5.20 Pyflubumide (314)

TOXICOLOGY

Pyflubumide is the ISO-approved common name for 3′-isobutyl-*N*-isobutyryl-1,3,5-trimethyl-4′-[2,2,2-trifluoro-1-methoxy-1-(trifluoromethyl)ethyl]-1*H*-pyrazole-4-carboxanilide (IUPAC), with the CAS number 926914-55-8. It is a novel acaricide and, so far, the only one with a carboxanilide structure. Its highly specific pesticidal mode of action is by inhibition of the mitochondrial complex II following formation of the active NH– form as a metabolite in the target pest.

Pyflubumide has not been evaluated before by JMPR and was reviewed by the present Meeting at the request of CCPR. Most critical studies contained statements of compliance with GLP and were conducted in accordance with current test guidelines. A few non-GLP pharmacological and mechanistic studies were also of good quality and were reported in detail. Since pyflubumide is a new compound, published information is very scarce.

Biochemical aspects

Following oral administration to rats of ^{14}C-radiolabelled pyflubumide as a single low dose of 1 mg/kg bw, the compound was rapidly absorbed (T_{max} 6 h) but only partially so. Based on urinary (< 6%) and biliary (ca 43%) excretion, cage wash, tissue and carcass residues after 72 hours, absorption accounted for ca 52% of the applied dose. Absorption of a single dose of 100 mg/kg bw is expected to be only marginally lower, however, a final conclusion cannot be drawn because this high dose was not administered to bile-cannulated rats. The absorbed portion was widely distributed throughout the body, with highest concentrations found in liver and kidneys, adrenals, bone marrow and fat. Elimination was nearly complete at the low- and high-dose levels after seven days, with faeces being the main route of elimination, accounting for 90% or more. In nursing rats, excretion of pyflubumide and of some of its metabolites via the milk was demonstrated. The milk:plasma radioactivity ratio was approximately 10:1, and the AUC was up to 7.5 times higher in milk than in plasma.

Extensive metabolism of pyflubumide was observed, at least of the systemically available portion. The main metabolic pathways comprised deacylation of the nitrogen atom, followed by hydroxylation and demethylation, whereas cleavage of the molecular backbone of pyflubumide was very limited. Eight or nine metabolites were identified in urine, faeces, plasma or milk, but each of these displayed a different mix of metabolites. In bile there were 12 metabolites. Main metabolites (exceeding 10% of administered dose in either excreta or plasma in ADME studies) were pyflubumide-NH (Metabolite B), pyflubumide-NH-1-H-RfOH (Metabolite F) and pyflubumide-NH-1-H-3′-(3-OH)-RfOH (Metabolite R). The unchanged parent compound was mainly detected in the GI tract and faeces, representing the non-absorbed part, but to a small extent also in milk.

The impact of sex, dose, or position of radiolabel on toxicokinetics or metabolism was low.

Toxicological data

In rats, the acute oral and dermal LD_{50} was > 2000 mg/kg bw whereas the inhalation LC_{50} was above 5.23 mg/L in a 4-h, nose-only, exposure experiment. Pyflubumide was not irritating to the skin or to the eyes of rabbits and proved negative for skin sensitization in a local lymph node assay.

Oral (feeding) short-term toxicity studies with pyflubumide were performed in mice (28-day and 90-day), rats (28-day and 90-day), and dogs (90-day and one-year). In the mouse, the main target organs of toxicity were the liver and the haematopoietic system. In the rat, the main target organs of toxicity were the liver, thyroid, haematopoietic system and heart. In the dog, the main target organs of toxicity were the heart, liver and adrenals.

In a 28-day study in mice, the dietary dose levels were 0, 20, 200 and 2000 ppm (equal to 0, 3.0, 32, and 297 mg/kg bw per day in males, 4.1, 40, and 396 mg/kg bw per day in females). A further group receiving 10 000 ppm was prematurely terminated due to excessive toxicity. The dose of 20 ppm

(equal to 3.0 mg/kg bw per day) was the NOAEL, based on increased liver weight with associated histopathology in both sexes, resulting from 200 ppm (equal to 32 mg/kg bw per day).

In a 90-day study in mice, dietary doses of 0, 40, 400 and 4000 ppm (equal to 0, 5.3, 51, and 505 mg/kg bw per day in males, 0, 6.4, 64, and 596 mg/kg bw per day in females) were administered. The NOAEL was 400 ppm (equal to 51 mg/kg bw per day), based on liver toxicity (increased liver weight with associated histopathology and clinical-chemistry parameters), slight effects on red blood parameters with an increase in spleen weight, follicular cell hypertrophy of the thyroid and eosinophilic changes in the zona fasciculata of the adrenals at 4000 ppm (equal to 505 mg/kg bw per day).

In a 28-day study in the rat, dietary dose levels of 0, 200 and 2000 ppm (equal to 0, 17, and 137 mg/kg bw per day in males, 0, 17, and 140 mg/kg bw per day in females) were fed to the animals. A further group receiving 20 000 ppm was prematurely terminated due to excessive toxicity. Treatment-related and adverse effects were seen at all dose levels, with effects on liver, heart and thyroid from the lowest dose of 200 ppm. A NOAEL could not be identified and the LOAEL was 200 ppm (equal to 17 mg/kg bw per day).

In a subsequent 90-day study in rats, animals were administered dietary doses of 0, 20, 200 and 1200 ppm (equal to 0, 1.2, 12, and 72 mg/kg bw per day in males, 0, 1.4, 14, and 81 mg/kg bw per day in females). An additional control group and second high-dose group were included to assess their recovery when fed an untreated diet for four weeks after dosing had ceased. The NOAEL was 20 ppm (1.2 mg/kg bw per day) based on increased heart weights in both males and females at 200 ppm (equal to 12 mg/kg bw per day). The adverse findings were only partly reversible during the recovery period.

In a 90-day feeding study in dogs, the dose levels were 0, 40, 300 and 2500 ppm (equal to 0, 1.2, 9.1, and 77 mg/kg bw per day in males, 0, 1.3, 9.5, and 75 mg/kg bw per day in females). The NOAEL was 300 ppm (equal to 9.1 mg/kg bw per day). Adverse, treatment-related effects were confined to the top dose of 2500 ppm (equal to 75 mg/kg bw per day) and consisted of cardiotoxicity (increased heart weights with associated histopathology and functional changes), increased liver weights with associated histopathology, clinical-chemistry parameters and rare histological kidney findings.

