TTC of 1.5 µg/kg bw per day. For both compounds, the IEDIs and IESTIs are below the TTC. The Meeting concluded that CGA245342 and Ia7 are not toxicologically significant plant metabolites of pymetrozine.

Ia17 has a structural alert for genotoxicity but has not been tested for genotoxicity. On the basis of the available information, the appropriate TTC for chronic exposure is 0.0025 µg/kg bw per day. The IEDI is below 0.0025 µg/kg bw per day. For the acute exposure assessment, a single-exposure TTC of 0.2 µg/kg bw was considered appropriate by the Meeting.² The IESTI for Ia17 is below 0.2 µg/kg bw, and Ia17 is considered not to be a relevant plant metabolite of pymetrozine.

CGA215525 has been proposed as a rat metabolite, but the data are inconsistent, and the Meeting was unable to make use of the toxicological data on pymetrozine in evaluating this metabolite. CGA215525 has a structural alert for genotoxicity, but there was no evidence of genotoxicity in an Ames test, and it is in Cramer class III. Therefore, the relevant TTC is 1.5 µg/kg bw per day. The IEDI is below this value. A single-exposure TTC for Cramer class III compounds of 5 µg/kg bw has been proposed by EFSA, and the Meeting concluded that the use of this value would be conservative. The IESTI is below this value. The Meeting concluded that CGA215525 is not a toxicologically significant plant metabolite of pymetrozine.

CGA96956 (trigonelline) is a natural component of a range of commodities, and exposures from other sources are orders of magnitude greater than those from pymetrozine. The Meeting concluded that CGA96956 is not a toxicologically significant plant metabolite of pymetrozine.

¹ See "Residue and analytical aspects" section below for chemical names of metabolites.

² This is based on the approach of the European Medicines Agency (EMA), which set a TTC of 2 µg/kg bw (120 µg/person) for single exposures to genotoxic impurities in pharmaceuticals. The chronic TTC value used by EMA is 10-fold higher than that used by WHO for potentially genotoxic compounds. Therefore, the EMA single-exposure TTC value of 2 µg/kg bw (120 µg/person) was divided by 10 to give a single-exposure TTC value of 0.2 µg/kg bw, applicable to potentially genotoxic metabolites of pesticides.

CGA23199 is a minor rat metabolite (< 3%), and its toxicity is considered not to have been adequately addressed by studies with pymetrozine. CGA23199 has no structural alerts for genotoxicity and is in Cramer class III, with a TTC of 1.5 µg/kg bw per day and a single-exposure TTC of 5 µg/kg bw. The IEDI and IESTI are below the applicable thresholds, and the Meeting concluded that CGA23199 is not a toxicologically significant plant metabolite of pymetrozine.

CGA128632 (nicotiny alcohol) has therapeutic uses as a vasodilator. The minimal therapeutic dose is approximately 1 mg/kg bw per day. There is a margin between the minimal therapeutic dose of over 1000 relative to the IEDI and of over 50 relative to the IESTI. The Meeting concluded that CGA128632 is not a toxicologically significant plant metabolite of pymetrozine.

CGA294849 has been proposed as a rat metabolite, but the data are inconsistent, and the Meeting was unable to make use of the toxicological data on pymetrozine in evaluating this metabolite. CGA294849 has a structural alert for genotoxicity, but has not been tested for genotoxicity. The IEDI and IESTI are above the applicable chronic TTC and single-exposure TTC values, respectively. The Meeting is unable to conclude on the toxicological significance of CGA294849.

CGA300407 does not have a structural alert for genotoxicity, but the Meeting was made aware that in vitro and in vivo genotoxicity studies exist in which positive results were reported. These data were not submitted, and therefore the Meeting is unable to conclude on the toxicological significance of CGA300407.

Human data

No adverse effects have been reported during health surveillance of pymetrozine production and formulation plant workers, and no significant effects have been reported in exposed users of pymetrozine-based products.

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

Toxicological evaluation

The Meeting established an ADI for pymetrozine of 0–0.03 mg/kg bw on the basis of the overall NOAEL of 3.1 mg/kg bw per day for effects on haematology, liver, thymus and testis from the 90-day and 1-year dog studies combined. A safety factor of 100 was applied. This is supported by the NOAEL of 3.7 mg/kg bw per day in the 2-year study of toxicity in rats. There is a margin of exposure of greater than 5000 between the upper bound of the ADI and the LOAEL of 154 mg/kg bw per day for tumours in female rats.

The Meeting established an ARfD for pymetrozine of 0.1 mg/kg bw, on the basis of the NOAEL of 10 mg/kg bw per day for developmental abnormalities and maternal body weight loss at the start of dosing in the developmental toxicity study in rabbits. A safety factor of 100 was applied.

A toxicological monograph was prepared.

Levels relevant to risk assessment of pymetrozine

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity ^a	Toxicity	100 ppm, equal to 11 mg/kg bw per day	2 000 ppm, equal to 243 mg/kg bw per day
		Carcinogenicity	100 ppm, equal to 11 mg/kg bw per day	2 000 ppm, equal to 243 mg/kg bw per day
Rat	Two-year study of toxicity and	Toxicity	100 ppm, equal to 3.7 mg/kg bw per day	1 000 ppm, equal to 39 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
	carcinogenicity ^a	Carcinogenicity	1 000 ppm, equal to 47 mg/kg bw per day	3 000 ppm, equal to 154 mg/kg bw per day
	Two-generation study of reproductive toxicity ^a	Reproductive toxicity	2 000 ppm, equal to 127 mg/kg bw per day ^b	–
		Parental toxicity	200 ppm, equal to 14 mg/kg bw per day	2 000 ppm, equal to 127 mg/kg bw per day
		Offspring toxicity	200 ppm, equal to 14 mg/kg bw per day	2 000 ppm, equal to 127 mg/kg bw per day
	Developmental toxicity study ^c	Maternal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
		Embryo and fetal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
Rabbit	Developmental toxicity study ^c	Maternal toxicity	10 mg/kg bw per day	75 mg/kg bw per day
		Embryo and fetal toxicity	10 mg/kg bw per day	75 mg/kg bw per day
Dog	Ninety-day and 1- year studies of toxicity ^{a,d}	Toxicity	100 ppm, equal to 3.1 mg/kg bw per day	200 ppm, equal to 5.0 mg/kg bw per day

^a Dietary administration.

^b Highest dose tested.

^c Gavage administration.

^d Two studies combined.

Estimate of acceptable daily intake (ADI)

0–0.03 mg/kg bw

Estimate of acute reference dose (ARfD)

0.1 mg/kg bw

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

Results from epidemiological, occupational health and other such observational studies of human exposure; all information on the toxicity of plant and animal metabolites

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

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption	Rapid, blood T_{\max} < 4 hours; > 80%
Dermal absorption	No study submitted
Distribution	Widely distributed; highest concentrations in liver and kidney
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Largely cleared within 24 hours; primarily via urine (> 50%), bile (10–30%) and faeces (15–30%); evidence of saturation at 100 mg/kg bw
Metabolism in animals	Extensive; mainly by oxidation reactions; cleavage between the two rings is not extensive

Toxicologically significant compounds in animals and plants	Pymetrozine and CGA313124 [CGA294849 and CGA300407] ¹
<i>Acute toxicity</i>	
Rat, LD ₅₀ , oral	5 820 mg/kg bw
Rat, LD ₅₀ , dermal	> 2 000 mg/kg bw
Rat, LC ₅₀ , inhalation	> 1.8 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Transiently, mildly irritating
Guinea-pig, dermal sensitization	Weakly sensitizing (maximization test)
<i>Short-term studies of toxicity</i>	
Target/critical effect	Haematology; liver lesions, thymus weight/atrophy and testes lesions
Lowest relevant oral NOAEL	3.1 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (rat)
Lowest relevant inhalation NOAEC	No data
<i>Long-term studies of toxicity and carcinogenicity</i>	
Target/critical effect	Liver lesions, thyroid hyperplasia, liver and spleen weights
Lowest relevant NOAEL	3.7 mg/kg bw per day (rat)
Carcinogenicity	Liver tumours (rat and mouse); lung tumours (mouse) Unlikely to pose a carcinogenic risk to humans from the diet
<i>Genotoxicity</i>	
	Unlikely to be genotoxic
<i>Reproductive toxicity</i>	
Target/critical effect	Lower pup weight at parentally toxic dose
Lowest relevant parental NOAEL	14 mg/kg bw per day
Lowest relevant offspring NOAEL	14 mg/kg bw per day
Lowest relevant reproductive NOAEL	127 mg/kg bw per day, highest dose tested
<i>Developmental toxicity</i>	
Target/critical effect	Skeletal malformations (rat) and abnormalities (rabbit)
Lowest relevant maternal NOAEL	10 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	10 mg/kg bw per day (rabbit)
<i>Neurotoxicity</i>	
Acute neurotoxicity NOAEL	< 125 mg/kg bw per day, lowest dose tested (rat)
Subchronic neurotoxicity NOAEL	68 mg/kg bw per day (rat)
Developmental neurotoxicity NOAEL	No data
<i>Other toxicological studies</i>	
Immunotoxicity	No specific studies
Mechanistic data	Hepatocyte proliferation (mice); induction of enzymatic activities (rats and mice)

¹ Toxicological significance cannot be determined on the basis of the available information.

