5.38 TRIFLUMEZOPYRIM (303)

TOXICOLOGY

Triflumezopyrim is the ISO-approved common name for 2,4-dioxo-1-(pyrimidin-5-ylmethyl)-3-[3-(trifluoromethyl)phenyl]-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-1-ium-3-ide (IUPAC name), with the CAS number 1263133-33-0.

Triflumezopyrim is a new insecticide belonging to the novel class of mesoionics that is intended to control a number of insect species in rice, including white-backed planthoppers, small brown planthoppers, green leafhoppers and, in particular, the brown planthopper *Nilaparvata lugens*, which has developed strong resistance to neonicotinoids such as imidacloprid. Triflumezopyrim acts by binding to and inhibiting the orthosteric site of the nicotinic acetylcholine receptor, deviating from action of neonicotinoids and other receptor agonists which, in contrast, stimulate the receptor, leading to over-excitation of the insect nervous system. Application timing is early in the growth of the rice, as soon as the population of hoppers reaches the economic threshold level.

Triflumezopyrim has not been evaluated previously by the JMPR and was reviewed by the present Meeting at the request of the CCPR. All critical studies contained statements of compliance with GLP and were conducted in accordance with current test guidelines.

Biochemical aspects

Following oral administration of a single dose of ^{14}C-radiolabelled triflumezopyrim at 10 mg/kg bw to rats, the compound was rapidly absorbed. Absorption accounted for 80–90% of the administered dose. Absorption was lower (60–70%) when a single high dose of 200 mg/kg bw was administered. The absorbed substance was rapidly and widely distributed throughout the body, with highest concentrations found in liver and kidneys. Relatively high levels were also found in skin and bone marrow in male rats and in the gastrointestinal tract and its contents in females, although absolute levels were low within 24 hours. There were no other marked sex differences in kinetics or metabolism, and dose and position of radiolabel also had little effect. Excretion was biphasic, rapid and nearly complete within 48 hours, mainly via urine and faeces. There was evidence of significant biliary excretion, followed by enterohepatic circulation. However, potential for accumulation was low.

Triflumezopyrim was extensively metabolized by hydroxylation, oxidation, hydrolysis, decarboxylation and rearrangement reactions at various positions in the molecule, resulting in a number of metabolites. Hydroxylation of the trifluoromethyl phenyl ring formed IN-R6U70, found in rat faeces (14–27% of the administered dose) and urine (0.7–2.2% of the administered dose). Most of the minor metabolites were present in urine and faeces at concentrations of less than 1%. Up to 41% of unchanged triflumezopyrim was excreted in urine and 18% in faeces. The pattern of absorption, distribution, metabolism and excretion was very similar when radiolabelled triflumezopyrim (10 mg/kg bw) was administered once daily for 14 consecutive days to female rats except that only six metabolites could be identified.

Toxicological data

The acute toxicity of triflumezopyrim was studied in in rats after oral administration ($LD_{50} \geq$ 4930 mg/kg bw), dermal administration (LD_{50} >5000 mg/kg bw) and inhalation ($LC_{50} > 5$ mg/L). Triflumezopyrim was not irritating to the skin of rabbits. Eye irritation studies in rabbits found no or only very mild effects. There was no evidence of skin sensitization in the guinea-pig.

Oral short-term toxicity studies (mostly feeding studies) were performed in mice, rats and dogs. In all three species, the liver was a target organ and adverse effects on the haematopoietic system were also observed. Some additional findings observed in only one or two studies might reflect the use of different batches.

In a 28-day study in the mouse, the dietary dose levels were 0, 200, 800, 2500 or 7000 ppm (equal to 0, 34, 129, 416 and 1100 mg/kg bw for males and of 0, 41, 161, 504 and 1340 mg/kg bw for

females, respectively). The NOAEL was 2500 ppm (equal to 416 mg/kg bw per day) based on reduced haematocrit and haemoglobin, increased reticulocyte counts and extramedullary haematopoiesis in the spleen. The effects on the liver (increased weight, hepatocellular hypertrophy and stimulation of microsomal UDPGT activity and a number of CYP enzymes) were considered adaptive rather than adverse, reflecting the mode of action behind most of the findings in the rodent liver.

In the 90-day feeding study in mice, dietary doses of 0, 200, 800, 2500 or 7000 ppm (equal to 0, 31, 125, 417 and 1130 mg/kg bw per day for males and 0, 44, 177, 476 and 1530 mg/kg bw per day for females, respectively) were administered. The NOAEL was 2500 ppm (417 mg/kg bw per day) based on adrenal hyperplasia at 7000 ppm (equal to 1130 mg/kg bw per day) in males, suggesting a possible additional effect of triflumezopyrim at the high dose, albeit of equivocal toxicological significance. In addition, findings at the two highest dose levels confirmed the adaptive liver effects seen in the 28-day study but not the haematological findings.

In a 14-day oral gavage study that also examined toxicokinetics and genotoxicity, rats were administered 0, 25, 300 or 1000 mg/kg bw per day with the high dose reduced to 600 mg/kg bw per day on day 5 of the study. The NOAEL was 25 mg/kg bw per day based on reductions in T_3 and/or T_4 levels at the high and mid dose, which may be related to the effects on the liver (increased organ weight, hypertrophy of hepatocytes and periportal vacuolation). Toxicokinetic parameters such as C_{max}, T_{max} and AUC confirmed the results of the absorption, distribution, metabolism and excretion studies. There was no evidence of genotoxicity (i.e. clastogenicity) as no micronucleus induction in reticulocytes was seen.

Three 28 or 90-day feeding studies in rats were performed. In the 28-day study, the dietary dose levels were 0, 200, 800, 4000 and 20 000 ppm (equal to 0, 17, 65, 309 or 653 mg/kg bw per day for males and 0, 16, 64, 317 and 627 mg/kg bw per day for females, respectively). In the 90-day studies, the dietary dose levels were 0, 100, 400, 1500 or 6000 ppm (equal to 0, 4.5, 18, 70 and 274 mg/kg bw per day for males and 0, 6, 23, 83 and 316 mg/kg bw per day for females, respectively, and 0, 4.2, 17, 63.9 and 257.1 mg/kg bw for males and 0, 5.1, 20.4, 74.2 and 278 mg/kg bw for females, respectively. Decreases in body weight and body weight gain and in feed consumption and efficiency were consistently seen in these studies. Induction of microsomal liver enzymes (certain CYPs and UDPGT) was observed, supporting the mode of action for liver weight increases and liver cell hypertrophy. Haematological changes were observed in the 28-day and the more recent 90-day study. The absence of an effect on red blood cells in the earlier 90-day study might be because the changes were relatively modest and occurred only at the highest dose. The same considerations apply to the increased uterine weight observed at the highest dose only in one study.

Although a lower NOAEL of 17 mg/kg bw per day (based on slight reductions in body weight gain and feed consumption in males only at the LOAEL of 65 mg/kg bw per day) was identified in the 28-day study, the nearly identical NOAELs of 64 and 70 mg/kg bw per day in the two 90-day studies conducted using a higher number of animals appear more robust.

Special investigations of neurotoxicity in one study did not find any neurotoxic potential.

In a 90-day study in dogs, triflumezopyrim was administered at dietary doses of 0, 100, 400, 1000 or 4000 ppm (equal to 0, 3, 12.2, 26.6 and 115 mg/kg bw per day for males and 0, 2.7, 12.2, 26.9 and 131.0 mg/kg bw per day for females, respectively), the NOAEL was 400 ppm (equal to 12.2 mg/kg bw per day) based on lower body weight gain and feed consumption, decreased thymus weights and thymus lymphoid depletion at 1000 ppm (equal to 26.6 mg/kg bw per day). Haematological effects such as extramedullary haematopoiesis in the liver or decreases in red blood cell parameters were confined to the highest dose.