A one-year study was performed in dogs using dietary dose levels of 0, 40, 300 and 2000 ppm (equal to 0, 1.1, 8.0, and 54 mg/kg bw per day in both sexes). The NOAEL was 40 ppm (equal to 1.1 mg/kg bw per day) based on histopathological changes in the adrenals (hypertrophy, lipid depletion and thickening of the zona fasciculata) at 300 ppm (equal to 8 mg/kg bw per day).

In the 18-month study on mice, pyflubumide was administered at dietary doses of 0, 40, 400 or 1600 ppm (equal to 0, 4.4, 45, and 176 mg/kg bw per day in males, 0, 4.0, 43, and 178 mg/kg bw per day in females). The NOAEL was 400 ppm (equal to 43 mg/kg bw per day) based on lower body weight in females, on increased organ weights of liver and spleen and on histopathological findings in liver, adrenals, spleen and thyroid, which were observed either in one or both sexes at 1600 ppm (equal to 176 mg/kg bw per day). Increased tumour incidences were noted for the liver and the lymph nodes at the same maximum dose. Benign liver adenomas were increased in males only, with no progression to carcinoma noted. A possible mode of action has not been investigated. Marginal increases in haemangiosarcomas of mesenteric lymph nodes (statistically significant in a test for trend in males, and above laboratory historical control data in both sexes) were observed at 1600 ppm. Relevance to human risk of haemangiosarcoma in mice is generally considered low. On the other hand, no mode of action has been proposed and/or investigated. Additional uncertainty comes from the small number of animals in the low- and mid-dose groups in which mesenteric lymph nodes had been examined microscopically. Overall, pyflubumide was carcinogenic in mice and a NOAEL for carcinogenicity of 400 ppm (43 mg/kg bw per day) was indicated by the study.

In a one-year chronic toxicity study in rats, pyflubumide was administered at dietary concentrations of 0, 10, 20, 120, and 600 ppm (equal to 0, 0.4, 0.9, 5.1 and 26 mg/kg bw per day in males, 0, 0.5, 1.1, 6.4, 32 mg/kg bw per day in females). The NOAEL was 20 ppm (equal to 0.9 mg/kg bw per day), based on the effects on heart (weight), liver (bile duct hyperplasia), red blood

cell parameters, kidney (urinary casts and tubular basophilic changes), ovary (weight) and skin (loss of fur) at 120 ppm (equal to 5.1 mg/kg bw per day).

In a separate two-year carcinogenicity study in rats, pyflubumide was administered at dietary concentrations of 0, 10, 20, 120 and 600 ppm (equal to 0, 0.4, 0.7, 4.5, and 23 mg/kg bw per day in males, 0, 0.5, 0.9, 6, and 29 mg/kg bw per day in females). The NOAEL for chronic toxicity in this study was 20 ppm (0.7 mg/kg bw per day) based on effects on liver (weight with associated bile duct hyperplasia), heart (weight, with associated fibrosis), adrenals (medullary hyperplasia) at 120 ppm (equal to 4.5 mg/kg bw per day). No evidence of carcinogenicity was obtained in the rat and the NOAEL for carcinogenicity was 600 ppm (equal to 23 mg/kg bw per day), the highest dose tested.

The Meeting concluded that pyflubumide is carcinogenic in mice but not in rats.

Pyflubumide was tested for genotoxicity in an adequate range of studies in vitro and in vivo which were all negative.

The Meeting concluded that pyflubumide is unlikely to be genotoxic.

In the view of the lack of genotoxicity, in the absence of carcinogenicity in the rat and since the higher incidence of tumours in the mouse was confined to the highest dose, far above expected human exposure, the Meeting concluded that pyflubumide is unlikely to pose a carcinogenic risk to humans via exposure from the diet.

In a two-generation study, pyflubumide was administered to rats at dietary dose levels of 0, 7.5, 15, 100 or 500 ppm (equal to 0, 0.4, 0.8, 5.3, and 26 mg/kg bw per day for males, 0, 0.7, 1.3, 8.6, and 42 mg/kg bw per day for females). The NOAEL for parental effects was 15 ppm (equal to 0.8 mg/kg bw per day), based on increased organ weights of heart, thyroid, liver, and ovaries and histopathological findings in the heart at the dose levels above. A reproductive toxicity NOAEL of 100 ppm (equal to 5.3 mg/kg bw per day) was established because of prolonged gestation and a lower pup viability index on the day of birth at the maximum dose level of 500 ppm (equal to 26 mg/kg bw per day) even though these effects were confined to the first generation. The offspring NOAEL was 15 ppm (equal to 0.8 mg/kg bw per day), based on gross and histological lung lesions in F_1 and F_2 pups from 100 ppm (equal to 5.3 mg/kg bw per day).

In a developmental study in rats, pyflubumide was administered by oral gavage at dose levels of 0, 5, 30, and 200 mg/kg bw per day. The maternal NOAEL was 30 mg/kg bw per day since body weight gain and food consumption were reduced at the top dose level. A few of the dams even lost some body weight. In addition, placenta weights were increased. The developmental NOAEL of 30 mg/kg bw per day was based on a significantly higher mean fetal weight at the next higher dose. There was no increase in malformations or individual variations.

In a developmental study in rabbits, pyflubumide was administered by oral gavage at doses of 0, 5, 20, and 80 mg/kg bw per day. The maternal NOAEL was 20 mg/kg bw per day, based on abortions and premature delivery, lower body weight gain (or even body weight loss), reduced food intake and higher placenta weights in the high-dose group. No effects on the fetuses were observed in rabbits up to the highest dose of 80 mg/kg bw per day which was thertefore considered the developmental NOAEL.

The Meeting concluded that pyflubumide is not teratogenic.

In an acute neurotoxicity study in rats in which gavage doses of 0, 500, 1000, and 2000 mg/kg bw were administered, a systemic NOAEL could not be established since body temperature on the day of dosing was reduced in all treated male and female groups, from the lowest dose onwards. In addition, body weight gain was decreased in all male groups over the first week of the post-observation period even though no clear dose response was observed. However, the maximum dose of 2000 mg/kg bw was considered the NOAEL for neurotoxicity. A separate neurotoxicity study with repeated administration was not submitted, but no concern was identified from the available studies.

The Meeting concluded that pyflubumide is not neurotoxic.

An immunotoxicity study was not submitted but no concern was identified from the available studies.

The Meeting concluded that pyflubumide is not immunotoxic.

A number of mechanistic studies were performed to further investigate the effects on the heart and thyroid as observed in many studies in different species, and effects on lungs seen in rat offspring.