Studies on metabolites

No in vivo data submitted on individual metabolites

CGA313124 – significant rat metabolite, addressed by studies with pymetrozine

Nicotinic acid, nicotinamide, CGA245342, CGA215525, CGA96956, CGA23199, CGA128632, Ia7 and Ia17 were considered to be not toxicologically significant plant metabolites based on comparisons of intakes from pymetrozine uses with other types of exposure or the appropriate TTC values

It was not possible to conclude on the toxicological significance of CGA294849 or CGA300407

Medical data

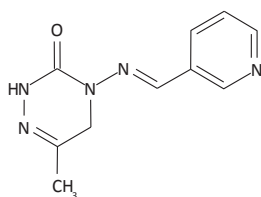
No notable adverse effects reported

Summary

	Value	Study	Safety factor
ADI	0–0.03 mg/kg bw	Ninety-day and 1-year studies of toxicity (dog)	100
ARfD	0.1 mg/kg bw	Developmental toxicity study (rabbit)	100

RESIDUE AND ANALYTICAL ASPECTS

Pymetrozine is a pyridine azomethine insecticide used to control homopteran insects (aphids and whiteflies) as well as pollen beetle selectively. Although it has no knockdown effect, pymetrozine rapidly affects the feeding behaviour of the insect pests. It was considered for the first time by the 2014 JMPR for toxicology and residues.

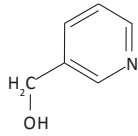
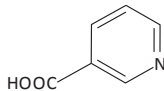
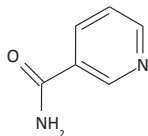
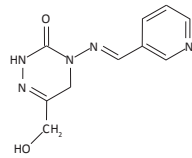
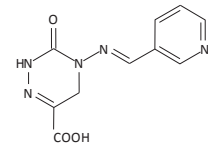
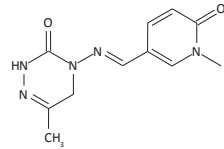
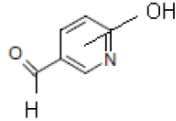
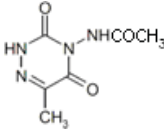
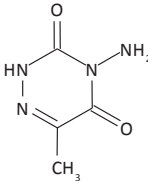
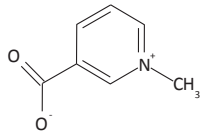


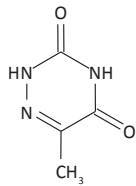
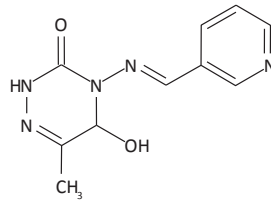
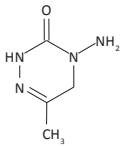
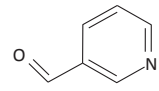
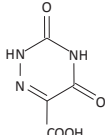
The IUPAC name of pymetrozine is (E)-4,5-dihydro-6-methyl-4-(3-pyridylmethylamino)-1,2,4-triazin-3(2H)-one.

The pymetrozine molecule contains a double bond about which E/Z isomerism is possible. However, pymetrozine technical material is manufactured by a process that yields almost exclusively the E isomer.

Pymetrozine labelled either in the pyridine- or triazine-moiety was used in the metabolism and environmental fate studies.

The following abbreviations are used for the metabolites discussed below:

CGA128632	3-pyridinemethanol	
CGA180777 (nicotinic acid)	3-pyridinecarboxylic acid	
CGA180778 (nicotinamide)	3-pyridinecarboxamide	
CGA313124	4,5-dihydro-6-hydroxymethyl-4-[(3-pyridinyl-methylene)amino]-1,2,4-triazine-3(2H)-one	
U5/IA2	4,5-dihydro-6-carboxy-4-[(3-pyridinyl methylene)-amino]-1,2,4-triazine-3(2H)-one	
IA7	4,5-dihydro-6-methyl-4-[(3-(1-methyl-6-oxo-1,6-dihydropyridinylmethylene)- amino)-1,2,4-triazine-3(2H)-one	
IA17	hydroxylated 3-pyridinecarboxaldehyde	
CGA259168	N-(4,5-dihydro-6-methyl-3,5-dioxo-1,2,4-triazine-4(2H)-yl)-acetamide	
CGA294849	4-amino-6-methyl-1,2,4-triazine-3,5(2H,4H)-dione	
CGA96956 (trigonelline)	1-methyl-3-pyridinecarboxylic acid	

GS23199	6-methyl-1,2,4-triazine-3,5(2H,4H)-dione	
CGA359009	4,5-dihydro-5-hydroxy-6-methyl-4-[(3-pyridinylmethylene)-amino]-1,2,4-triazine-3(2H)-one	
CGA215525	4-amino-6-methyl-1,2,4-triazine-3(2H)-one	
CGA300407 (nicotinaldehyde)	3-pyridinecarboxaldehyde	
CGA266591	2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid	

Animal metabolism

Information was available on metabolism of pymetrozine in laboratory animals, lactating goats and laying hens.

In the rat the extent of oral absorption is high (> 80%), based on urinary and biliary data. Pymetrozine is widely distributed in the body. High concentrations of both triazine- and pyridine-labelled material were found in the liver and kidney. The labelled material was rapidly excreted via urine (50–75% in 24 hours). Absorbed pymetrozine was extensively metabolized, with unmetabolized parent compound representing approximately 10% of the excreted radiolabel. Compounds containing both ring structures represented over 50% of the identified metabolites. The kinetics, excretion pattern, tissue distribution of radioactivity and metabolite profile were similar for both radiolabelled sites and administered dose levels as well as when the administration of radiolabelled pymetrozine was preceded by 14 days of administration of the unlabelled material (see WHO Monograph).

One study on the metabolism in lactating goats was available for each of the labels. Over four consecutive days the goats received daily doses of radiolabelled pyridine-¹⁴C- or triazine-¹⁴C-pymetrozine at rates equivalent to 7.5 ppm (0.39 mg/kg bw) or 10 ppm (0.54 mg/kg bw) in the diet, respectively. In both studies approximately 5-6% of the total dose was recovered from milk or tissues of the animals. Most of the administered radioactivity was recovered in faeces (15–17%) and urine (47–52%).

Following application of pyridine-¹⁴C-pymetrozine highest TRR levels were found in liver (1.5 mg eq./kg), kidney (0.72 mg eq./kg) and milk (0.33 mg eq./kg). Into muscle (0.068 mg eq./kg) and fat (0.027 mg eq./kg) the overall transfer of radioactivity was minor.

Parent pymetrozine was identified in all tissues and milk, however only in muscle (11% TRR) the contribution to the TRR was more than 10%. In tissues nicotinamide (CGA180778), which is formed by cleavage of the parent substance, was the major residue representing 44% TRR in muscle, 24% TRR in fat, 37% TRR in liver and 27% TRR in kidney.