In a 1-year study in dogs, triflumezopyrim was administered at dietary doses of 0, 40, 100, 400 or 2000 ppm (equal to 0, 1.5, 3.3, 11.1 and 53.2 mg/kg bw per day for males and of 0, 1.2, 3.4, 10.8 and 55.9 mg/kg bw per day for females, respectively), the NOAEL was 2000 ppm (equal to 53.2 mg/kg bw per day), the highest dose tested. The reasons for these differences between the two dog studies are unknown but may be due to the use of different test batches.

In an 18-month study in mice, triflumezopyrim was administered at dietary doses of 0, 200, 800, 2500 or 7000 ppm (equal to 0, 20, 84, 248 and 727 mg/kg bw per day for males and 0, 22, 88, 283 and 810 mg/kg bw per day for females). The NOAEL was 800 ppm (equal to 84 mg/kg bw per day) based on a marked increase in liver weight (up to 16%) in both sexes and increased occurrence of centrilobular hypertrophy of hepatocytes in males at 2500 ppm (equal to 248 mg/kg bw per day). The progression of hypertrophy to tumours at the highest dose indicates that these liver effects in mice are potentially adverse. Moreover, an increase in extramedullary haematopoiesis in the spleen was observed in males at the two highest dose levels. In females, splenic haematopoiesis and spleen weights were significantly increased at the highest dose level. In addition, there was an increase in hepatic haematopoiesis in high dose females.

A significant increase in liver adenomas was observed in males at the highest dose level. There is some evidence from the 28-day study in mice and from a mechanistic study that this oncogenic effect might be related to CAR activation leading to increased gene expression, induction of hepatic CYP enzymes and hepatocellular hypertrophy. These events in rodents can be accompanied by cell proliferation and may eventually result in the development of liver tumours provided exposure is sufficiently high and long-lasting. Binding to and activation of CAR plays a crucial role in this mode of action, which is shared by phenobarbital. This mode of action is generally considered of low relevance to humans.

In female mice, there was an increase in the incidence of bronchoalveolar carcinoma and (combined) adenoma and carcinoma at the highest dose level, as indicated by a statistically significant positive trend. On the other hand, there were no significant differences in the pairwise comparison. No plausible mode of action has been described. However, mechanistic studies have shown that triflumezopyrim is not metabolized either by mouse or human lung microsomes and that there was no increase in proliferation of the bronchoalveolar epithelium in female mouse lung following 3 or 7 days of dietary administration of triflumezopyrim. Although these results do not exclude the relevance of the oncogenic effect, it appears that any such response would require prolonged duration of exposure to a high dose.

In a 2-year chronic toxicity and carcinogenicity study in rats, triflumezopyrim was administered at dietary concentrations of 0, 100, 500, 2000 or 8000 ppm (equal to 0, 3, 15.9, 70.6 and 283.8 mg/kg bw per day for males and 0, 3.2, 17.3, 73.8 and 395.9 mg/kg bw per day for females, respectively). Because of marked decreases in body weight and body weight gain and on feed consumption and efficiency, the maximum tolerated dose (MTD) was clearly exceeded in males at the highest dose and in females at the two highest dose levels, with effects observed, in particular in females, even during the first year of the study. At termination, mean body weight of surviving females at 2000 ppm was more than 20% lower than that of the controls; in surviving females at 8000 ppm, mean body weight was nearly 43% lower than that of the controls. The NOAEL was 500 ppm (15.9 mg/kg bw per day) based on effects on body weight, feed intake and efficiency, increases in liver and uterus weights and non-neoplastic histopathological findings in liver, lungs, testes and uterus.

Although no carcinogenic effects were observed in male rats, there was a significant increase in the incidence of liver adenoma and in (benign) granular cell tumours and malignant uterine tumours (squamous cell carcinoma and endometrial adenocarcinoma) in high dose females. (The possible explanation for the liver tumours is the same as for mice.) For uterine tumours, an endocrine-mediated mechanism based on a reduction in prolactin and subsequent disturbances in estrogen and progesterone levels has been proposed. This mode of action is supported, in part, by mechanistic studies and by evidence from the open literature. However, the Meeting considered that the extremely reduced body weight in high dose females was more likely to have contributed to uterine tumour development.

The Meeting concluded that triflumezopyrim showed some evidence of carcinogenicity in male (liver) and female mice (lungs). The increase in uterine and liver tumours occurred only at an excessively high dose. The findings in the rat were considered not relevant for human risk assessment at dietary exposure levels.

The Meeting noted that the trend tests for carcinogenic effects used by the sponsor in the long-term studies were performed by rank order, not by administered doses. There are arguments for and against both approaches.

Triflumezopyrim was tested for genotoxicity in an adequate range of studies, both in vitro and in vivo. There was limited evidence of genotoxicity in vitro but no evidence in vivo.

The Meeting concluded that triflumezopyrim is unlikely to be genotoxic in vivo.

In view of the lack of genotoxicity in vivo and because tumours were observed only at very high doses, the Meeting concluded that triflumezopyrim is unlikely to pose a carcinogenic risk to humans at levels occurring in the diet.

In a two-generation study in rats, triflumezopyrim was administered at dietary doses of 0, 100, 500, 1500 or 3000 ppm (equivalent to 0, 7, 35, 105 and 210 mg/kg bw per day). The NOAEL for parental toxicity was 500 ppm (equivalent to 35 mg/kg bw per day) based on decreased body weight, body weight gain and feed consumption in adult rats at 1500 ppm (equivalent to 105 mg/kg bw per day). The NOAEL for offspring toxicity was 1500 ppm (equivalent to 105 mg/kg bw per day) based on decreased body weight gain and subsequent delay in preputial separation at 3000 ppm (equivalent to 210 mg/kg bw per day). The NOAEL for reproductive toxicity was 3000 ppm (equivalent to 210 mg/kg bw), the highest dose tested.

In a developmental toxicity study in rats, triflumezopyrim was administered by gavage at dose levels of 0, 25, 50, 100 and 200 mg/kg bw per day on gestation days 6 through 20. The NOAEL for maternal toxicity was 100 mg/kg bw per day based on reduced body weight gain and feed consumption, which started soon after commencement of treatment, at 200 mg/kg bw per day. The increase in skeletal variations indicative of developmental delay was seen in fetuses at 100 and 200 mg/kg bw per day, but this was not considered an acute effect, and the NOAEL for embryo/fetal toxicity was 50 mg/kg bw per day.

In a developmental toxicity study in rabbits, triflumezopyrim was administered at doses of 0, 50, 100, 250 or 500 mg/kg bw per day. The NOAEL for maternal toxicity was 250 mg/kg bw per day based on lower body weight gain, feed intake and reduced defecation and haematological effects. The NOAEL for embryo/fetal toxicity was 500 mg/kg bw per day, the highest dose tested, based on lack of effects up to the highest dose of 500 mg/kg bw per day, when maternal toxicity was already apparent.

The Meeting concluded that triflumezopyrim is not teratogenic.

In an acute neurotoxicity study in rats, the NOAEL was 100 mg/kg bw based on reductions in body temperature and motor activity at 500 mg/kg bw and above. These findings were, however, accompanied by or secondary to transient body weight losses. There were no neuropathological findings. There was no evidence of neurotoxicity in a 90-day rat study that included FOB observations up to 274 mg/kg bw per day, the highest dose tested.

The Meeting concluded that triflumezopyrim is not neurotoxic.

In an immunotoxicity study in which female rats received dietary doses of 0, 100, 500, 2000 or 6000 ppm for 28 days (equal to 0, 8.8, 41, 166 and 474 mg/kg bw per day), no evidence of immunotoxicity was observed.

The Meeting concluded that triflumezopyrim is not immunotoxic.

Toxicological data on metabolites and/or degradates

No data were available. Computational analysis of the plant metabolites IN-Y2186 and IN-RPD47 did not identify any structural alerts for genotoxicity and indicated that their functional group profiles were covered by that of triflumezopyrim, which was considered unlikely to be genotoxic in vivo.