With regard to the heart gross and histopathological findings as well as the higher organ weight and clinical signs (tachycardia, lower blood pressure) observed in various studies in rats and/or dogs, mechanistic studies in the rat were carried out by single intravenous administration and on excised rat tissue. These suggested a mode of action that is considered plausible: pyflubumide or its metabolites cause vasodilatation with subsequent decrease in blood pressure. As a reflex response, heart action is increased, resulting in tachycardia and, following long-lasting maintenance of these pathophysiological conditions, morphological heart changes may ensue. This mechanism was considered relevant to humans.

Thyroid effects such as organ weight increase or follicular cell hyperplasia could be clearly attributed to inhibition of thyroid peroxidase (TPO) resulting in a lower availability of iodine, reduced concentrations of circulation triiodothyronine (T_3) and thyroxine (T_4) and, because of hormonal feedback regulation, an increase in thyroid stimulating hormone (TSH) release.

It could be demonstrated that pyflubumide and a number of its metabolites are excreted by lactating rat females to a significant extent via the milk. In cross-fostering experiments, it was shown that the lung lesions in rat pups, as observed in the two-generation study, can be clearly attributed to postnatal exposure via the milk but were not due to in utero exposure. Young pups exhibited similar lung changes after repeated gavage application of a dose of 10 mg/kg bw per day or above from PND four to 13. It seems that there is a critical window of sensitivity for this effect. Alveolar dilatation was already observed when the test substance was applied by oral gavage administration of pups at a dose level of 50 mg/kg bw on two consecutive days, provided the pups were not older than seven days.

Toxicological data on metabolites and/or degradates

The pyflubumide plant metabolites 1,3,5-trimethylpyrazole-4-carboxylic acid (Metabolite H) and 3′-isobutyl-4′-[2,2,2-trifluoro-1-methoxy-1-(trifluoromethyl)ethyl]isobutylanilide (Metabolite L) were of low acute oral toxicity since the LD_{50} in rats, in both cases, was greater than 2000 mg/kg bw. In addition, these two metabolites proved negative in the Ames test. If an evaluation of these metabolites becomes necessary, the TTC approach (Cramer class III) is considered appropriate and applicable.

A mechanistic study revealed that the metabolite pyflubumide-NH-RfOH (Metabolite D) had a higher potency than the parent compound in causing vasodilatation of aorta specimens in vitro. When administered by oral gavage to rat pups from PND 4–13 at a dose level of 50 mg/kg bw per day, it caused alveolar dilatation, similar to the parent compound. In ADME studies, this metabolite was detected following single oral application of 100 mg/kg bw of pyflubumide, at a rate of up to 8.4% of the applied dose in rat plasma but was not found in excreta. In addition, it accounted for up to 7% of total residues in milk following single oral administration of the same dose to rats.

The NH-form of pyflubumide (Metabolite B, that is the acaricidal compound), also caused alveolar dilatation in rat pups when administered by oral gavage from PND 4–13 at a dose level of 50 mg/kg bw per day, meaning that is was of similar potency with regard to this effect as the parent compound. This is of particular relevance since it was the main metabolite in rat milk, accounting for up to 58% of total milk residues. In the ADME studies, at a dose level of 100 mg pyflubumide/kg bw, it had been detected only in faeces at rates between 11% and 19% of the applied total dose, but not in urine, whereas it occurred in plasma only in traces. With regard to vasodilatation in vitro, Metabolite B was of similar potency to the parent. Metabolite B has a similar structure to the parent compound. On balance, it appears reasonable to apply the ADI and ARfD as established for pyflubumide to this metabolite also. With regard to its excretion via the milk it should be taken into consideration that the ARfD is based on, and the ADI at least supported by, the reproduction study. Metabolite B can be assumed to have been tested in that study.

The metabolite pyflubumide-RfOH (Metabolite U) proved a potent inhibitor of TPO in vitro, but was inactive in an in vitro test for vasodilatation. This metabolite is a proposed intermediate in rat metabolism. It was identified as a minor metabolite in plasma, accounting for up to 4.5%, but was not found in excreta or milk. Based on its very close structural similarity to the parent compound, this metabolite is assumed not to be more toxic than its parent. Accordingly, ADI and ARfD of pyflubumide are applicable to Metabolite U, too.

Microbiological data

Not available.

Human data

Not available since pyflubumide is a new compound.

The meeting concluded that the existing database on pyflubumide is adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI for pyflubumide of 0–0.007 mg/kg bw that was derived from the NOAEL of 0.7 mg/kg bw per day based on findings in liver, heart, and adrenals in the two-year study of toxicity and carcinogenicity in rats, using a safety factor of 100. This was supported by the parental and offspring NOAELs in the two-generation study in rats (0.8 mg/kg bw per day) and by the NOAEL in the one-year study in dogs (1.1 mg/kg bw per day).

The upper range of the ADI provides a margin of over 25 000 to the LOAEL for liver adenomas and haemangiosarcomas in mice.

The Meeting established an ARfD of 0.008 mg/kg bw on the basis of the offspring NOAEL of 0.8 mg/kg bw per day for lung lesions which have been shown to occur as an acute effect in the two-generation rat study, using a safety factor of 100.

The ADI and ARfD are applicable to the metabolites pyflubumide-NH (Metabolite B) and pyflubumide-RfOH (Metabolite U).

A toxicological monograph was prepared.

Levels relevant to risk assessment of pyflubumide

Species	Study	Effect	NOAEL	LOAEL
Mouse	90-day study of toxicity	Toxicity	400 ppm, equal to 51 mg/kg bw per day	4000 ppm, equal to 505 mg/kg bw per day
	18-month chronic/ carcinogenicity study	Toxicity	400 ppm, equal to 43 mg/kg bw per day	1600 ppm, equal to 176 mg/kg bw per day
		Carcinogenicity	400 ppm, equal to 43 mg/kg bw per day	1600 ppm, equal to 176 mg/kg bw per day
Rat	Acute neurotoxicity study[b]	Neurotoxicity Toxicity	2000 mg/kg bwc -	- 500 mg/kg bw
	90-day study of toxicity	Toxicity	20 ppm, equal to 1.2 mg/kg bw per day	200 ppm, equal to 12 mg/kg bw per day
	One-year study of chronic toxicity[a]	Toxicity	20 ppm, equal to 0.9 mg/kg bw per day	120 ppm, equal to 5.1 mg/kg bw per day
	Two-year study of toxicity and carcinogenicity[a]	Toxicity Carcinogenicity	20 ppm, equal to 0.7 mg/kg bw per day 600 ppm, equal to 23 mg/kg bw per day[c]	120 ppm, equal to 4.5 mg/kg bw per day -
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity Parental toxicity Offspring toxicity	100 ppm, equal to 5.3 mg/kg bw per day 15 ppm, equal to 0. 8 mg/kg bw per day 15 ppm, equal to 0. 8 mg/kg bw per day	500 ppm, equal to 26 mg/kg bw per day 100 ppm, equal to 5.3 mg/kg bw per day 100 ppm, equal to 5.3 mg/kg bw per day
	Developmental toxicity study[b]	Maternal toxicity Embryo/foetal toxicity	30 mg/kg bw per day 30 mg/kg bw per day	200 mg/kg bw per day 200 mg/kg bw per day
Rabbit	Developmental toxicity study[b]	Maternal toxicity Embryo/foetal toxicity	20 mg/kg bw per day 80 mg/kg bw per day[c]	80 mg/kg bw per day
Dog	Thirteen-week study of toxicity[a]	Toxicity	300 ppm, equal to 9.1 mg/kg bw per day	2500 ppm, equal to 77 mg/kg bw per day
	One-year study of toxicity[a]	Toxicity	40 ppm, equal to 1.1 mg/kg bw per day	300 ppm, equal to 8.0 mg/kg bw per day