In most tissues CGA313124 (pymetrozine-hydroxy) was also a major metabolite identified with levels of 10% TRR in muscle and 11% TRR in kidney. In milk, CGA313124 (36% TRR) and its phosphate conjugate (39% TRR) were the only major metabolites identified. In addition, I_{A17} was present in liver at 10% of the TRR.

For the triazine-¹⁴C-label again highest TRR levels were found in liver (1.1 mg eq./kg), kidney (0.57 mg eq./kg) and milk (0.45 mg eq./kg). Muscle (0.047 mg eq./kg) and fat (0.098 mg eq./kg) contained lower residues.

Unchanged pymetrozine was again found in all tissues and milk, but only in muscle as a major residue representing 10% of the TRR. In tissues CGA313124 was the dominant residue found in levels of 9.5% TRR in muscle, 25% TRR in fat, 5% TRR in liver and 15% TRR in kidney. In kidney 5U/I_{A2} was another major metabolite present at 12% of the TRR. Several triazine-based cleavage products were identified, however at individual levels below 10% TRR each.

In milk, again CGA313124 (40% TRR) and its phosphate conjugate (41% TRR) were the only major metabolites identified.

For laying hens groups of hens received daily doses of [pyridine-¹⁴C]-pymetrozine or [triazine-¹⁴C]-pymetrozine at rates equivalent to approximately 10 ppm for four consecutive days (0.79 mg/kg bw). The animals were sacrificed ca. 6 hours after the last dose. Approximately 0.4–1.3% of the total dose in both studies was recovered from eggs or tissues of the animals. Most of the radioactivity administered was found in the excreta (76–81% AR). Total radioactive residues were 0.006–0.016 mg eq./kg in eggs, 0.021–0.043 mg eq./kg in muscle, 0.019–0.024 mg eq./kg in fat, 0.16–0.54 mg eq./kg in kidney and 0.11–0.99 mg eq./kg in liver. For both labels parent pymetrozine was found in very low levels, not exceeding 5% of the TRR. In meat, fat and eggs yolk it was below the LOQ of the method or was undetected.

Following administration of the pyridine-¹⁴C-label, nicotinamide (CGA180778) was the major residue in meat (77% TRR), skin + fat (63% TRR), egg white (28% TRR) and liver (70% TRR). In kidney, nicotinic acid (CGA180777) was the major residue, representing 65% of the TRR. Further major metabolites identified were I_{A7}, present at levels of 17% TRR in skin + fat, 15% TRR in egg white and 13% TRR in kidney as well as CGA300407 with 11% TRR in egg white.

For the triazine-¹⁴C-label CGA259168 was the major residue in meat (39% TRR), skin + fat (24% TRR), egg white (45% TRR), egg yolk (13% TRR) and kidney (11% TRR). I_{A7} was mainly found in kidney (49% TRR), followed by liver (27% TRR), skin + fat (22% TRR) and egg white (11% TRR). The only other major metabolite found was CGA294849 present in meat at levels of 11% of the TRR.

In summary pymetrozine is quickly degraded in goats and hens. A large quantity of the parent molecule is cleaved, resulting in formation of nicotinic acid (up to 65% TRR) and nicotinamide (up to 70% TRR) for the pyridine-moiety and several metabolites for the triazine-moiety. Another important metabolic step is the oxidation of the parent to CGA313124, which is found in most tissues and mainly in milk, including its phosphate conjugate (up to 40% and 41% TRR, respectively).

In goats, I_{A17} represented up to 10% TRR in the liver. In hen tissues, pymetrozine is also metabolised into I_{A7} (13–41% TRR in fat, egg white and kidney). Both metabolites were not identified in the rat.

Plant metabolism

The Meeting received plant metabolism studies for pymetrozine following foliar application of either [pyridine-¹⁴C]-pymetrozine or [triazine-¹⁴C]-pymetrozine to tomatoes (protected), potatoes, paddy rice and cotton (protected). For paddy rice, the metabolism following granular application was also investigated.

Following foliar application of [pyridine-¹⁴C]-pymetrozine to tomatoes at rates of 2×0.25 kg ai/ha, total radioactive residues in the fruits declined from 1 mg eq./kg (1h) to 0.23 mg eq./kg (7 days) and finally to 0.016 mg eq./kg 27 days after the last application. In the leaves corresponding TRR levels were 14 mg eq./kg (1 hour), 7.4 mg eq./kg (7 days) and 2.4 mg eq./kg (27 days).

In the samples collected directly after treatment (1 hour), pymetrozine located in the fruit and leaf surface was the dominant residue, representing 78% TRR and 60% TRR, respectively.

After 15 days, the pymetrozine surface residues declined to 5.9% TRR in the fruits and 16% TRR in the leaves. Most of the radioactivity was recovered in the extracts. In the fruits, trigonelline (CGA96956) was the only major residue representing 70% of the TRR. In leaves, trigonelline (26% TRR) and sugar conjugates of CGA128632 (23% TRR) were major residues besides the parent.

[Triazine-¹⁴C]-pymetrozine was applied to tomato plants with three foliar application with 0.47 kg ai/ha each. In the fruits collected (3, 7 and 14 days after treatment) TRR levels were 0.51–0.58 mg eq./kg. In the leaves TRR levels declined from 28 mg eq./kg (3 d) to 22 mg eq./kg (7 days) and finally to 17 mg eq./kg (14 days).

In all samples unchanged pymetrozine was the major residues, representing 32–57% TRR in the fruits and 31–50% TRR in the leaves. The only other major metabolite identified was CGA294849 present at levels of 14% TRR in fruits collected 14 days after harvest.

In the first study investigating the metabolism of pymetrozine in potatoes either [pyridine-¹⁴C]- or [triazine-¹⁴C]-pymetrozine were applied to potato plants with three foliar sprayings at rates of 0.15 kg ai/ha (low-dose) or 1.05 kg ai/ha (high-dose) each 61 days after planting. In the foliage samples collected after 7, 14 and 19 days TRR levels were 6.4–11.7 mg eq./kg following low-dose and 29–46 mg eq./kg following high-dose treatment. In the tubers TRR levels amounted 0.11–0.36 mg eq./kg (low-dose) and 0.34–1.1 mg eq./kg (high-dose).

For the [pyridine-¹⁴C]-label, trigonelline (CGA96956) was the major residue in tubers (7, 14 and 29 days after last treatment) representing 54–75% of the TRR. In addition, nicotinic acid (CGA180777) and its glycoside represented major residues present up to 22% of the TRR. Unchanged parent pymetrozine was detected in all samples, however its levels did not exceed 2.2% of the TRR. No further major metabolites were identified in the tubers.

In the foliage, unchanged pymetrozine was present at higher levels of up to 18% TRR in day 7 samples. The only major metabolite present was CGA128632 and its glycoside, representing 1.1–3.1% TRR and 9.5–18% TRR, respectively. The major part of the radioactivity in the foliage remained unextracted (54–70% TRR).

For the [triazine-¹⁴C]-label, neither parent (0.2–4.9% TRR) nor metabolites (up to 5.7% TRR) represented major residues in tubers. Most of the radioactivity was distributed into multiple minor fractions too low for identification. The foliage showed GS23199 (1.4–2.4% TRR) and its glycoside (7.6–16% TRR) as major residues. Parent pymetrozine was found in lower amounts of 6.3–10% of the TRR. Again, the amount of unextracted radioactivity in the foliage was high, representing 37–45% of the TRR.

In two additional studies either [pyridine-¹⁴C]- or [triazine-¹⁴C]-pymetrozine were applied to potato plants with two foliar sprayings at rates of 0.2 kg ai/ha each. In the leaves, residues declined from 9.5–11 mg eq./kg (1h after treatment) to 1.3–1.8 mg eq./kg (55 days, final harvest). Special investigation of radioactive residues in new leaves above or below the treated plant parts reveals

approximately 3–4 times higher residues on the upper leaves than in the lower leaves. In tuber collected 55 days after the final application, TRR levels were 0.051–0.072 mg eq./kg.

The identification of the radioactivity in the tubers showed no pymetrozine above the LOQ of 0.001 mg eq./kg. The only major residues identified were nicotinic acid (CGA180777) and its glycoside for the pyridine-label (22 and 29% TRR, respectively) and GS23199 (11% TRR) and its glycoside (1.7% TRR) for the triazine-label.