Human data

No health problems have been reported in the small number of employees who have been involved in the handling, testing or manufacture of triflumezopyrim.

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

Toxicological evaluation

The Meeting established an ADI for triflumezopyrim of 0–0.2 mg/kg bw on the basis of a NOAEL of 15.9 mg/kg bw per day for effects on body weight and body weight gain, feed consumption and efficiency, increased liver and uterus weights and non-neoplastic histopathological findings in liver, lungs, testes and uterus in the long-term study in rats. A safety factor of 100 was applied. A slightly lower NOAEL (12.2 mg/kg bw per day) obtained in the 90-day dog study was based on effects on body weight and effects secondary to this such as lymphoid depletion in thymus; however, these effects were not confirmed in a 1-year study in dogs. Hence, the NOAEL in the rat carcinogenicity study was considered a more robust basis on which to establish the ADI.

The upper bound of the ADI provides a margin of exposure of at least 3600 relative to the dose level at which liver adenomas were increased in male mice (727 mg/kg bw per day). The margin was at least 4000 relative to the dose level resulting in an increased incidence of bronchoalveolar tumours in female mice (810 mg/kg bw per day).

The Meeting established an ARfD of 1 mg/kg bw on the basis of the NOAEL of 100 mg/kg bw in the acute neurotoxicity study in rats. A safety factor of 100 was applied. The same NOAEL was obtained for maternal toxicity in the developmental study in rats, which is also a suitable basis on which to establish an ARfD. Although a lower NOAEL was identified for embryo/fetal toxicity in the same developmental toxicity study (increased skeletal variations likely indicative of delayed development), these findings are unlikely to result from a single exposure and, therefore, are not an appropriate basis for the ARfD.

A toxicological monograph was prepared.

Levels relevant to risk assessment of triflumezopyrim

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity[a]	Toxicity	800 ppm, equal to 84 mg/kg bw per day	2 500 ppm, equal to 248 mg/kg bw per day
		Carcinogenicity	2 500 ppm, equal to 248 mg/kg bw per day	7 000 ppm, equal to 727 mg/kg bw per day
Rat	Acute neurotoxicity study[b]	Neurotoxicity	100 mg/kg bw	500 mg/kg bw
	Two-year studies of toxicity and carcinogenicity[a]	Toxicity	500 ppm, equal to 15.9 mg/kg bw per day	2 000 ppm, equal to 70.6 mg/kg bw per day (males)
		Carcinogenicity	2 000 ppm, equal to 73.8 mg/kg bw per day (females)	8 000 ppm, equal to 396 mg/kg bw per day[d]
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	3 000 ppm, equivalent to 210 mg/kg bw per day[c]	–
		Parental toxicity	500 ppm, equivalent to 35 mg/kg bw per	1 500 ppm, equivalent to

Species	Study	Effect	NOAEL	LOAEL
			day	95 mg/kg bw per day
		Offspring toxicity	1 500 ppm, equivalent to 105 mg/kg bw per day	3 000 ppm, equivalent to 210 mg/kg bw per day
	Developmental toxicity study[b]	Maternal toxicity	100 mg/kg bw per day	200 mg/kg bw per day
		Embryo/fetal toxicity	50 mg/kg bw per day	100 mg/kg bw per day
Rabbit	Developmental toxicity study[b]	Maternal toxicity	250 mg/kg bw per day	500 mg/kg bw per day
		Embryo and fetal toxicity	500 mg/kg bw per day [c]	–
Dog	Thirteen-week study of toxicity	Toxicity	400 ppm, equal to 12.2 mg/kg bw per day	1 000 ppm, equal to 26.6 mg/kg bw per day
	One-year study of toxicity[a]	Toxicity	2 000 ppm, equal to 53.2 mg/kg bw per day[c]	–

[a] Dietary administration.

[b] Gavage administration.

[c] Highest dose tested in study.

[d] MTD was clearly exceeded at this dose level, and observed effects were not relevant for human risk assessment at dietary exposure levels.

Estimate of acceptable daily intake (ADI)

0–0.2 mg/kg bw

Estimate of acute reference dose (ARfD)

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

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Very rapid and >80% at low dose (10 mg/kg bw); lower (60–70%) at high dose (200 mg/kg bw)
Dermal absorption	No data
Distribution	Rapid and extensive; highest concentrations in liver, kidney, skin, bone marrow and gastrointestinal tract
Potential for accumulation	Low

Rate and extent of excretion	Rapid and nearly complete via urine (40–48%) and faeces (43–53%) with a significant contribution of biliary elimination (up to ~30%) within 48 hours
Metabolism in animals	Variety of pathways (hydroxylation, hydrolysis, oxidation, decarboxylation, significant elimination also in chemically unchanged form; up to 41% in urine and 18% in faeces)
Toxicologically significant compounds in animals and plants	Parent compound
Acute toxicity	
Rat, LD_{50}, oral	>4 930 mg/kg bw
Rat, LD_{50}, dermal	>5 000 mg/kg bw
Rat, LC_{50}, inhalation	>5 mg/L (air, 4 h nose-only exposure to aerosol)
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Mildly irritating in one study, non-irritating in another
Guinea-pig, dermal sensitization	Non-sensitizing (Magnusson–Kligman)
Short-term studies of toxicity	
Target/critical effect	Decrease in body weight and feed consumption/efficiency; anaemia; decrease in thymus weight; lymphoid depletion
Lowest relevant oral NOAEL	12.2 mg/kg bw per day (90 d, dog)
Lowest relevant dermal NOAEL	1 000 mg/kg bw per day (28 d, rat, highest dose tested)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Decrease in body weight; liver, lung, uterus
Lowest relevant NOAEL	Rat: 15.9 mg/kg bw per day (500 ppm)
Carcinogenicity	Carcinogenic in mice (liver adenomas, bronchoalveolar tumours) at high doses [a]; effects in rats (liver adenomas, uterine tumours) confined to a dose clearly exceeding the MTD and, therefore, not relevant for human risk assessment
Genotoxicity	
	Unlikely to be genotoxic in vivo [a]
Reproductive toxicity	
Target/critical effect	No effects on reproduction
Lowest relevant parental NOAEL	35 mg/kg bw per day
Lowest relevant offspring NOAEL	105 mg/kg bw per day
Lowest relevant reproductive NOAEL	210 mg/kg bw per day (highest dose tested)
Developmental toxicity	
Target/critical effect	Skeletal variations and developmental delay
Lowest relevant maternal NOAEL	100 mg/kg bw per day (rat)
Lowest relevant embryo/fetal NOAEL	50 mg/kg bw per day (rat)
Neurotoxicity	
Acute neurotoxicity NOAEL	100 mg/kg bw (rat)
Subchronic neurotoxicity NOAEL	274 mg/kg bw per day (rat, 90 d)

Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity	No evidence of immunotoxicity
Studies on toxicologically relevant metabolites	
	No relevant metabolites identified
Human data	
	No reports of health effects in those involved in its manufacture or handling

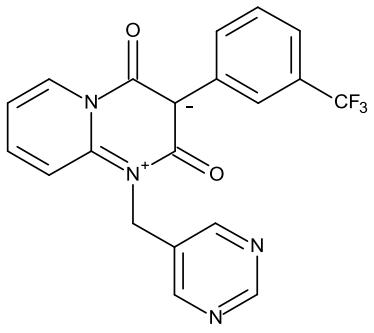
[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

Summary

	Value	Study	Safety factor
ADI	0–0.2 mg/kg bw	Two-year, rat	100
ARfD	1 mg/kg bw	Acute neurotoxicity, rat; developmental toxicity, rat	100