a Dietary administration.

b Gavage administration.

c Highest dose tested in study.

Acceptable daily intake (ADI) for pyflubumide, pyflubumide-NH and pyflubumide-RfOH expressed as pyflubumide

0–0.007 mg/kg bw

Acute reference dose (ARfD) for pyflubumide, pyflubumide-NH and pyflubumide-RfOH expressed as pyflubumide

0.008 mg/kg bw

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

Epidemiological, occupational health or other human observational data if they become available.

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid (T_{max}, 6 h) but incomplete (52% at low dose of 1 mg/kg bw)
Dermal absorption	No data
Distribution	Widely distributed, highest residues in liver, kidney, adrenals, bone marrow and fat
Potential for accumulation	Limited evidence for retention in fat
Rate and extent of excretion	Nearly complete within 7 days, mainly via faeces (≥90%); biliary excretion accounting for main part of absorbed dose (43%), urine less important (< 6%); excretion via milk also proven (milk:plasma ratio about 10:1)
Metabolism in animals	Extensive with 8–12 (some unique) metabolites occurring in the different matrices
Toxicologically significant compounds in animals and plants	Pyflubumide, *N*-deisobutylated pyflubumide (P-NH, "NH- form", Metabolite B), Pyflubumide-RfOH (Metabolite U)
Acute toxicity	
Rat, LD_{50}, oral	> 2000 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.23 mg/L (four-hour nose-only exposure)
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Not irritating
Dermal sensitization	Not sensitizing (local lymph node action)
Short-term studies of toxicity	
Target/critical effect	Adrenals (histopathological lesions in cortex and medulla)
Lowest relevant oral NOAEL	1.1 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Heart (organ weight, histopathology); thyroid (organ weight, histopathology); adrenals (histopathology); liver (histopathology, organ weight); bw increase in rats
Lowest relevant NOAEL	0.7 mg/kg bw per day (rat)
Carcinogenicity	Carcinogenic in mice[a]
Genotoxicity	No evidence of genotoxicity in vitro or in vivo[a]
Reproductive toxicity	
Target/critical effect	Reproductive toxicity: prolonged gestation and lower viability index at birth Offspring toxicity: histological lung lesions in rat pups due to lactational exposure Parental toxicity: increased weight of heart, liver, thyroid and ovary, myocardial fibrosis, increased body weight gain and food intake
Lowest relevant parental NOAEL	0.8 mg/kg bw per day
Lowest relevant offspring NOAEL	0.8 mg/kg bw per day
Lowest relevant reproductive NOAEL	5.3 mg/kg bw per day
Developmental toxicity	
Target/critical effect	Maternal: higher placenta weight in rats and rabbits, reduced body weight and food intake in rats and rabbits, abortions in rabbits Developmental: higher fetal weight in rats; none in rabbits
Lowest relevant maternal NOAEL	20 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	30 mg/kg bw per day (rat)
Neurotoxicity	

Acute neurotoxicity NOAEL	2000 mg/kg bw (i.e. no specific neurotoxic potential up to highest dose tested); not established for systemic effects (LOAEL 500 mg/kg bw)
Subchronic neurotoxicity NOAEL	No data, no evidence from routine studies
Developmental neurotoxicity NOAEL	No data
Immunotoxicity	No data; no concern from routine studies
Studies on toxicologically relevant metabolites	
Pyflubumide-NH (Metabolite B)	Alveolar dilatation in very young rat pups after gavage application of 50 mg/kg bw per day from PND 4–13; NOAEL 2 mg/kg bw per day Significant excretion via milk demonstrated in rats
Pyflubumide-RfOH (Metabolite U)	Inhibition of TPO but no vasodilatation in vitro
Human data	Not available for this new compound

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

Summary

	Value	Study	Safety factor
ADI[a]	0–0.007 mg/kg bw	Two-year, (rat)	100
ARfD[a]	0.008 mg/kg bw	Two-generation study; offspring toxicity (rat)	100

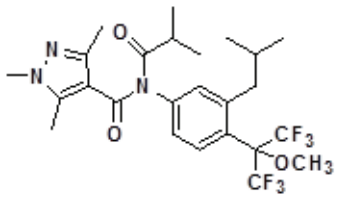
[a] Applies to pyflubumide, pyflubumide-NH, pyflubumide-RfOH, expressed as pyflubumide

RESIDUE AND ANALYTICAL ASPECTS

Pyflubumide(3'-isobutyl-N-isobutyryl-1,3,5-trimethyl-4'-[2,2,2-trifluoro-1-methoxy-1-(trifluoro-methyl) ethyl]-pyrazole-4-carboxanilide) (IUPAC name) is a new pyrazole carboxamide acaricide used for control of mites. It inhibits mitochondrial electron transport system complex II (succinic dehydrogenase complex).