In the foliage pymetrozine was the dominant residue directly after treatment (42–58% TRR). In samples collected after longer intervals, the radioactivity was distributed into several minor fractions mostly too low for identification. The only identified major metabolite was conjugated CGA128632 (up to 28% TRR) for the pyridine-label. Unextracted radioactivity in potato foliage averaged at 36% TRR for both labels.

Paddy rice was treated with either [pyridine-¹⁴C]- or [triazine-¹⁴C]-pymetrozine with one foliar treatment of 0.25 kg ai/ha 45 days before harvest. TRR levels found were 1.7–2.1 mg eq./kg in foliage (19 days after treatment), 5.3–6.3 mg eq./kg in straw and 0.14–0.24 mg eq./kg in grain (both samples 45 days after treatment).

The identification of the radioactivity in foliage and straw showed unchanged pymetrozine as the only major residue, representing 86–89 % TRR and 63–74% TRR, respectively.

In the grain no metabolites were identified exceeding 10% TRR. The parent substance was detected in all samples, however its levels were low (0.8–2.3% TRR). In the grain 63–86% of the TRR remained unextracted.

In addition paddy rice was treated with granules of [pyridine-¹⁴C]- or [triazine-¹⁴C]-pymetrozine at rates corresponding to 0.6 kg ai/ha to seedling boxes. Foliage was collected 1, 41 and 69 days later, grain husks and straw at maturity after 116 days.

Total radioactive residues were highest in foliage directly after treatment with 33–42 mg eq./kg and declined to 0.72–0.82 mg eq./kg after 69 days. At harvest dry straw contained TRR levels of 2.6 mg eq./kg. In the grain the radioactivity was much lower, representing 0.21–0.52 mg eq./kg.

In the foliage parent pymetrozine was the major residue directly after treatment (1 day, 38–60% TRR), but quickly declined to < 10% TRR in all other samples collected after a longer interval. In grain, pymetrozine was not found above the LOQ of 0.001 mg eq./kg (0.2% TRR).

Major metabolites identified in foliage and straw after application of pyridine-¹⁴C-pymetrozine were trigonelline (CGA96956) with 9.5–28% TRR and free and conjugated nicotinic acid (CGA180777) with a total of 17–26% TRR. For the triazine-¹⁴C-label no metabolites exceeding 10% of the TRR were identified except for CGA359009 (15% TRR) and GS23199 (17% TRR) in foliage samples one day after treatment.

Grain contained very few identified metabolites. The only major metabolites were trigonelline (CGA96956, 11% TRR) and free and conjugated nicotinic acid (CGA180777, 26% TRR). Most of the radioactivity in grain remained unextracted (56–86% TRR).

The metabolism of pymetrozine in cotton was investigated by application of either [pyridine-¹⁴C]- or [triazine-¹⁴C]-labelled active substance under glasshouse conditions. The plants were treated with two foliar spraying at rates equivalent to 0.2 kg ai/ha each. After 93 days samples of treated leaves (0.6–5.9 mg eq./kg), new grown leaves (0.03–0.2 mg eq./kg), stem (1.6–1.7 mg eq./kg), hulls (2.7–4.8 mg eq./kg) fibres (0.065–0.17 mg eq./kg) and seeds (0.043–0.21 mg eq./kg) were collected.

For the [pyridine-¹⁴C]-label unchanged pymetrozine was the major residue in all green plant parts, hulls and fibres, representing 28–83% of the TRR. The only metabolite exceeding 10% of the TRR in the plant was trigonelline (CGA96956, 0.6–23% TRR). In the seeds pymetrozine was detected at levels of 7.4–9% of the TRR. Most of the parent substance (35–58%) was found in cotton oil extracted from the seeds. The major residues in the seeds was trigonelline (CGA96956), representing 50% of the TRR.

For the [triazine-¹⁴C]-label only pymetrozine was present in major amount in the plant (28–66% TRR). Minor residues identified were CGA294849 and GS23199 (< 4% TRR each). In the seeds pymetrozine was present at TRR levels of 7.4%. On processing of seeds, 35% of the parent substance was recovered in the oil.

In summary pymetrozine is deposited on the plant surface and more or less quickly adsorbed. Unchanged parent represented 7.4–75% of the TRR in treated parts. In the plant tissue, the active substance is quickly degraded by cleavage, forming nicotinic acid, nicotinamide or trigonelline from the pyridine-moiety. Additional major metabolites found were CGA359009 (rice: 15% TRR), GS23199 including conjugates (potato tuber: 13% TRR; potato foliage: 18% TRR; rice: 17% TRR) and CGA294849 (tomato fruits: 14% TRR).

CGA128632 including its conjugates, which were major metabolites in tomato foliage (23% TRR) and potato foliage (up to 36% TRR) were not identified in the rat.

Environmental fate in soil

The Meeting received information on the fate of pymetrozine under aqueous hydrolysis. In addition, the Meeting received information on the uptake and metabolism of pymetrozine in rotational crops under confined and field conditions.

Hydrolysis in aqueous buffer solutions revealed a moderate to quick decline of the parent under acidic conditions (pH5 or less) while samples at pH 7 and pH 9 were stable (> 90% remaining). The major degradation products identified were CGA300407 for the pyridine-label and CGA215525 for the triazine-label, which are formed by direct cleavage of the parent molecule.

Confined rotational crop studies on mustard greens, radish and wheat were conducted at rates equivalent to a soil application of 0.41 kg ai/ha using either [pyridine-¹⁴C]- or [triazine-¹⁴C]-pymetrozine. Plantback intervals were 30, 60, 90, 120 and 360 days. Total radioactive residues in edible commodities were in the range of 0.018–0.049 mg eq./kg (wheat grain), 0.025–0.13 mg eq./kg (mustard leaves) and 0.026–0.061 mg eq./kg (radish tubers) for [triazine-6-¹⁴C]-pymetrozine and of 0.036–0.11 mg eq./kg (wheat grain), 0.011–0.053 mg eq./kg (mustard leaves) and 0.014–0.042 mg eq./kg (radish tubers) for [pyridine-5-¹⁴C]-pymetrozine. In potential feed items TRR levels were 0.047–0.48 mg eq./kg and 0.021–0.23 mg eq./kg in wheat forage and fodder for [triazine-6-¹⁴C]- and [pyridine-5-¹⁴C]-label, respectively.

In all crop samples unchanged pymetrozine was found in minor amounts not exceeding 10% of the TRR. Highest concentrations were found in wheat forage (0.011 mg/kg) while all other matrices with detected residues gave concentrations between 0.001 mg/kg and 0.01 mg/kg.

In crops planted in soil treated with [pyridine-¹⁴C]-pymetrozine nicotinic acid incl. its glycoside (CGA180777, up to 24% TRR or 0.016 mg eq./kg), trigonelline (CGA96956, up to 32% TRR or 0.021 mg eq./kg), nicotinamide (CGA180778, up to 17% TRR, 0.005 mg eq./kg) and CGA-128632-glycoside (up to 11% TRR, 0.011 mg eq./kg) were found as major metabolites.

After application of [triazine-¹⁴C]-pymetrozine most of the radioactivity was represented by GS23199 and its glycosides (total up to 39% TRR or 0.056 mg eq./kg in wheat forage) or CGA266591 (up to 34% TRR or 0.027 mg eq./kg).

For longer plantback intervals, unextracted radioactivity increased ranging from 19–78% TRR.

Two additional studies investigating the uptake of total radioactive residues from the soil, either [pyridine-¹⁴C]- or [triazine-¹⁴C]-pymetrozine were applied to bare soil at rates equivalent to 0.5 kg ai/ha. Lettuce, wheat, sugar beet and maize were cultivated as succeeding crops after plantback intervals of 63, 91 or 307 days.

TRR levels found in the various matrices were low. In edible commodities TRR levels from all plantback intervals were between 0.002–0.01 mg eq./kg. In feed commodities TRR levels ranged up to 0.061 mg eq./kg in wheat straw.