RESIDUE AND ANALYTICAL ASPECTS

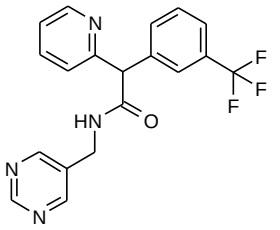
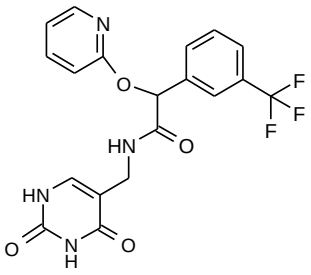
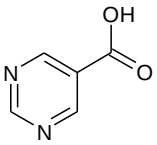
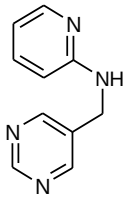
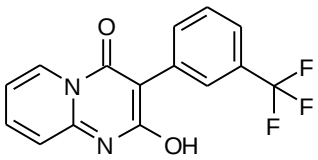
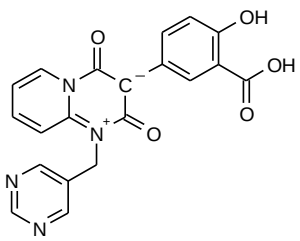
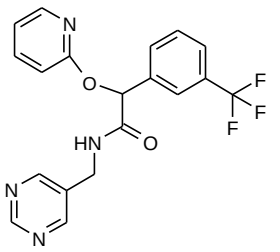
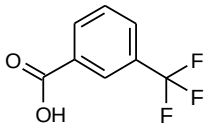
Triflumezopyrim (ISO common name) is an insecticide used to control planthoppers in rice. Triflumezopyrim was scheduled by the 48th Session of the CCPR for evaluation of residues and toxicology for the first time by the present Meeting. The 2017 Meeting received information and studies on the environmental fate in soil and water, plant metabolism in rice, confined rotational crop metabolism, animal metabolism in lactating goats and laying hen, analytical methods, storage stability, supervised field trials on rice, processing data on rice and animal feeding. Triflumezopyrim is registered by several countries for use on rice.

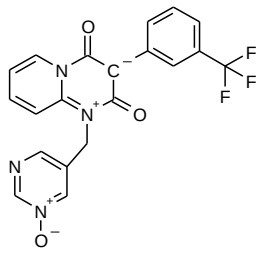
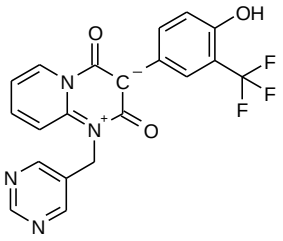
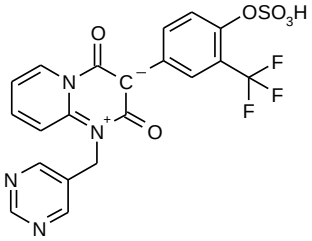
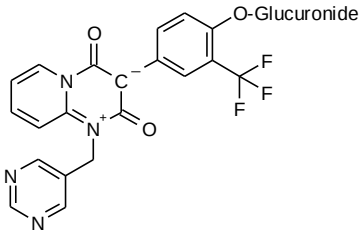


The IUPAC and CA name of triflumezopyrim is 3,4-dihydro-2,4-dioxo-1-(pyrimidin-5-ylmethyl)-3-(α,α,α-trifluoro-*m*-tolyl)-2*H*-pyrido[1,2-*a*]pyrimidin-1-ium-3-ide.

Metabolism and environmental fate studies were conducted using [fused pyrimidine-3-^{14}C]triflumezopyrim, [methylene-^{14}C]triflumezopyrim and [pyridine-2,6-^{14}C]triflumezopyrim. Moreover, [fused pyrimidine-3-^{13}C]triflumezopyrim was used.

The following abbreviations are used for the metabolites discussed below:

IN-RUB93	2-(2-pyridyl)-N-(pyrimidin-5-ylmethyl)-2-[3-(trifluoromethyl)phenyl]acetamide	
IN-SBY68	N-[(2,4-dioxo-1H-pyrimidin-5-yl)methyl]-2-(2-pyridyloxy)-2-[3-(trifluoromethyl)phenyl]acetamide	
IN-RPA16	pyrimidine-5-carboxylic acid	
IN-RPA19	N-(pyrimidin-5-ylmethyl)pyridin-2-amine	
IN-RPD47	2-hydroxy-3-[3-(trifluoromethyl)phenyl]pyrido[1,2-a]pyrimidin-4-one	
IN-R6U72 (hydroxy acid)	5-[2,4-dioxo-1-(pyrimidin-5-ylmethyl)pyrido[1,2-a]pyrimidin-1-ium-3-id-3-yl]-2-hydroxy-benzoic acid	
IN-SBV06	2-(2-pyridyloxy)-N-(pyrimidin-5-ylmethyl)-2-[3-(trifluoromethyl)phenyl]acetamide	
IN-Y2186	3-(trifluoromethyl)benzoic acid	

IN-R3Z91 (N-oxide)	1-[(1-oxidopyrimidin-1-ium-5-yl)methyl]-3-[3-(trifluoromethyl)phenyl]pyrido[1,2-a]pyrimidin-1-ium-3-ide-2,4-dione	
IN-R6U70	3-[4-hydroxy-3-(trifluoromethyl)phenyl]-1-(pyrimidin-5-ylmethyl)pyrido[1,2-a]pyrimidin-1-ium-3-ide-2,4-dione	
R6U70 sulfate (sulphate conjugate of IN-R6U70)	[4-[2,4-dioxo-1-(pyrimidin-5-ylmethyl)pyrido[1,2-a]pyrimidin-1-ium-3-id-3-yl]-2-(trifluoromethyl)phenyl] hydrogen sulfate	
R6U70 glucuronide (glucuronic acid conjugate of IN-R6U70)	6-[4-[2,4-dioxo-1-(pyrimidin-5-ylmethyl)pyrido[1,2-a]pyrimidin-1-ium-3-id-3-yl]-2-(trifluoromethyl)phenoxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid	

Environmental fate in soil & water

The Meeting received information for triflumezopyrim on soil and aqueous photolysis, aqueous hydrolysis and aerobic soil metabolism.

Half-lives of ^{14}C-triflumezopyrim for soil and aqueous photolysis were estimated at 12 days and 2–3 days, respectively assuming of 1st order kinetics. During aqueous photolysis, metabolite IN-RUB93 was identified at up to 66–85%.

Degradation in water and water/sediment systems was investigated under dark and irradiated conditions. When kept in the dark, half-lives for triflumezopyrim in water alone and in the water/sediment system were estimated to be between 23–41 days and 283–320 days, respectively, while in irradiated systems, half-live times were estimated to be between 5–9 days and 33–36 days, respectively.

In aerobic soil metabolism studies, moderate degradation of triflumezopyrim was observed with estimated half-lives in various soils ranging from 53–133 days. Several metabolites were identified, but only IN-SBY68 and IN-RPD47 occurred in significant amounts of 5–9% AR.Under the more realistic conditions of flooded soil the half-lives were estimated at 184 days. In sterile soil half-lives were longer at an estimated 740 days.

The Meeting received one confined rotational crop metabolism study.

The study was conducted with lettuce, radish and wheat with triflumezopyrim applied at a rate equivalent to 0.1 kg ai/ha to a sandy loam soil under glasshouse conditions with plant-back intervals (PBIs) of 30, 120 and 268 days. Only wheat straw samples (from all PBIs) and one wheat hay sample at 30-day PBI contained total residues > 0.010 mg eq/kg and were further analysed. Parent triflumezopyrim and several metabolites were identified in these samples, but levels were consistently < 0.01 mg eq/kg.

In summary the Meeting concluded that triflumezopyrim is persistent in soil suggesting a potential for accumulation. It should be noted that metabolite IN-SBY68 is a soil metabolite only. As it was not detected in the rotational crop study it was not considered relevant for plant commodities.

The Meeting concluded that a significant transfer of triflumezopyrim residues from soil to succeeding crops is not expected.

Plant metabolism

The Meeting received two rice plant metabolism studies for triflumezopyrim following soil and foliar application of ^{14}C- pyrimidine-, ^{14}C-methylene- and ^{14}C-pyridine-radiolabelled active substances.