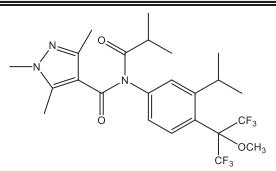
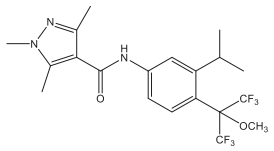
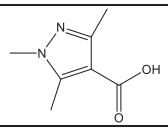
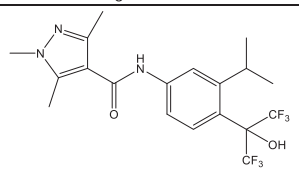
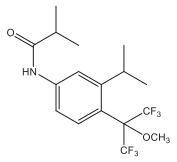
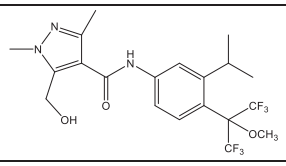
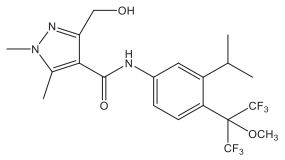
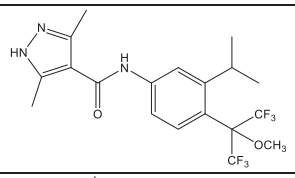
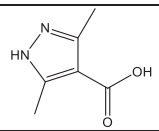
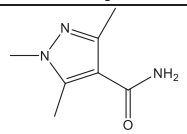
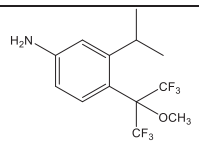
Pyflubumide was scheduled by the Forty-eighth Session of the CCPR in 2016 for toxicological and residue evaluation by the 2019 JMPR as a new compound. No specification has been established by the Joint FAO/WHO Meeting on Pesticide Specifications for pyflubumide.

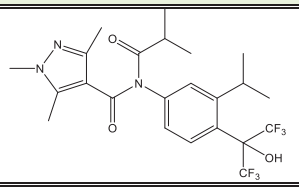
The Meeting received information on identity, physical and chemical properties, metabolism and environmental fate, residue analysis and storage stability, use pattern, supervised trials on apple and tea, and processing studies on apple and tea.



The following abbreviated names were used for the metabolites referred to in this appraisal.

Table 1 List of compounds appearing in this appraisal

Compound Name/Codes	IUPAC name	Structure
Pyflubumide/ NNI-0711	3'-isobutyl-*N*-isobutyryl-1,3,5-trimethyl-4'-[2,2,2-trifluoro-1-methoxy-1-(trifluoromethyl) ethyl]pyrazole-4-carboxanilide	
P-NH/ NNI-0711-NH Pyflubumide-NH	3'-isobutyl-1,3,5-trimethyl-4´-[2,2,2-trifluoro-1-methoxy-1-(trifluoromethyl)ethyl]pyrazole-4-carboxanilide	
P-acid/ NNI-0711-acid Pyflubumide-acid	1,3,5-trimethylpyrazole-4-carboxylic acid	
P-NH-RfOH/ NNI-0711-NH-RfOH Pyflubumide-NH-RfOH	3'-isobutyl-1,3,5-trimethyl-4´-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]pyrazole-4-carboxanilide	
P-aniline-isobutyryl/ NNI-0711-aniline-isobutyryl Pyflubumide-aniline-isobutyryl	3'-isobutyl-4-[2,2,2-trifluoro-1-methoxy-1-(trifluoromethyl)- ethyl]phenyl]isobutylanilide	
P-NH-5-CH_2OH/ NNI-0711-NH-5-CH_2OH Pyflubumide-5-CH_2OH	5'-hydroxymethyl)-3'-isobutyl-1,3-dimethyl-4´-[2,2,2-trifluoro-1-methoxy-1-(trifluoromethyl)ethyl] pyrazole-4- carboxanilide	
P-NH-3-CH_2OH/ NNI-0711-NH-3-CH_2OH Pyflubumide-3-CH_2OH	3-(hydroxymethyl)-3'-isobutyl-1,5-dimethyl-4'-[2,2,2-trifluoro-methoxy-1-(trifuluoromethyl) ethylpyrazole-4-caroxanilide	
P-NH-1-H/ NNI-0711-NH-1-H Pyflubumide- NH-1-H	3'-isobutyl-3,5-dimethyl-4´-[2,2,2-trifluoro-1-methoxy-1-(trifluoromethyl)ethyl]pyrazole-4-carboxanilide	
P-acid-1-H/ NNI-0711-acid-1-H Pyflubumide- acid-1-H	3,5-dimethylpyrazole-4-carboxylic acid	
P-amide/ NNI-0711-amide Pyflubumide-amide	1,3,5-trimethylpyrazole-4-carboxamide	
P-aniline/ NNI-0711-aniline Pyflubumide-aniline	3-isobutyl-4-[2,2,2-trifuluoro-1-methoxy-(trifuluoromethyl)ethyl] aniline	

Compound Name/Codes	IUPAC name	Structure
Pyflubumide-RfOH NNI-0711-RfOH	3'-Isobutyl-N-isobutyryl-1,3,5-trimethyl-4'-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl] pyrazol-4-carboxanilide	

Based on the information on physical and chemical properties, pyflubumide is not volatile and much more soluble in organic solvents than in water with a $LogP_{ow}$ of 5.34 indicating that translocation of pyflubumide in plants is unlikely to be significant. Photolysis seemed to be the major degradation pathway of pyflubumide.

Plant metabolism

The Meeting received information on the fate of pyflubumide in apple, eggplant and spinach after one foliar spray application. For the studies, pyflubumide labelled with ^{14}C at the phenyl ring ([U-phenyl-^{14}C]-pyflubumide; abbreviated as phenyl-label hereafter) and at position 3 or 5 of the pyrazole ring ([pyrazole-3(5)-^{14}C]-pyflubumide; abbreviated as pyrazole-label hereafter) were used. In metabolism studies, total radioactive residues (TRR) are expressed in mg pyflubumide equivalents/kg.

Apple

Phenyl- or pyrazole-labelled pyflubumide was applied to apple plants, grown outdoors, as a foliar spray once at a rate of 360 or 350 g ai/ha, (concentration: ca. 10 g ai/hL). Fruit and leaf samples were collected 0–51 days after the application.

TRR after the treatment with either of the labelled pyflubumide decreased in the fruit from 0.16–0.19 mg eq/kg at 0 DAT to 0.090–0.096 mg eq/kg at 7 DAT and then to 0.058–0.068 mg eq/kg at 51 DAT. In leaves, TRR decreased from 17 mg eq/kg at 0 DAT to 12 mg eq/kg at 7 DAT and then to 5.1–5.4 mg eq/kg at 51 DAT.

Distribution of radioactivity in fruits and leaves was similar between the two ^{14}C-labelled pyflubumide treatments. Most of the radioactivity was recovered in the acetone surface wash of fruits and leaves, accounting for 77–98% TRR and 86–98% TRR, respectively at 0–7 DAT, decreasing to 54–65% TRR at 51 DAT. Acetone, acetone/water, and acetone/1 M HCl (1:1, v/v) further extracted additional radioactivity. Total extractability was 86–100% TRR throughout the study period.