Field rotational crop studies were conducted on four locations in the USA. Pymetrozine was applied to either tomatoes, peppers, cucumbers or lettuce at rates of 4×0.1 kg ai/ha (7 day interval). After 30 days the crop was destroyed and wheat, turnips or lettuce were planted as rotational crops. In all samples collected (mature and immature) no pymetrozine or GS23199 above their LOQ of 0.02 mg/kg were found. However, for GS23199 no hydrolysis step was conducted to release conjugates, which posed the main part of total GS23199 identified in confined rotational crop studies.

In summary the Meeting concluded that the transfer of residues into rotational crops is low. Parent pymetrozine is quickly degraded, not resulting in significant residues at harvest.

The metabolite GS23199, mainly present as sugar-conjugate, was the major residue in most samples (up to 39% TRR). Its concentrations ranged up to a maximum of 0.056 mg eq./kg in wheat forage. In edible commodities highest residues were found in mustard leaves amounting 0.008 mg eq./kg. Approximating the maximum seasonal application rate of 0.45 kg ai/ha based on the submitted GAPs and the involved interception of the treated crop, the Meeting concluded that no residues of GS23199 (including its sugar conjugate) above 0.01 mg/kg are expected in edible commodities obtained from rotational crops.

Other potential metabolites formed are either identical to naturally occurring substances (CGA180777 and CGA180778) or also present at levels below 0.01 mg/kg under confined conditions (e.g., CGA266591).

Methods of residue analysis

The Meeting received analytical methods for the analysis of pymetrozine in plant and animal matrices. The basic principle employs extraction by homogenisation with aqueous borate buffer/methanol or n-hexane with acetonitrile/water partitioning for fatty samples. The extracts were cleaned by C18 solid-phase extraction. Residues are determined by liquid chromatography (LC) in combination with tandem mass spectroscopy (MS/MS) or UV (300 nm). The methods submitted are suitable for measuring residues with a LOQ of 0.01 mg/kg (LC-MS/MS) to 0.02 (HPLC-UV).

In addition specialised methods using LC-MS/MS methods for measuring the metabolites CGA300407 (LOQ: 0.005 mg/kg, high water and acidic matrices) and CGA313124 (LOQ: 0.01 mg/kg, animal matrices) were submitted.

The application of multi-residue methods was not tested.

In-trial validation of the analytical methods submitted was achieved at LOQs of 0.001 mg/kg up to 0.05 mg/kg, depending on the matrix.

Stability of residues in stored analytical samples

The Meeting received information on the storage stability of pymetrozine in plant and animal matrices. In addition the storage stability of GS23911 was investigated in plant matrices and the storage stability of CGA313124 in animal matrices.

Plant matrices

In fortified samples, depending on the matrix, parent pymetrozine decomposes rather quickly. In different studies the following intervals were identified, which showed at least 70% of the initial pymetrozine concentration:

Oranges	at least 24 months
Peaches	up to 1 month

Tomato, fruits	up to 6 months
Tomato, paste	up to 6 months
Cucumbers	up to 2 months
Melons	at least 24 months
Lettuce	up to 1 month
Potatoes	up to 1 month
Cottonseed	at least 25 months
Cotton oil	at least 24 months
Hops, dry	at least 12 months

The Meeting noted that pymetrozine residues may degrade in stored samples, however the rate differs strongly depending on the specific commodity. No reasons for the observed degradation could be identified. Due to the inconsistency within commodity groups (e.g., like for cucurbits), specific data on the storage stability for each commodity is required.

In addition to the maximum storage intervals listed above, the Meeting noted that pymetrozine residues were stable for a period of up to one month in all fortified samples and decided that supervised field trial data analysed within one month are suitable for an estimation.

One study investigating the storage stability of incurred residues in plant commodities was submitted involving re-analysis for stored samples after 8–13 months. However, since the initial analysis of the samples was performed after 9–14 months, which is longer than the maximum storage interval identified, the data was not considered appropriate to conclude on the overall stability of the residue.

For the metabolite GS23911 no degradation was observed in stored plant matrices within 24 months (cucumber, tomato fruit + paste, cotton seed + oil, hops dry).

Animal matrices

In fortified samples of animal origin, pymetrozine showed a significant degradation after 6 months in muscle and after 12 months in liver. The metabolite CGA313124 was also tested and was stable for up to 3 months in muscle and a maximum of 6 months in liver. In milk, both analytes proved stable for at least 18 months.

Definition of the residue

Livestock animal metabolism studies were conducted on laying hens (10 ppm) and lactating goats (7.5–10 ppm).

Nicotinic acid (CGA180777) and nicotinamide (CGA180778) were identified as major residues (up to 77% TRR) in livestock animals, however due to their natural occurrence (Vitamin B group) they are not suitable as a marker substance for enforcement purposes in animal commodities. Parent pymetrozine was present in all goat tissues, most hen tissues and eggs (for eggs triazine-label only), however only in low amounts up to 11% TRR. In milk no parent pymetrozine was found. Nearly the entire residue was identified as CGA313124 and its phosphate conjugate. The Meeting recognized that pymetrozine is strongly metabolized in livestock animals. However, being the only representative analyte in most commodities, the Meeting concluded that parent pymetrozine is a suitable marker for the purpose of MRL setting in animal tissues and eggs. For milk, the residue for enforcement purposes is defined as CGA313124. Analytical methods are capable of measuring pymetrozine in animal matrices and CGA313124 in milk at LOQs of 0.01 mg/kg each.

For the estimation of the dietary intake nicotinic acid (CGA180777) and nicotinamide (CGA180778) add to natural background levels of the vitamin B group and are not considered relevant. Apart from these analytes, pymetrozine gave highest residues in goat tissues (except kidney) and CGA313124 (incl. its phosphate conjugate) in milk and kidney. CGA313124 was identified in the rat metabolism and is covered by the toxicological reference values for the parent substance. The Meeting concluded that pymetrozine is the relevant residue in mammalian tissues while CGA313124 (incl. its phosphate conjugate) is relevant for milk.

In hens tissues and eggs CGA259168 (up to 45% TRR), I_{A7} (up to 49% TRR) and CGA294849 (up to 11% TRR) were major residues present at concentrations up to 0.079 mg eq./kg at 10 ppm dose. Parent pymetrozine itself was a minor residue in all samples. CGA294849 was identified as a minor metabolite in hens muscle and liver, representing up to 9% of TRR. The Meeting concluded, that parent pymetrozine is a relevant residue for the dietary intake of poultry tissues and eggs.

The significance of the animal metabolites CGA245342, CGA294849, I_{A7} and I_{A17} was assessed with the TTC approach based on exposure levels related to the uses evaluated. Exposure to I_{A17} did not exceed the TTC value for chronic exposure of 0.0025 µg/kg bw per day (EMEA for genotoxic impurities) as well as the single-exposure TTC of 0.2 µg/kg bw. CGA245342 and I_{A7} gave estimated exposure levels below 1.5 µg/kg bw per day (Cramer Class III), respectively. Based on the assessed uses, these metabolites are not considered relevant for the dietary intake.

CGA294849 was also assessed with the TTC approach with the major part of the exposure resulting from plant commodities. CGA294849 has a structural alert for genotoxicity but has not been tested. Since the exposure assessment exceeded the applicable TTC values, no conclusion on the relevance of CGA294849 for dietary intake assessment can be made.

In all samples residue concentrations in fat tissues were in the same order of magnitude as in muscle tissues. The log P_{ow} of pymetrozine is < 0. The Meeting decided that residues of pymetrozine are not fat soluble.

In plants following foliar treatment, pymetrozine was the major residue in plant parts directly contacted, representing 28–89% of the TRR. The major degradation products in all matrices were either trigonelline (CGA96956) present at level between 9–70% of the TRR or nicotinic acid (CGA180777) present up to 26% TRR, depending on the label. The pyridine-cleavage product CGA128632 (including sugar conjugates) was a major metabolite in tomato fruits (11% TRR) and in tomato and potato foliage (up to 26% TRR). The counterpart for the triazine-moiety was identified as GS23199 (including sugar conjugates) representing 11–18% of the TRR in rice straw and potato foliage. The metabolic pattern in rotational crops was comparable to the degradation products identified in primary treated crops.