For the soil regime, triflumezopyrim was applied at a rate equivalent to 0.3 kg ai/ha to the soil around emerged rice plants (BBCH 13, 3 leaves unfolded) grown in pots. The plant pots were flooded two days after the soil treatment and kept under flooded conditions for the duration of the study. Samples were collected at 44 DAT (foliage, roots) and at grain maturity, 127/131 DAT (straw, chaff, grain and root).

Maximum TRR levels found for the different labels were highest in roots (0.40 mg eq/kg), followed by foliage (0.12 mg eq/kg), straw, (0.073 mg eq/kg), chaff (0.064 mg eq/kg) and grain (0.014 mg eq/kg).

Samples were sequentially extracted with methanol followed by methanol/water at various ratios. Extracted radioactivity ranged between 37–49% TRR in foliage, 38–43% TRR in straw, 41–54% TRR in chaff and 19–37% TRR in grain.

Among the identified components, parent triflumezopyrim was present at 8–19% TRR (0.001–0.002 mg eq/kg) in rice grain. In foliage, straw and chaff triflumezopyrim ranged between 11–23% TRR (0.005–0.015 mg eq/kg). Other metabolites were identified but ranged individually between 0.4–7.8% TRR (< 0.001–0.007 mg eq/kg).

For the foliar regime, two spray applications (BBCH 23, 3 tillers detectable; BBCH 69, end of flowering) were performed at a rate of 0.035 kg ai/ha each (total 0.07 kg ai/ha). Plants were sampled at 0, 7 (all labels) and 14 days after the last application (DALA) (pyridine label only) and at grain maturity, 64/68 DALA (straw, chaff, grain and root).

TRR levels found were highest in chaff (up to 0.55 mg eq/kg), followed by foliage (up to 0.28 mg eq/kg), straw, (up to 0.12 mg eq/kg), grain (up to 0.12 mg eq/kg) and roots (up to 0.043 mg eq/kg).

Samples were sequentially extracted with methanol followed by methanol/water at various ratios. Extracted radioactivity ranged between 79–95% TRR for foliage (0, 7 DAT), 56% TRR for foliage (14 DALA), 40–54% TRR for straw, 30–43% TRR for chaff and 21–52% TRR for grain.

Among the identified components in the initial solvent extracts, parent triflumezopyrim was present at 2.9–9.1% TRR (0.003–0.006 mg eq/kg) in rice grain.

In initial solvent extracts of feed commodities, parent triflumezopyrim was present in foliage (0, 7, 14 DALA) at 26–82% TRR (0.027–0.23 mg eq/kg), in straw at 4.8–7.3% TRR (0.004–0.008 mg eq/kg), in chaff at 12–15% TRR (0.043–0.083 mg eq/kg). Additionally, parent triflumezopyrim was detected in the solubilizates of the post-extraction solids of chaff at 0.4–8.5% TRR (0.002–0.047 mg eq/kg). A notable identified metabolite was IN-RPA19 in foliage (0, 7 DALA) at up to 19% TRR (0.030 mg eq/kg). Moreover, conjugates of IN-R3Z91 were detected in chaff at

significant amounts after alkaline hydrolysis at 13% TRR (0.041 mg eq/kg). Additional metabolites were identified at much lower levels.

In a second study, the metabolic fate of radiolabelled triflumezopyrim was investigated following soil and foliar application. Application rates and test design were identical to the first study with the exception of sampling times. Additionally, post extraction solids were subjected additionally to a 10N base reflux with subsequent lignin precipitation.

Plants receiving the soil treatment were sampled at 51 DAT (foliage, roots) and at maturity, 119 DAT (straw, chaff, grain and root).

Maximum TRR levels found were highest in roots (0.12 mg eq/kg), followed by straw (0.11 mg eq/kg), chaff (0.093 mg eq/kg), foliage (0.066 mg eq/kg), and grain (0.013 mg eq/kg).

Samples were sequentially extracted with methanol followed by methanol/water (7:3, v/v), resulting in extraction rates of 47–49% TRR for foliage, 38–46% TRR for straw, 26–39% TRR for chaff and below LOQ for grain.

In foliage, straw and chaff, triflumezopyrim ranged between 5–24% TRR (0.002–0.016 mg eq/kg). Other metabolites were identified but ranged individually between 0.3–4.6% TRR (< 0.001–0.004 mg eq/kg).

Plants receiving the foliar treatments were sampled at 14 days after the first treatment and, in agreement with the critical GAP, 21 days after the second treatment (straw, chaff, grain and root).

TRR levels found were highest in chaff (up to 0.94 mg eq/kg), followed by straw (up to 0.34 mg eq/kg), foliage, (up to 0.13 mg eq/kg), roots (up to 0.10 mg eq/kg) and grain (up to 0.076 mg eq/kg).

Samples were sequentially extracted with methanol followed by methanol/water (7:3, v/v), resulting in extraction rates of 64–78% TRR for foliage, 55–71% TRR for straw, 43–53% TRR for chaff and 47–57% TRR for grain.

Among the identified components in the solvent extracts, parent triflumezopyrim was present at 22% TRR (0.009–0.017 mg eq/kg) in rice grain at 21 DALA. Moreover, metabolite IN-Y2186 was quantified at 12% TRR (0.009 mg eg/kg)

In the solvent extracts of feed commodities parent triflumezopyrim was present in foliage at 18–22% TRR (0.017–0.028 mg eq/kg), in straw at 19–20% TRR (0.044–0.064 mg eq/kg), in chaff at 17–25% TRR (0.15–0.16 mg eq/kg). Notable identified metabolites in feed commodities were IN-RPA19 in foliage, straw and chaff at up to 9%TRR (0.039 mg eq/kg) and IN-R6U72 (not detected in the first study) in foliage, straw and chaff at up to 16% TRR (0.032 mg eq/kg). Additional metabolites were identified at much lower levels.

Up to about 30% TRR in straw was released from PES using aggressive extraction techniques indicating that these residues are likely from the incorporation of ^{14}C into natural products.

Within the plants, parent triflumezopyrim was the predominant identified residue is in all matrices. Nevertheless, a large fraction of the active substance did degrade rather quickly into numerous metabolites before some of the observed radioactivity was incorporated into natural products. Among the metabolites identified, IN-RPA19 in foliage, IN-R6U72 in foliage and straw, IN-Y2186 in grain and conjugates of IN-R3Z91 in chaff can be considered as major metabolites, while all other identified metabolites can be considered as minor. All major identified metabolites were also found in the rat.

Animal metabolism

Information was available on the metabolism of triflumezopyrim in laboratory animals, lactating goats and laying hens. The evaluation of the metabolism studies in rats was carried out by the WHO group.

In lactating goats, the metabolic fate of triflumezopyrim was investigated using ^{14}C-radiolabelled triflumezopyrim. The compound was administered for seven consecutive days to three

lactating goats (one per label) in gelatine capsules at 22 ppm (0.67 mg/kg bw) for [pyrimidine-^{14}C]-, 25 ppm (0.60 mg/kg bw) for [methylene-^{14}C]- or 20 ppm (0.58 mg/kg bw) for [pyridine-^{14}C]-triflumezopyrim.

Most of the administered radioactivity was recovered from faeces (36–53% AR) and urine (19–29% AR). For all three labels, kidney gave the highest TRR (0.58–0.93 mg eq/kg), followed by liver (0.48–0.81 mg eq/kg), milk (0.28–0.60 mg eq/kg), muscle (0.024–0.041 mg eq/kg) and fat (0.007–0.044 mg eq/kg).

TRRs in milk did not reach a plateau over the investigated timeframe of 7 days.

Milk and tissue samples were sequentially extracted with acetonitrile followed by acetonitrile/water in various ratios, with the exception of fat, where dichloromethane was used prior to acetonitrile followed by acetonitrile/water. Resulting extraction rates were 99% TRR in milk, 78–83% TRR in liver, 96–98% TRR in kidney and 91–95% TRR in muscle and 84–95% TRR in fat.