The most abundant radioactive residue in the surface wash and extracts was the parent pyflubumide accounting for 88–92% TRR in fruits and leaves (16 mg/kg) at 0 DAT and decreased to 50–56% TRR at 7 DAT and then to 17–28% at 51 DAT. P-NH was the only identified metabolite. Its proportion increased from 1.2–2.7% TRR at 0 DAT to 13–18% TRR at 14–28 DAT and 12–16% TRR by 51 DAT. Its concentration peaked at 7–14 DAT around 0.013–0.018 mg eq/kg in fruits and 1.3–1.6 mg eq/kg in leaves. Beta-glucosidase did not release radioactive compounds from surface wash and acetone extract, suggesting that glucose conjugates were not present.

Total unidentified residues in washes and extracts increased over time accounting for up to 61% TRR at 51 DAT. They consisted of multiple (e.g. up to 23 peaks in surface washes) minor peaks in HPLC and each peak accounted for < 10% TRR and < 0.01 mg eq/kg.

Unextracted radioactivity increased from < 0.2% TRR at 0 DAT to a maximum of 14% TRR at 51 DAT, and the concentration in pyflubumide equivalents also increased. Treatments of the unextracted residues from 28 and 51 DAT leaf samples with 1 or 6 M HCl or 1 M KOH at 50 °C for 4 hours released < 1% TRR but the treatment with 24% KOH released up to 5% TRR.

Eggplant

Phenyl- or pyrazole- labelled pyflubumide was applied as a foliar spray at a rate of 490 or 550 g ai/ha

(ca. 20 g ai/hL) to eggplants, grown in a greenhouse, equipped with a UV-transparent ceiling.

The TRR in fruits and leaves after treatment with labelled pyflubumide decreased from 0 DAT (0.76–1.4 mg eq/kg in fruits and 55–74 mg eq/kg in leaves) to 7 DAT (0.66–0.88 mg eq/kg in fruits and 31–48 mg eq/kg in leaves). Most of the radioactivity was recovered in acetone surface wash throughout the study period in fruits and leaves: 93–99% TRR for fruits, and 86–96% TRR for leaves. Acetone and acetone/water mixture further extracted additional radioactivity. A total of 95–100% TRR in fruits and leaves were recovered in washes and extracts. A very small proportion of radioactivity remained unextracted in fruits (up to 5.0% TRR) and leaves (up to 5.2% TRR). TRR of only < 0.01–0.03 mg eq/kg was found in roots (sampled only at 14 DAT) indicating that there is little transfer from the sprayed parts of the plant to the roots.

Most of the radioactivity in the surface washes and extracts was the parent pyflubumide (90–98% TRR for fruits and 90–99% TRR for leaves) with some small amounts of radioactive metabolites/components. P-NH, also found in the apple study, P-aniline-isobutyryl, P-acid, P-NH-RfOH (only on/in leaves) and P-NH-5-CH_2OH (only on/in leaves at DAT 14) were detected. None of them exceeded 1.3% TRR in either fruits or leaves. In fruit samples they were found at a maximum of 0.01 mg eq/kg and in leaf samples up to 0.59 mg eq/kg.

Spinach

Phenyl- or pyrazole-labelled pyflubumide was applied to spinach as a single foliar spray at a rate of 550 or 570 g ai/ha (ca. 20 g ai/hL) grown in a greenhouse equipped with a UV-transparent ceiling.

A single application of either ^{14}C-labelled pyflubumide resulted in similar total radioactive residues (TRR) in leaves, decreasing over time from 12–13 mg eq/kg at 0 DAT to the lowest of 4.7–5.8 mg eq/kg at 14 DAT. TRR in roots and new leaf growth (post-application) were < 0.01–0.03 mg eq/kg indicating that there is little translocation from the sprayed parts to roots or new leaves.

The distribution of radioactivity in leaves was similar between the two ^{14}C-labelled pyflubumide treatments. Most of the radioactivity was recovered in the chloroform surface wash of leaves, accounting for 84–92% TRR (11–12 mg eq/kg) at 0–1 DAT. The radioactivity in the surface wash decreased to 83–87% TRR (5.0–6.3 mg eq/kg) at 21 DAT.

Acetone and acetone/water further extracted additional radioactivity (8.2–17% TRR at 0–1 DAT; and 13–16% TRR at 21 DAT). Total extractability was almost 100% TRR throughout the study period.

The most abundant radioactive residue in the surface wash and extracts was the parent pyflubumide accounting for almost 100% TRR (12–13 mg/kg) at 0 DAT but decreased to 83–91% (5.0–6.4 mg/kg) at 21 DAT. Only P-NH and P-acid were identified as metabolites at 14–21 DAT at a maximum of 3.2% TRR (0.19 mg eq/kg) at 21 DAT. There was one unknown metabolite detected in the extracts, which accounted for 4.1–5.0% TRR (0.28–0.31 mg eq/kg) at 21 DAT and was suspected to be a position-isomer of the parent based on its molecular weight.

Up to 6.3% TRR remained at the origin after TLC (indicating a polar fraction). The beta-glucosidase treatment decreased the radioactivity at the TLC origin and released P-acid (1.3–1.4% TRR), indicating that a fraction of the material was possibly a glucoside of P-acid.

Summary of plant metabolism

When pyflubumide was applied as a single foliar spray to apple, eggplant and spinach, metabolism of pyflubumide was qualitatively similar. Pyflubumide was the major component of the residue. Up to 6 metabolites, P-NH (apple, eggplant and spinach), P-aniline-isobutyryl (eggplant), P-acid (eggplant and spinach), P-NH-RfOH (eggplant leaf) and P-NH-5-CH_2OH (eggplant leaf) were identified. However, among them, only P-NH accounted for more than 10% TRR, with a maximum of 18% TRR (0.018 mg eq/kg) in apple and lower levels up to 3.2% TRR in eggplant and spinach (< 0.01 mg eq/kg in eggplant fruit and up to 0.19 mg eq/kg in spinach leaf).

All identified metabolites, except P-NH-5-CH_2OH found in eggplant leaf, were also reported in the rat metabolism study.

Animal metabolism

Metabolism studies on laboratory animals were reviewed in the framework of toxicological evaluation by the current JMPR. No other animal metabolism studies were provided to the Meeting.

Environmental fate

The Meeting received information on hydrolysis, photolysis and aerobic degradation in soil for pyflubumide.

Hydrolysis

Pyflubumide was hydrolysed faster at pH 9 than pH 4 or 7 in buffers. Estimated half-lives at 25 °C are 32 days at pH 4, 28 days at pH 7 and 6.6 days at pH 9. Regardless of pH, major hydrolysates which increased over time and occurred > 10% AR were P-NH, P-aniline-isobutyryl and P-acid. Hydrolysis is not expected to be a significant route of degradation at environmental pH.