The Meeting concluded that pymetrozine is present in major amounts in most plant matrices and therefore qualifies as a marker substance for enforcement purposes. The major plant metabolites trigonelline (CGA96956) and nicotinic acid (CGA180777) occur naturally in plants and are unspecific markers for the residue. Analytical methods are capable of measuring pymetrozine in all plant matrices at a LOQ of 0.01 mg/kg.

For dietary intake purposes nicotinic acid (CGA180777) and trigonelline (CGA96956) add insignificantly to natural background levels. The Meeting noted that no metabolism study on leafy crops was submitted. In the foliage of tomatoes and potatoes used as a substitute, the cleavage products CGA128632 (up to 26% TRR) and GS23199 (up to 18% TRR) and their sugar conjugates were major residues. However, CGA128632 was not found in rats. In addition, CGA294849 was found in tomato fruit representing 7.4% TRR after 3 days increasing to 14% TRR after 14 days.

The Meeting also noted that pymetrozine may degrade under acidic food processing condition, resulting in the formation of CGA300407 (up to 42% TRR), based on hydrolysis data for pyridine-labelled active substance. The hydrolysis of triazine-labelled active substance conducted at

pH5 (25 °C and 75 °C), showed CGA215525 as the major degradation product (up to 48% TRR). No data on hydrolysis under simulated processing conditions were submitted for the triazine-label.

Besides parent pymetrozine, which is a major residue in plant commodities and should to be taken into account for dietary intake assessment, the relevance of the plant metabolites GS23199, CGA128632 and CGA294849 as well as of the degradation products formed during processing (CGA215525 and CGA300407) was assessed with the TTC approach.

Based on the exposure levels (IEDI and IESTI) estimated for the uses evaluated, GS23199 (Cramer Class III) and CGA215525 (Cramer Class III) were not considered relevant for dietary intake.

CGA128632 has therapeutic uses as a vasodilator with a minimal therapeutic dose of 1 mg/kg bw. In view of the margin compared to the estimated exposure levels (> 1000 to the IEDI and > 50 to the maximum IESTI), CGA128632 is not considered a relevant metabolite of pymetrozine for dietary intake.

CGA294849 was also assessed with the TTC approach with the major part of the exposure resulting from plant commodities. CGA294849 has a structural alert for genotoxicity but has not been tested. Since the exposure assessment exceeded the applicable TTC values, no conclusion on the relevance of CGA294849 for dietary intake assessment can be made.

The processing degradate CGA300407 does not have a structural alert for genotoxicity but the Meeting was made aware that positive genotoxicity results, in vitro and in vivo, exist for this compound. No conclusion on the relevance of CGA300407 can be made.

If future uses for pymetrozine result in changes of the dietary intake, reconsideration on the relevance of metabolites in plant and animal matrices and after processing may become necessary.

Definition of the residue for compliance with MRL for plant commodities, mammalian tissues, poultry tissues and eggs: *pymetrozine*

Definition of the residue for compliance with MRL for milk: *CGA313124 (4,5-dihydro-6-hydroxymethyl-4-[(3-pyridinyl-methylene)amino]-1,2,4-triazine-3(2H)-one)*

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

The residue is not fat-soluble.

Results of supervised residue trials on crops

The Meeting received supervised trial data for applications of pymetrozine on various fruit and vegetables crops as well as for oilseeds and rice conducted in China, Europe and the USA.

The Meeting recognized that pymetrozine may degrade under freezer storage conditions. All supervised field trials exceeding the maximum storage interval identified for the specific commodities are not taken into account for the evaluation of GAPs and the resulting residues. In addition residues of pymetrozine were considered stable in all plant commodities for maximum storage period of one month.

Citrus fruits

Pymetrozine is registered in Portugal for the use on citrus fruit at rates of 1×0.01 kg ai/hL with a PHI of 21 days. Supervised field trials conducted in the Europe according to this GAP were submitted.

In lemons (whole fruits) residues of pymetrozine were (n=4): 0.02, 0.02, 0.03, 0.07 mg/kg.

In mandarins (whole fruits) residues of pymetrozine were (n=4): < 0.02, 0.02, 0.03, 0.03 mg/kg.

In oranges (whole fruits) residues of pymetrozine were (n=13): 0.006, 0.007, 0.01, 0.012, < 0.02, 0.02(4), 0.03, 0.04, 0.05 and 0.06 mg/kg.

The Meeting noted that pymetrozine is registered in Portugal for the whole citrus group. Supervised field trials on oranges, lemons and mandarins indicated no significant difference in the datasets (Kruskal-Wallis-Testing). Therefore the Meeting decided to extend its estimations on the whole group of citrus fruits based on the combined dataset from all three commodities:

Pymetrozine residues in citrus fruits (n=21): 0.006, 0.007, 0.01, 0.012, < 0.02, < 0.02, 0.02(7), 0.03(4), 0.04, 0.05, 0.06 and 0.07 mg/kg.

In the pulp (flesh) corresponding residues were (n=21): < 0.005(4) and < 0.02(17) mg/kg.

The Meeting estimated a maximum residues level of 0.15 mg/kg for pymetrozine in citrus fruit and a median and highest residue of 0.02 mg/kg in citrus pulp.

Pome fruit

Pymetrozine is registered in Italy for the use on apples and pears at a rate of 1×0.25 kg ai/ha with a PHI of 14 days. Supervised field trials conducted in Italy according to this GAP were submitted.

However, the Meeting noted that for pome fruit no data on the storage stability were provided. In view of the general degradation of pymetrozine in stored commodities, specific data on the storage stability in pome fruits is required to assess the validity of the supervised field trials.

Apricot

Pymetrozine is registered in Belgium for use on apricots at the rate of 2×0.1 kg ai/ha with a PHI of 21 days. Supervised field trials were conducted in Europe at rates of 3×0.25 kg ai/ha.

The supervised field trials submitted for apricots were all conducted as decline studies. Since the active substance almost completely degraded within the 21 days investigated, the Meeting concluded that the additional treatment in comparison to the GAP from Belgium has no influence on the residue concentrations at harvest, allowing the use of the proportionality approach to adjust for the higher application rates involved.

Pymetrozine residues in apricots treated with 3×0.25 kg ai/ha were (n=4): < 0.01(3) and 0.01 mg/kg.

Under consideration of a proportionality factor of 0.4 (0.1 kg ai/ha divided by 0.25 kg ai/ha), scaled residues were (n=4): 0.004 and < 0.01(3) mg/kg.

Based on scaled residues from Europe, the Meeting estimated a maximum residues level of 0.01 mg/kg and a median and highest residue of 0.01 mg/kg for pymetrozine in apricots.

Peach and nectarines

Pymetrozine is registered in Spain for the use on peach and nectarines at the rate of 2×0.25 kg ai/ha with a PHI of 14 days. Supervised field trials were conducted in Europe at rates of 3×0.25 kg ai/ha.

The supervised field trials submitted for peaches were all conducted with one additional application compared to the GAP. However, taking into account low residues in samples analysed directly before the final treatment and the results from decline studies on peaches, the Meeting concluded that the additional treatment does not add significantly to the residue concentrations at harvest.

Pymetrozine residues in peach (n=6): < 0.01(4), 0.04, 0.04 mg/kg.

Based on the dataset on peach the Meeting estimated a maximum residues level of 0.07 mg/kg, a median residue of 0.01 mg/kg and a highest residue of 0.04 mg/kg for pymetrozine in peach. The Meeting decided to extrapolate the estimations also to nectarines.

Strawberries

Pymetrozine is registered in Belgium for the use on field and protected strawberries at the rate of 3×0.2 kg ai/ha with a PHI of 3 days. Supervised field trials conducted in United Kingdom matching the GAP were submitted.

Pymetrozine residues in field strawberries were (n=2): 0.02 and 0.06 mg/kg.

Pymetrozine residues in protected strawberries were (n=2): 0.12 mg/kg.

The Meeting concluded that the data submitted for the use of pymetrozine on strawberries was insufficient for a maximum residue level estimation.

Broccoli

Pymetrozine is registered in Belgium for the use on broccoli at rates of 3×0.2 kg ai/ha with a PHI of 14 days. Supervised field trials conducted in Switzerland and United Kingdom matching the GAP were submitted.