Triflumezopyrim was the principal extracted component in day 4–6 composite milk (81–83% TRR; 0.23–0.49 mg/kg), liver (37–54% TRR; 0.20–0.37 mg/kg), kidney (70–83% TRR; 0.42–0.73 mg/kg), muscle (64–89% TRR; 0.015–0.035 mg/kg), and fat (70–93% TRR; 0.006–0.031 mg/kg) from all radiolabels.

In solvent extracts, the predominant metabolite in milk, liver and kidney was unconjugated IN-R6U70 and/or its glucuronic acid and sulphate conjugates (total of 12–40% TRR; 0.048–0.22 mg/kg). Other metabolites occurring at lower levels (< 0.027 mg/kg) were also identified.

In laying hens, the metabolic fate of triflumezopyrim was investigated using ^{14}C-radiolabelled triflumezopyrim. Each of the compounds was administered for 14 consecutive days to 3 groups of laying hens (5 hens per group) in gelatine capsules at 14 ppm (7.6 mg/kg bw) for [pyrimidine-^{14}C]-, 14 ppm (7.6 mg/kg bw) for [methylene-^{14}C]- and 15 ppm (7.8 mg/kg bw) for [pyridine-^{14}C]-triflumezopyrim.

Most of the administered radioactivity was recovered from excreta (83–90% AR). For all three labels, liver gave the highest TRR (0.28–0.38 mg eq/kg), followed by muscle (0.005–0.012 mg eq/kg) and fat (0.004–0.014 mg eq/kg).

TRR levels in eggs reached a plateau after approximately one week.

Egg and tissue samples were sequentially extracted with acetonitrile followed by acetonitrile/water in various ratios. Resulting extraction rates were 79–92% TRR in egg, 73–79% TRR in liver, 56–85% TRR in muscle and 93–94% TRR in fat.

Triflumezopyrim was the principal extracted component in day 9–13 composite eggs (48–65% TRR; 0.012–0.016 mg/kg) and liver (50–52% TRR; 0.14–0.20 mg/kg) from all radiolabels.

Among the identified metabolites only IN-R3Z91 in liver occurred in significant amounts (10–14% TRR; 0.027–0.053 mg/kg). Other metabolites occurring at lower levels (< 0.011 mg/kg) were also identified.

In summary, parent triflumezopyrim was the predominant residue in rat, lactating goat and laying hen. Only moderate metabolic degradation of triflumezopyrim was observed. In goat liver and kidney, IN-R6U70 in its conjugated and unconjugated form was the predominant metabolite, as well as in milk in its unconjugated form only. In the tissues of laying hens this metabolite occurred only in minor amounts, while IN-R3Z91 in liver was the only metabolite exceeding 10% TRR or 0.05 mg eq/kg. All major identified metabolites were also found in the rat.

Methods of analysis

The Meeting received analytical methods for the determination of triflumezopyrim, IN-RPA16, IN-RPD47, IN-R3Z91 IN-RPA19, IN-Y2186 and IN-R6U72 in plant matrices as well as for the determination of triflumezopyrim in animal matrices.

For matrices of plant origin, the basic principle employs extraction with methanol/water (70/30, v/v), followed by SPE clean-up using an HLB cartridge. Residues are determined by LC-MS/MS with an LOQ of 0.01 mg/kg per analyte.

In animal matrices, triflumezopyrim was determined in tissues, milk and eggs by extraction with acetonitrile/water (1/1, v/v) (no additional clean-up is performed) and LC-MS/MS detection with a LOQ of 0.01 mg/kg.

For enforcement, the applicability of a multi-residue method was successfully demonstrated for triflumezopyrim (IN-RPA-16 was not successfully validated) in plant and animal matrices with the QuEChERS method, using LC-MS/MS detection with a LOQ of 0.01 mg/kg. Other metabolites were not tested.

The Meeting concluded that suitable data generation and monitoring methods are available to measure triflumezopyrim in plant and animal commodities.

Stability of residues in stored analytical samples

The Meeting received information on the storage stability of triflumezopyrim and metabolites IN-RPA16, IN-RPD47, IN-R3Z91 and IN-Y2186 in rice plant matrices (whole plant, grain, straw) stored at -18 °C.

The storage stability in different frozen rice commodities of triflumezopyrim and all metabolites was demonstrated for at least 16 months and 6 months, respectively.

The storage stability of triflumezopyrim in animal matrices was not tested, with samples from a feeding study with lactating cows analysed within 30 days after collection.

Definition of the residue

From the plant metabolism studies in rice the foliar treatment regime and samples taken at 21 DALT were considered most relevant, as the critical GAP employs the same application method and is in agreement with the PHI of 21 days.

Parent triflumezopyrim was the predominant residue in rice grain at 22% TRR (0.009–0.017 mg/kg) as well as metabolite IN-Y2186 at up to 12% TRR (0.009 mg eq/kg). In feed matrices at 21 DALT, residues of triflumezopyrim ranged from 19–20% TRR in straw and 17–25% TRR in chaff. A metabolite found at significant levels at 21 DALT was IN-R6U72 in straw at up to 14% TRR (0.032 mg eq/kg)

In the confined rotational crop study total radioactive residues were < 0.01 mg eq/kg with the exception of straw and one hay sample. Parent triflumezopyrim (up to 30% TRR) and several metabolites (<10% TRR each) were identified in these samples, but concentrations were consistently < 0.01 mg eq/kg.

The Meeting concluded that triflumezopyrim is the major residue in rice and rotational crops (although at very low levels) and is a suitable marker compound for compliance with MRLs. Analytical multi-residue methods are capable of measuring triflumezopyrim in all plant matrices.

For dietary exposure purposes, the only metabolite found at potentially significant levels in rice grain was IN-Y2186 (up to 12% TRR, 0.009 mg eq/kg). In supervised field trials where IN-Y2186 was measured, the metabolite was found above the LOQ in five out of eight trials, ranging up to 0.017 mg/kg in the grain (parent triflumezopyrim concentrations up to 0.064 mg/kg).

The Meeting concluded that residues of IN-Y2186 may add significantly to the overall dietary exposure of triflumezopyrim residues. Since IN-Y2186 was observed in the rat and is of no greater toxicity than parent triflumezopyrim and is covered by its toxicological reference values, the Meeting decided to include the metabolite into the residue definition for dietary exposure purposes.

In lactating goats, triflumezopyrim was the principal extracted component in day 4–6 composite milk, liver, kidney, muscle and fat ranging from 36–89% TRR. The only major metabolite,

IN-R6U70 and its glucuronic acid and sulphate conjugate was identified in milk, liver and kidney at levels ranging between 14–49% of parent.

A cow feeding study was conducted at treatment rates of 1.3, 4.0 and 14 ppm. In the 1.3 and 4.0 ppm treatment groups no residues >0.01 mg/kg were detected, while in the 14 ppm treatment group residues of triflumezopyrim occurred in liver (0.034 mg/kg), kidney (0.023 mg/kg) milk (0.021 mg/kg) and cream (0.026 mg/kg). A plateau for the parent compound in milk was reached after approximately one week. Analysis for metabolites was not performed.

In laying hens, triflumezopyrim was the principal extracted component in day 9–13 composite eggs and liver from all radiolabels ranging from 48–65% TRR. The only major metabolite IN-R3Z91 occurred in liver at 10–14% TRR, however at lower proportions (19–27%) than parent triflumezopyrim, depending on the radiolabel.

Livestock animals may be exposed to metabolites of triflumezopyrim through plant parts utilised for feed purposes. Plant metabolism and supervised field trial studies indicate IN-Y2186, IN-RPA19, IN-R6U72 and IN-R3Z91 to be present at concentrations comparable to the parent compound. The Meeting noted that these metabolites, based on their structures, are expected to have higher water solubilities than parent compound. The Meeting considered that these metabolites would be more readily excreted and hence less likely to accumulate in milk, eggs and tissues than parent. Noting that these compounds were present in rice fodder and forage at comparable levels to the parent compound, it is considered that these metabolites would be found at lower levels than parent compound in animal matrices after feeding treated rice. Therefore, inclusion in the residue definition for animal commodities is not necessary.