Photolysis in buffer and natural water

In irradiated pH 4 buffer solution, pyflubumide was rapidly decomposed with a mean half-life of 1.2 days compared to that of about 34 days in the dark controls. Therefore, irradiation was regarded to be a significant factor contributing to environmental degradation of the compound. Major degradates occurring > 10% AR were P-NH, P-aniline-isobutyryl, P-acid and P-amide, which were further photolysed.

Aerobic degradation in soil

Pyflubumide degraded in a clay loam soil under laboratory conditions with a half-life of 37 days. The main degradate formed was P-NH and it reached up to 82% AR after 112 days. Consequential mineralization to carbon dioxide was confirmed and a small amount of unextracted radioactivity existed. P-NH was the only degradate found above 10% AR. Pyflubumide is not persistent in soil.

Residues in succeeding or rotational crops

No information was provided to the Meeting.

Methods of analysis

An analytical method for the determination of residues of pyflubumide in data development was provided to the current Meeting for apple and its processed commodities, as well as dry tea leaves and tea infusion.

In general, the method employs extraction by homogenization with acetone and partitioning with hexane for analysis of pyflubumide, P-NH and P-aniline-isobutyryl. The extract is cleaned up and analysed by HPLC-MS or HPLC-MS/MS. The method was validated for apple matrices and found to be suitable for data development to determine pyflubumide, P-NH, P-aniline-isobutyryl and P-acid with an LOQ of 0.01 mg/kg for apple and 0.005 mg/kg for apple processed products. The mean recoveries were within the acceptable range (71–119%). The method was also validated for tea matrices and found to be suitable for data development with LOQs of 0.01 mg/kg in dry tea leaves and tea infusion. The mean recoveries were in the acceptable range (70–114%).

A QuEChERS method was validated and found to be suitable for multi-residue analysis with LOQs of 0.005 mg/kg for pyflubumide and P-NH in apple, grapes, wheat grain, dry tea leaves and canola seeds. The mean recoveries were in the acceptable range (74–110%).

No information on analytical methods for commodities of animal origin was submitted to the Meeting.

Stability of residues in stored analytical samples

The stability of pyflubumide and P-NH during frozen storage at -20°C or below was investigated in homogenized apple and dry tea leaves. The control samples from supervised trials were spiked with pyflubumide or P-NH and stored under the same conditions as treated samples. These spiked samples were analysed after all the treated samples were analysed to confirm the stability of analytes. The Meeting considered that these compounds were stable in homogenized apple for at least 87 days (longer than the storage period of trial samples) and dry tea leaves for at least 107 days (longer than the storage period of trial samples) under frozen conditions.

Definition of the residue

Plant commodities

The predominant residue was parent pyflubumide: 50–92% TRR in apple fruits and leaves at 0–7 DAT, > 90% TRR in eggplant fruits during 0–14 DAT and 83–100% TRR in spinach leaves during 0–21 DAT.

Suitable analytical methods are available for plant commodities to determine pyflubumide.

The Meeting considered that pyflubumide was a suitable marker for enforcement of MRLs.

For dietary risk assessment, the Meeting noted that in the plant metabolism studies, P-NH (apple, eggplant and spinach), P-aniline-isobutyryl (eggplant), P-acid (eggplant and spinach), P-NH-5-CH_2OH (eggplant leaf) and P-NH-RfOH (eggplant leaf) were identified. Among them only P-NH accounted for > 10% TRR (apple). These metabolites were also found in the rat metabolism although some of them at trace levels.

P-NH occurred at up to 11–12% AR after simulated sterilization at pH 6. It increased in proportion compared to the parent during the processing of apple.

In the supervised trials, pyflubumide and P-NH were analysed. In the apple trials P-NH was below the LOQ of 0.01 mg/kg or slightly higher (up to 0.03 mg/kg). However, in the tea trials, P-NH was sometimes found at higher levels than the parent, perhaps due to the processing of fresh leaves to dry leaves. The current Meeting noted that the ADI and ARfD covers the parent, P-NH and pyflubumide-RfOH (detected in rat but not detected in plant metabolism studies).

P-aniline-isobutyryl was below the LOQ in three apple trials in which it was analysed and <LOQ (0.007 mg eq/kg) in apple processed commodities except dry pomace (0.056–0.083 mg eq/kg). It was not analysed in the tea trials or processing studies.

P-acid was <LOQ (0.04 mg eq/kg) in apple RAC and <LOQ (0.02 mg eq/kg) in apple processed commodities except dry pomace (0.08 mg eq/kg). It was not analysed in the tea trials or processing studies.

The Meeting concluded that dietary exposure to P-aniline-isobutyryl or P-acid would be insignificant and therefore decided not to include these metabolites in the residue definition for dietary risk assessment.

The Meeting considered that in addition to pyflubumide, P-NH should be included in the residue definition for risk assessment.

Animal commodities

The Meeting did not receive information on livestock metabolism, feeding studies or analytical methods for animal commodities. There would be some dietary burden arising from the use of apple wet pomace for feed.

The Meeting considered that it is not possible to determine residue definitions for pyflubumide in animal commodities due to the lack of information.

Conclusion

Based on the above, the Meeting recommended the following residue definitions.

Definition of the residue for compliance with the MRL for plant commodities: *Pyflubumide.*

Definition of the residue for for dietary risk assessment for plant commodities: *Sum of pyflubumide and 3'-isobutyl-1,3,5-trimethyl-4′-[2,2,2-trifluoro-1-methoxy-1-(trifluoromethyl)ethyl]pyrazole-4-carboxanilide (P-NH), expressed as pyflubumide*.

Results of supervised residue trials on crops

The Meeting received supervised trial data for pyflubumide on apple and tea.

Apple

Critical GAP in Japan for apple allows one application at a concentration of 10 g ai/hL and a PHI of 1 day.

Ten supervised trials were conducted on apple in Japan. Pyflubumide was applied once as foliar spray at a spray concentration of 10 g ai/hL (eight trials) or 20 g ai/hL (two trials).

Pyflubumide from trials matching the critical GAP in Japan were in rank order (n = 8): 0.13, 0.23, 0.23, 0.34, 0.44, 0.45, 0.46 and 0.52 mg/kg.

Total residues (sum of pyflubumide and P-NH expressed in pyflubumide) from trials matching the critical GAP in Japan were in rank order (n = 8): 0.15, 0.25, 0.25, 0.36, 0.46, 0.47, 0.48 and 0.55 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg, STMR of 0.41 mg/kg and HR of 0.55 mg/kg for apple.

The Meeting noted that the calculated IESTI for raw apples were up to 160% of the ARfD for the general population and up to 390% for children. However, no alternative GAP is available.