However, the Meeting noted that for broccoli no data on the storage stability were provided. In view of the general degradation of pymetrozine in stored commodities, specific data on the storage stability in broccoli is required to assess the validity of the supervised field trials.

Cauliflower

Pymetrozine is registered in Belgium for the use on cauliflower at rates of 3×0.2 kg ai/ha with a PHI of 14 days. Supervised field trials conducted in France and Switzerland matching the GAP were submitted, however all samples were cut into segments at harvest before storage.

In 2013 the JMPR pointed out that cutting of large commodities in the field is against the recommended Codex sampling procedure and may cause problems due to an enhanced degradation of the residue. Testing strategies to investigate the stability of the residue were outlined in the 2013 JMPR Report. However, for pymetrozine such data was not submitted. In view of the short interval of the storage stability in various matrices, the possible effect of cutting cannot be assessed.

The Meeting decided that the data on cauliflower is invalid for recommendations of maximum residue levels for pymetrozine.

Head cabbage

Pymetrozine is registered in Germany for the use on head cabbage at rates of 3×0.2 kg ai/ha with a PHI of 7 days. Supervised field trials conducted in Europe matching the GAP were submitted. However some of the samples were cut into segments at harvest before storage, making them invalid for the assessment (see cauliflower).

In Portugal the use of pymetrozine is registered on head cabbage at rates of 3×0.2 kg ai/ha with a PHI of 14 days. Supervised field trials conducted in Europe matching the GAP were submitted.

However, the Meeting noted that for cabbages no data on the storage stability were provided. In view of the general degradation of pymetrozine in stored commodities, specific data on the storage stability in head cabbage is required to assess the validity of the supervised field trials.

Cucumbers

Pymetrozine is registered in Greece for the use on protected cucumbers at rates of 2×0.45 kg ai/ha with a PHI of 3 days. Residue data from Europe under protected conditions matching GAP application rates were submitted.

However, the supervised field trials submitted for cucumbers were all conducted with one additional application compared to the GAP. Taking into account the low residues in samples analysed directly before the final treatment and the results from decline studies on cucumbers, the Meeting concluded that the additional treatment does not add significantly to the residue concentrations at harvest.

Pymetrozine residues in cucumbers (n=8): 0.045, 0.07, 0.08, 0.083, 0.088, 0.09, 0.11 and 0.21 mg/kg.

Four additional trials on cucumbers matching the GAP from Greece were reported, but the samples were stored 3-10 months before analysis, which is longer than the maximum storage interval of 2 month for pymetrozine in cucumbers.

The Meeting estimated a maximum residues level of 0.3 mg/kg, a median residue of 0.0855 mg/kg and a highest residue of 0.21 mg/kg for pymetrozine in cucumbers.

Melons

Pymetrozine is registered in Portugal for the use on protected melons at rates of 3×0.3 kg ai/ha with a PHI of 3 days. Supervised field trials conducted in Europe matching the GAP were submitted. However some of the samples were cut into segments at harvest before storage, making them invalid for the assessment (see cauliflower). Residues in the remaining trials were:

Pymetrozine residues in whole melon fruits (n=2): 0.045 and 0.16 mg/kg.

The Meeting concluded that the data submitted for the use of pymetrozine on melons was insufficient for a maximum residue level estimation.

Peppers, sweet

Pymetrozine is registered in Czech Republic for the use on protected sweet peppers at rates of 3×0.36 kg ai/ha with a PHI of 3 days. Supervised field trials conducted in Europe under protected conditions matching the GAP were submitted.

Pymetrozine residues in protected sweet peppers (n=8): 0.16, 0.43, 0.43, 0.54, 0.64, 0.83, 1.1 and 1.4 mg/kg.

The Meeting estimated a maximum residues level of 3 mg/kg, a median residue of 0.59 mg/kg and an highest residue of 1.4 mg/kg for pymetrozine in pepper, sweet.

Tomatoes

Pymetrozine is registered in The Netherlands for the use on protected tomatoes at rates of 3×0.45 kg ai/ha with a PHI of 1 day. Supervised field trials conducted in Europe under protected conditions matching the GAP were submitted.

Pymetrozine residues in protected tomato fruits (n=8): 0.08, 0.14, 0.18, 0.27, 0.3, 0.33, 0.39 and 0.77 mg/kg.

The Meeting estimated a maximum residues level of 1.5 mg/kg, a median residue of 0.285 mg/kg and a highest residue of 0.77 mg/kg for pymetrozine in tomatoes.

Leafy vegetables, except brassica leafy vegetables

Pymetrozine is registered in the USA for the use on leafy vegetables at rates of 2×0.1 kg ai/ha with a PHI of 7 days. Supervised field trials conducted in the USA on head lettuce, leaf lettuce and spinach matching the GAP were submitted. However, most of the trials were stored for more than 1 month, which was identified as the maximum storage interval without a significant degradation of the residues. The results from trials analysed within this interval were:

Pymetrozine residues in head lettuce (n=2): < 0.02 and 0.1 mg/kg.

The Meeting concluded that the data submitted for the use of pymetrozine on leafy vegetables, except brassica leafy vegetables, was insufficient for a maximum residue level estimation.

Potatoes

Pymetrozine is registered in the United Kingdom for the use on potatoes at rates of 2×0.15 kg ai/ha with a PHI of 7 days. Supervised field trials conducted in Northern Europe at a higher rate of 2×0.2 kg ai/ha were submitted.

Pymetrozine residues in potato tubers (n=4): $< 0.01(4)$ mg/kg.

The Meeting concluded that the data submitted for the use of pymetrozine on potatoes was insufficient for a maximum residue level estimation.

Asparagus

Pymetrozine is registered in the USA for the use on asparagus in vegetative state at rates of 6×0.1 kg ai/ha to the mature ferns with a PHI of 170 days. Supervised field trials conducted in the USA on asparagus treated with rates of 3×0.19 kg ai/ha were submitted involving PHIs of 172-267 days. The results were:

Pymetrozine residues in asparagus (n=6): $< 0.02(6)$ mg/kg.

Although samples of asparagus were stored longer than the maximum storage interval of 1 month for this commodity, the Meeting concluded to make estimations for the commodity. Taking into account the insignificant amounts of pymetrozine found in samples from confined rotational crop studies and the long interval between treatment and harvest without a direct application to the harvested commodity, the Meeting estimated a maximum residues level of 0.02^* mg/kg and a median and highest residue of 0 mg/kg for pymetrozine in asparagus.

Celery

Pymetrozine is registered in the USA for the use on celery at rates of 2×0.1 kg ai/ha with a PHI of 7 days. Supervised field trials conducted in the USA matching the GAP were submitted.

However, the Meeting noted that for celery no data on the storage stability were provided. In view of the general degradation of pymetrozine in stored commodities, specific data on the storage stability in celery is required to assess the validity of the supervised field trials.

Artichoke, globe

Pymetrozine is registered in France for the use on globe artichokes at rates of 2×0.2 kg ai/ha with a PHI of 14 days. Supervised field trials conducted in France matching the GAP were submitted.

Pymetrozine residues in artichokes (n=3): $< 0.02(3)$ mg/kg.

The Meeting concluded that the data submitted for the use of pymetrozine on artichoke is insufficient for a maximum residue level estimation.

Rice

Pymetrozine is registered in China for the use on rice at rates of 2×0.15 kg ai/ha with a PHI of 14 days. Supervised field trials conducted in China matching the GAP were submitted.

However, in the supervised field trials no data on the maximum storage interval between sampling and analysis were reported. In addition, storage stability data for cereal commodities was not provided, denying an assessment on the validity of the trials.

The Meeting concluded that the data submitted for the use of pymetrozine on rice is insufficient for a maximum residue level estimation.

Pecan

Pymetrozine is registered in the USA for the use on pecans at rates of 2×0.14 kg ai/ha with a PHI of 14 days. Supervised field trials conducted in the USA matching the GAP were submitted.

However, the Meeting noted that for pecan no data on the storage stability were provided. In view of the general degradation of pymetrozine in stored commodities, specific data on the storage stability in pecan is required to assess the validity of the supervised field trials.