For compliance with MRLs the Meeting concluded that triflumezopyrim is a suitable marker in all animal commodities. Analytical multi-residue methods are capable of measuring triflumezopyrim in all animal matrices.

In muscle and fat tissues of all animals investigated, residue concentrations of parent triflumezopyrim were comparable. In addition, TRR levels found in skim milk and cream did not differ significantly. In whole milk > 80% of the TRR were identified as parent. The log P_{ow} of triflumezopyrim is 1.2. The Meeting decided that residues of triflumezopyrim are not fat soluble.

For dietary exposure purposes, parent triflumezopyrim was the predominant residue in all matrices investigated. In addition, IN-R6U70 and its conjugates were found in goats at relative amounts of up to 49% of parent, while in laying hens the only major metabolite was IN-R3Z91 in liver, being present at relative amounts of up to 27% of the parent. However, in view of the very low livestock animal dietary burden for triflumezopyrim of maximal 0.26 ppm, not resulting in residues at or above the LOQ in animal products, the contribution of both metabolites to the overall dietary exposure was considered as insignificant by the Meeting. Therefore, the Meeting decided that the residue definition for the dietary intake of animal commodities is triflumezopyrim only. Reconsideration may be required if additional uses increase the livestock animal dietary burden significantly.

Definition of the residue (for compliance with the MRL) for plant and animal commodities: *Triflumezopyrim*

Definition of the residue (for the estimation of dietary intake) for plant commodities: *Sum of triflumezopyrim and 3-(trifluoromethyl)benzoic acid (IN-Y2186), expressed as triflumezopyrim.*

Definition of the residue (for the estimation of dietary intake) for animal commodities: T*riflumezopyrim*

The residue is not fat-soluble.

Results of supervised residue trials on crops

The Meeting received supervised trial data for applications of triflumezopyrim on rice only. The trials were conducted in China, India and Thailand.

The critical GAP is from China with a maximum rate of 2 × 25 g ai/ha with a PHI of 21 days. Supervised field trials from China, India and Thailand matching the cGAP were submitted.

MRL Setting

Rice grain

For MRL setting of rice grain, the ranked order of residues of *triflumezopyrim* following GAP treatment was (n=23): 0.003, 0.007(2), 0.008, 0.009, 0.010, 0.016, 0.018, < 0.020, 0.021, 0.022, 0.025, 0.032 (2), 0.034, 0.049, 0.051, 0.054, 0.057, 0.064, 0.083, 0.087, 0.18 mg/kg.

The Meeting estimated a maximum residue level of 0.2 mg/kg for *triflumezopyrim* in rice grains and a median residue of 0.025 mg/kg for animal dietary burden calculation.

Husked rice

For MRL setting of husked rice, the ranked order of residues of *triflumezopyrim* husked rice from field trials following GAP treatment was (n=6): 6×< 0.01 mg/kg.

Noting that all residues were < 0.01 mg/kg and that even trials with higher treatment rates (2 × 37.5 g ai/ha resulted in residue < 0.01 mg/kg, the Meeting estimated a maximum residue level of 0.01 mg/kg for *triflumezopyrim* in husked rice.

Dietary exposure

For estimating the dietary exposure, no residue data on husked rice according to the residue definition *Sum of triflumezopyrim and 3-(trifluoromethyl)benzoic acid (IN-Y2186), expressed as triflumezopyrim* are available. However, field trials from Thailand determining both, parent triflumezopyrim and IN-Y2186 in rice grain were provided, matching the cGAP. A molecular weight conversion factor of 2.095 ($M_{Triflumezopyrim}/M_{IN-Y2186}$ = 398.3 g/mol/190.1 g/mol) was applied to express IN-Y2186 as triflumezopyrim equivalents. The ranked order of total residue was (n=8): 0.007 (2), 0.010, 0.029, 0.076, 0.088, 0.090, 0.098 mg/kg.

The Meeting estimated a STMR of 0.053 mg/kg for triflumezopyrim and IN-Y2186 in rice grain. As no processing data from rice grain to husked rice and polished rice was available for the sum of triflumezopyrim and IN-Y2186, the Meeting decided to take a conservative approach by assuming that after the respective processing steps the entire residue found in rice grain was also present in husked and polished rice. Application of a weight adjustment factor of 0.8 for rice grain to husked rice resulted in a STMR of 0.066 mg/kg, while a weight adjustment factor of 0.775 for husked rice to polished rice resulted in a STMR of 0.086 mg/kg.

Animal feedstuffs

Rice hulls

Residues following GAP treatment (±25%) were (n=6): 0.049, 0.072, 0.15, 0.19, 0.30, 0.31 mg/kg.

The Meeting estimated a median residue of 0.17 mg/kg for *triflumezopyrim* in rice hulls.

Rice straw

Supervised field trials from China, India and Thailand according to the cGAP were submitted.

For MRL setting of rice straw, residues following GAP treatment (±25%) were (n=23): 0.007, 0.008 (2), 0.009, 0.01, < 0.02 (2), 0.022, 0.028, 0.057, 0.062, 0.063, 0.072, 0.077, 0.099, 0.10 , 0.12, 0.14, 0.15 (2), 0.16, 0.20, 0.21 mg/kg.

The Meeting estimated a maximum residue level of 0.4 mg/kg (DM, based on 90% DM content) for triflumezopyrim in rice straw and a median and highest residue of 0.063 and 0.21 mg/kg (as received), respectively, for animal dietary burden calculation.

Fate of residues during processing

The Meeting received information on the hydrolysis of [pyridine-^{14}C]-, [methylene-^{14}C]- and [pyrimidine-^{14}C]-radiolabelled triflumezopyrim as well as one processing study using unlabelled triflumezopyrim on rice.

In a hydrolysis study using radiolabelled triflumezopyrim typical processing conditions were simulated (pH 4, 5 and 6 with 90°C, 100°C and 120°C for 20, 60 and 20 minutes). No degradation of the parent was observed.

The fate of triflumezopyrim during processing of raw agricultural commodity (RAC) was investigated in rice. However, no processing data was provided for the sum of triflumezopyrim and IN-Y2186. Therefore, only processing factors according to the residue definition for MRL setting (parent triflumezopyrim) could be derived.

The Meeting concluded that no residues are expected in husked and polished rice since residues were < 0.01 mg/kg during processing. In conclusion the Meeting decided to set a maximum residue level of 0.01 mg/kg for polished rice.

Residues in animal commodities

Farm animal feeding studies

The Meeting received one feeding study involving triflumezopyrim on lactating cows. No poultry feeding study was submitted.

Residues were < 0.01 mg/kg in all samples of the 1.3 and 4 ppm treatment rates. In milk, residues of triflumezopyrim in the 13 ppm group were up to 0.025 mg/kg (mean: 0.022 mg/kg). Skim milk and cream were analysed individually in the 13 ppm dosing group only, showing residues of up to 0.021 mg/kg (mean: 0.019 mg/kg) for skim milk and up to 0.029 mg/kg (mean: 0.026 mg/kg) for cream. In tissues, muscle and fat did not contain residues of triflumezopyrim at or above 0.01 mg/kg. Only liver and kidney samples from the 13 ppm dosing group contained residues with maximum at 0.036 mg/kg (mean: 0.034 mg/kg) and 0.024 mg/kg (mean: 0.023 mg/kg), respectively.

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, Triflumezopyrim, ppm of dry matter diet							
	US-Canada		EU		Australia		Japan	
	max.	Mean	max.	mean	max.	Mean	max.	Mean
Beef cattle	0.008	0.008	0.023	0.007	0.16[a]	0.061[b]	0.13	0.041
Dairy cattle	0.008	0.008	0.014	0.006	0.075	0.043	0.06	0.019
Poultry – broiler	0.007	0.01	0.001	0.001	0.017[c]	0.017[d]	0.0007	0.0007
Poultry – layer	0.001	0.012	0.0007	0.001	0.017[c]	0.017[d]	0.003	0.003

[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 STMR estimates for mammalian meat and milk

[c] Highest maximum broiler or laying hen burden suitable for MRL estimates for poultry products and eggs

[d] Highest mean broiler or laying hen burden suitable for STMR estimates for poultry products and eggs

none no relevant feed items

Animal commodities maximum residue levels

For beef and dairy cattle a maximum and mean dietary burden of 0.16 ppm and 0.061 ppm were estimated, respectively. The estimated dietary burdens are evaluated against a lactating cow feeding study involving administration of triflumezopyrim at 1.34, 4.03 and 13.48 ppm. At the lowest level of 1.34 ppm no parent residues >º0.01 mg/kg were found in whole milk, skim milk, cream, muscle, liver, kidney or fat.

The Meeting concluded that the dietary burden is 8–22 times lower than the lowest dose administered in the cow feeding study (1.34 ppm). Therefore, no residues > 0.01 mg/kg are expected in milk, cream and cattle tissues.

For poultry no farm animal feeding studies were provided. Laying hen metabolism studies involved administration of up to 14–15 ppm triflumezopyrim in the diet. Residues of triflumezopyrim were up to 0.25 mg/kg in liver. The maximum dietary burden for broiler and layer poultry of 0.017 ppm is at least 824 times lower than the dose administered in the hen metabolism study. Therefore, no residues > 0.01 mg/kg are expected in eggs, egg yolks and hen tissues.

In conclusion, the Meeting decided to set a maximum residue level of 0.01* mg/kg for matrices of animal origin, as well as a STMR and HR of 0 mg/kg.

RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed in Annex 1 are suitable for establishing maximum residue limits and for IEDI/IESTI assessmentThe

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

Definition of the residue for the dietary intake for plant commodities: *Sum of triflumezopyrim and 3-(trifluoromethyl)benzoic acid (IN-Y2186), expressed as triflumezopyrim*

Definition of the residue for the dietary intake for animal commodities: *Triflumezopyrim*

The residue is not fat-soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The evaluation of triflumezopyrim has resulted in recommendations for MRLs and STMRs for raw and processed commodities. The International Estimated Daily Intakes for the 17 GEMS/Food cluster diets, based on this years estimated STMRs, were in the range 0–0.2% of the maximum ADI of 0.2 mg/kg bw. The results are shown in Annex 3 to the 2017 Report.

The Meeting concluded that the long-term dietary exposure to residues of triflumezopyrim from uses that have been considered by the Meeting is unlikely to present a public health concern.

Short-term dietary exposure

The International Estimated Short Term Intake (IESTI) for triflumezopyrim was calculated from recommendations for STMRs for raw and processed commodities in combination with consumption data for corresponding food commodities. The results are shown in Annex 4.

The IESTI for the diets submitted to the JMPR represented 0% of the ARfD (1 mg/kg bw). The Meeting concluded that the short-term dietary exposure to residues of triflumezopyrim from uses considered by the Meeting is unlikely to present a public health concern.

6 FUTURE WORK

The items listed below are tentatively scheduled to be considered by the Meetings in 2019. The compounds listed include those recommended as priorities by the CCPR at its Forty-ninth and earlier Sessions and compounds scheduled for re-evaluation within the CCPR periodic review programme.

Updated calls for data are available at least ten months before each JMPR meeting from the web pages of the Joint Secretariat.

http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmpr/en/

NEW COMPOUNDS

TOXICOLOGY EVALUATIONS	RESIDUE EVALUATIONS
Afidopyropen (999) (Insecticide) [USA]	Afidopyropen 999) (insecticide)
Metconazole (999) (Fungicide) Japan	Metaconazole
Orthosulfamuron (999) (Herbicide)	Orthosulfamuron
Pyflubumide (999) (Acaricide)	Pyflubumide
Pyridate (999) (Herbicide)	Pyridate
Pyrifluquinazon(999) (Insecticide) Japan	Pyrifluquinazon
SYN546330/spiropidion (999) (insecticide)	SYN546330/spiropidion (999) (insecticide)
Triflumuron (999) (Insecticide)	Triflumuron
Valifenalate (999) (Fungicide)	Valifenalate

PERIODIC RE-EVALUATIONS	
TOXICOLOGY	**RESIDUE**
Aldicarb (117)	Aldicarb (117)
Amitraz (122)	Amitraz (122)
Azinphos-methyl (002)	Azinphos-methyl (002)
Carbosulfan (145)/Carbofuran (096)	Carbosulfan (145)/Carbofuran (096)
Dimethoate (027)	Dimethoate (027)
Fenarimol (192)	Fenarimol (192)
Phosalone (060)	Phosalone (60)
Tolclofos-methyl (191)	Tolclofos-methyl (191)

NEW USES AND OTHER EVALUATIONS	
TOXICOLOGY	**RESIDUE**
	Trinexapac-ethyl (271)
	Picoxystrobin (258)
	Benzovindiflupyr (261)
	Bifenthrin(178)
	Penthiopyrad (253)
Isoprothiolane (299)	Isoprothiolane (299)
	Clofentezine (156)
	Cyclaniliprole (296)
	Cypermethrins (118)
	Fenpyroximate (193)
	Fluazifop-p-butyl (283)
	Fluensulfone (265)
	Lambda-cyhalothrin (146)
	Isoxaflutole (268)
	Pyriofenone (999)
	Pyrifluquinazon (999)
	Spirotetramat (234)
	Thiamethoxam(245)

NEW USES AND OTHER EVALUATIONS	
TOXICOLOGY	**RESIDUE**
	Tolfenpyrad (269)
XDE-777	XDE-777 (999)
	Buprofezin (173)
	Acephate (095)
	Acetamiprid (246)
	Bifenthrin (178)
	Carbendazim (72)
	Chlorpyrifos (017)
	Clofenapyr (254)
	Clothianidin (238)
	Cypermethrin (118)
	Deltamethrin (35)
	Diazinon (022)
	Dicofol (026)
	Dimethoate (027)
	Fenpropathrin (185)
	Imidacloprid (206)
	Metalaxyl (138)
	Methomyl (094)
	Parathion (059)
	Phosalone (060)
	Phorate (112)
	Profenofos (171)
	Propiconazole (160)
	Thiamethoxam (245)
	Triazophos (143)
	Spiromesifen (294)
	Lambda-cyhalothrin (146)

NEW USES AND OTHER EVALUATIONS - EXTRAORDINARY MEETING	
TOXICOLOGY	**RESIDUE**
	Chlorantraniliprole (230)
Chlorothalonil (81)	Chlorothalonil (081)
	Mesotrione (277)
	Thiabendazole (065)
	S-Methoprene (147)
	Acetochlor (280)
	Tebuconazole (189)
	Flupyradifurone (285)
Boscalid (221)	Boscalid (221)
	Mandestrobin (999)
	Pendimethalin (292)
	Fosetyl-Al (302)
	Cyantraniliprole (263)
	Cyprodinil (207)
	Azoxystrobin (229)
	Dicamba (240)
	Flonicamid (282)
	Metaflumizone (236)

7 CORRIGENDA

Pesticide Residues in Food 2016. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues. FAO Plant Production and Protection Paper, 229, 2016

Changes are shown in bold

Fipronil (202)

Recommendations Page 92
Definition of the residue (for dietary risk assessment) for animal commodities*: fipronil, fipronil-desulfinyl, fipronil-sulfone and fipronil-thioether for plant and animal commodities, expressed as fipronil*

Annex 1 Page 425

Definition of the residue (for dietary risk assessment) for animal commodities*: fipronil, fipronil-desulfinyl, fipronil-sulfone and fipronil-thioether for plant and animal commodities, expressed as fipronil*