Chestnut, hazelnut and walnut

Pymetrozine is registered in France for the use on chestnut, hazelnut and walnut at rates of 2×0.1 kg ai/ha with a PHI of 14 days. Supervised field trials on walnuts conducted in France matching the GAP were submitted.

However, the Meeting noted that for chestnuts, hazelnuts or walnuts no data on the storage stability were provided. In view of the general degradation of pymetrozine in stored commodities, specific data on the storage stability for respective commodities is required to assess the validity of the supervised field trials.

Rape

Pymetrozine is registered in Belgium, France and Germany for the use on oilseed rape rates of 1×0.075 kg ai/ha at BBCH 59 (first petals visible, flower buds still closed). The PHI is covered by the growth stage. Supervised field trials conducted in Northern and Southern Europe at slightly exaggerated rates of 1×0.1 kg ai/ha were submitted.

However, the Meeting noted that for rape seeds no data on the storage stability were provided. In view of the general degradation of pymetrozine in stored commodities, specific data on the storage stability in rape seeds is required to assess the validity of the supervised field trials.

Cotton

Pymetrozine is registered in Greece for the use on cotton rates of 2×0.2 kg ai/ha with a PHI of 35 days. Supervised field trials conducted in Southern Europe matching the registered application rate but with one additional treatment were submitted.

Pymetrozine residues in delinted seeds (n=6): $< 0.02(6)$ mg/kg.

The Meeting estimated a maximum residues level of 0.02 mg/kg and a median residue of 0.02 mg/kg for pymetrozine in cotton seeds.

Animal feeds

Rice straw

Pymetrozine is registered in China for the use on rice at rates of 2×0.15 kg ai/ha with a PHI of 14 days. Supervised field trials conducted in China matching the GAP were submitted.

However, in the supervised field trials no data on the maximum storage interval between sampling and analysis were reported. In addition, storage stability data for cereal commodities was not provided, denying an assessment on the validity of the trials.

The Meeting concluded that the data submitted for the use of pymetrozine on rice straw is insufficient for an estimation.

Cotton seed hulls

Pymetrozine is registered in Greece for the use on cotton rates of 2×0.2 kg ai/ha with a PHI of 35 days. Supervised field trials conducted in Southern Europe matching the registered application rate but with one additional treatment were submitted.

Pymetrozine residues in cotton seed hulls (n=6): < 0.02(4), 0.02 and 0.02 mg/kg.

The Meeting estimated a maximum residues level of 0.04 mg/kg and a median residue of 0.02 mg/kg for pymetrozine in cotton seed hulls.

Fate of residues during processing

The Meeting received information on the hydrolysis of radio-labelled pymetrozine as well as processing studies using unlabelled material in tomatoes and sweet peppers.

In a hydrolysis study using [pyridine-¹⁴C]-pymetrozine typical processing conditions were simulated (pH 4,5 and 6 with 90°C, 100°C and 120°C for 20, 60 and 20 minutes). While no degradation of the residue was observed under pH6 (120°C for 20 minutes), a significant loss of parent substance occurred at pH 4 and pH5. The cleavage product CGA300407 was identified as the primary degradation product present at 33% of the TRR at pH4 and at 42% of the TRR at pH5.

No hydrolysis study simulating processing conditions was conducted using [triazine-¹⁴C]-pymetrozine. However, the hydrolysis in buffer solutions for the environmental fate was investigated showing an identical degradation of the active substance. The counterpart to CGA300407 was identified as CGA215525, which is expected to pose the remaining part of the residue in processed products.

The fate of pymetrozine residues has been examined simulating household and commercial processing of tomatoes and sweet peppers. Estimated processing factors for the commodities considered at this Meeting are summarised below.

Raw commodity	Processed commodity	Pymetrozine Individual processing factors	Mean or best estimate processing factor	Median residue in mg/kg
Tomato (median: 0.285 mg/kg)	Juice, raw	0.05	0.05	0.014
	Puree	< 0.03(4), < 0.4	< 0.03	0.008
	Paste	< 0.04, < 0.4	< 0.22	0.063
	Canned/preserve	< 0.03(4), 0.07	0.03	0.008
	pomace, wet	0.08, < 0.4	0.24	0.068
Sweet pepper (median: 0.59 mg/kg)	Cooked fruit	< 0.02(3)	< 0.02	0.012

The Meeting considered that maximum residue levels for processed commodities are covered by their raw agricultural commodities.

Residues in animal commodities

Farm animal feeding studies

The Meeting received feeding studies involving pymetrozine on lactating cows.

Three groups of lactating cows were dosed daily at levels of 1, 3 and 10 ppm in the diet for 28 consecutive days. Milk was collected throughout the whole study and tissues were collected on day 29 within 24 hrs after the last dose.

In milk and tissues of all dose groups no detectable residues of pymetrozine above the LOQ of 0.01 mg/kg were found.

The metabolite CGA313124 was also not found in tissues. In milk, CGA313124 was not detected for the 1ppm dose group but was present at levels of 0.02 mg/kg for the 3 ppm group and of 0.05 mg/kg for the 10 ppm group.

The Meeting noted that tissue samples were stored up to 10-13 months, which is longer than the maximum storage interval identified for pymetrozine in muscle. However, taking into account that based on goat metabolism studies liver is expected to be the tissue with highest residue concentrations, which was analysed for the parent residue within the interval supported by storage stability data, the general result of pymetrozine residues being < 0.01 mg/kg in cow tissues is accepted.

Estimated maximum and mean dietary burdens of livestock and animal commodities maximum residue levels

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

	Livestock dietary burden, pymetrozine, ppm of dry matter diet							
	US-Canada		EU		Australia		Japan	
	max.	mean	max.	mean	max.	mean	max.	mean
Beef cattle	< 0.01	< 0.01	none	none	0.03	0.03	none	none
Dairy cattle	< 0.01	< 0.01	none	none	0.03 ^a	0.03 ^b	none	none
Poultry - broiler	none	none	none	none	none	none	none	none
Poultry - layer	none	none	none	none	none	none	none	none

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

^b Highest mean beef or dairy cattle burden suitable for median estimates for mammalian meat and milk

none no relevant feed items

Animal commodity maximum residues levels

For beef and dairy cattle maximum and mean dietary burdens of 0.03 ppm were estimated, respectively. In farm animal feeding studies on lactating cows no detectable residues of pymetrozine in tissues were found for all dose groups up to 10 ppm.

The Meeting estimated median and highest residue values of 0 for mammalian meat, edible offal and fat and corresponding maximum residue levels of 0.01* mg/kg.

For milk, CGA313124 was not detected in the milk samples for the 1 ppm group. Under consideration of the maximum and mean dietary burden for dairy cattle being 33 times lower than this dose level, the Meeting estimated a maximum residue level of 0.01* mg/kg and a median residue of 0 mg/kg, respectively for milks.

For poultry no relevant feed items were identified. The Meeting estimated median and highest residue values of 0 mg/kg for poultry meat, edible offal of and fat as well as for eggs. The Meeting also estimated maximum residue levels of 0.01* mg/kg for poultry meat, edible offal of and fat as well as for eggs.

RECOMMENDATIONS

Definition of the residue for compliance with MRL for plant commodities, mammalian tissues, poultry tissues and eggs: *pymetrozine*

Definition of the residue for compliance with MRL for milk: *CGA313124 (4,5-dihydro-6-hydroxymethyl-4-[(3-pyridinyl-methylene)amino]-1,2,4-triazine-3(2H)-one)*

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

The residue is not fat-soluble.

FURTHER WORK OR INFORMATION

- storage stability data on more individual commodities
- supervised field trials analysed within the maximum storage periods
- stability data for pymetrozine during homogenization of field samples
- field rotational crop studies including analysis of conjugates
- applicability of multi-residue analytical methods
- a hydrolysis study simulating industrial processing using [6-triazine-¹⁴C]-pymetrozine
- processing data including analysis of CGA300407 and CGA215525

DIETARY RISK ASSESSMENT

Because the Meeting was unable to conclude on the toxicological relevance of the metabolites CGA294849 and CGA300407, the Meeting could not reach a conclusion on a residue definition for the dietary intake.

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