Tea

Critical GAP in Japan for tea allows one application at a concentration of 10 g ai/hL and PHI of 7 days.

Eight independent supervised trials were conducted on tea in Japan. Pyflubumide was applied once as a foliar spray at a concentration of 10 g ai/hL (six trials) or 5 g ai/hL (two trials).

Pyflubumide in dried green tea leaves from trials matching the critical GAP in Japan were in rank order (n = 6): 1.7, 2.9, 6.1, 12, 19 and 23 mg/kg. In two other trials where spray concentrations were 5 g ai/ha with the same water volume, unscaled pyflubumide residues were: 0.85 and 25 mg/kg. Using a scaling factor of 2, scaled residues were: 1.7 and 50 mg/kg.

Combined pyflubumide residues were in rank order (n = 8): 1.7, 1.7, 2.9, 6.1, 12, 19, 23 and 50 mg/kg.

Total residues (sum of pyflubumide and P-NH expressed in pyflubumide) from trials matching the critical GAP in Japan were in rank order (n = 6): 3.3, 6.5, 9.1, 17, 27 and 34 mg/kg. In other trials at a concentration two times higher, unscaled total residues were: 3.1 and 34 mg/kg. Using a scaling factor of 2, scaled residues were: 6.2 and 68 mg/kg.

Combined total residues were in rank order (n = 8): 3.3, 6.2, 6.5, 9.1, 17, 27, 34 and 68 mg/kg.

The Meeting estimated a maximum residue level of 80 mg/kg and STMR of 13 mg/kg for tea, green, black (black, fermented and dried).

The calculated IESTI for tea leaves were up to 230% of the ARfD for the general population and up to 150% for children. However, the calculated IESTI for tea infusion were 2% of the ARfD for general population (no value for children). The Meeting noted that as the $LogP_{ow}$ of pyflubumide is 5.34 and P-NH has a similar structure, it is unlikely that tea infusion would contain pyflubumide or P-NH at concentrations higher than the detection limit.

Fate of residues during processing

High temperature hydrolysis

The hydrolysis of phenyl-labelled and pyrazole-labelled pyflubumide was studied in a sterile buffered aqueous solution under conditions simulating pasteurization, baking/brewing/boiling, and sterilization.

Pyflubumide was stable under the condition representing pasteurization (pH 4, 90 °C, 20 minutes) with 96–97% AR recovered at the end of incubation. Under baking/brewing/boiling (pH 5, 100 °C, 60 minutes) and sterilization (pH 6, 120 °C, 20 minutes) conditions, 71–74% and 82–84% AR was recovered as parent at the end of incubation, respectively. Degradation products identified were: pasteurization, P-NH (3.0–4.4% AR); baking/brewing/boiling, P-NH (18–19% AR), P-aniline-isobutyryl (10% AR) and P-acid (8.8% AR); sterilization, P-NH (11–12% AR), P-aniline-isobutyryl (5.3% AR) and P-acid (6.7% AR). No other degradation products were detected.

Processing

The Meeting received information on processing of apples to pasteurized juice, wet pomace, dry pomace, pasteurized sauce and dried apples; and dry tea leaves to tea infusion. Processing factors of apple processed products and tea leaves to tea infusion are summarized below together with STMR-P values.

Table 2 Processing factors for apple processed commodities and tea infusion for dietary risk assessment (sum of pyflubumide and P-NH expressed as pyflubumide)

Processed commodity	Individual processing factor	Mean or Best estimate	STMR/STMR-P	HR/HR-P
Apple			0.41	0.55
Pasteurized juice	< 0.002, 0.002, 0.004	0.003[a]	0.001	-
Pasteurized sauce	< 0.02, < 0.02, < 0.02	< 0.02	0.008	-
Dried apple	0.029, 0.039, 0.08	0.05	0.02	0.028
Tea leaves, dry			13	-
Tea infusion	0.00006, 0.00015, 0.00021, 0.00021, 0.00027, 0.00034, 0.00042, < 0.00072	0.0003	0.004	-

[a] Mean of two finite processing factors

Table 3 Processing factors for apple processed commodities for animal dietary burden calculation (pyflubumide only)

Processed commodity	Individual processing factor	Mean or Best estimate	Median residue
Apple			0.39
Wet pomace	2.4, 3.4, 3.7	3.2	1.2
Dry pomace	11.7, 15.8, 18.2	15.2	5.9

Using the best estimates of processing factors and the STMR values for apple and dry tea leaves, the STMR-P values were calculated for processed commodities of apple and tea infusion.

The median residue for apple wet pomace was calculated for animal dietary burden calculation.

Residues in Animal Products

No feeding study was conducted on cattle or laying hens.

As no livestock metabolism studies or analytical method for foods of animal origin was available, the Meeting did not establish residue definitions for animal commodities. Therefore, the Meeting did not calculate animal dietary burden.

The Meeting concluded it was not possible to estimate maximum residue levels for foods of animal origin.

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 and IESTI assessment.

Definition of the residue for compliance with the MRL for plant commodities: Pyflubumide

Definition of the residue for dietary risk assessment for plant commodities : Sum of pyflubumide and 3'-isobutyl-1,3,5-trimethyl-4´-[2,2,2-trifluoro-1-methoxy-1-(trifluoromethyl)ethyl]pyrazole-4-carboxanilide, expressed as pyflubumide

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The current Meeting established an ADI of 0–0.007 mg/kg bw.

The International Estimated Dietary Intakes (IEDIs) of pyflubumide were calculated for the 17 GEMS/Food Consumption Cluster Diets using the STMR or STMR-P values estimated by the current Meeting. The results are shown in Annex 3 of the 2019 JMPR Report.

The calculated IEDIs were 3–20% of the maximum ADI (0.007 mg/kg bw). The Meeting concluded that the long-term exposure to residues of pyflubumide resulting from the uses considered by the current JMPR is unlikely to present a public health concern.

Acute dietary exposure

The current Meeting established an ARfD of 0.008 mg/kg bw.

The International Estimated Short-Term Intakes (IESTIs) of pyflubumide were calculated for commodities using the HRs and STMRs/STMR-Ps estimated by the current Meeting. The results are shown in Annex 4 of the 2019 JMPR Report.

The calculated IESTIs were 1–230% of the ARfD for the general population and 1–390% of the ARfD for children.

For apple (raw), the IESTI represents 160% of the ARfD for the general population and 390% for children. For tea (dried leaf), the IESTI represents 230% of the ARfD for the general population and 150% for children. No alternative GAPs for apple or tea were available. On the basis of the information provided to the JMPR, the Meeting concluded that the acute dietary exposure to pyflubumide from the consumption of apple and tea may present a public health concern.

The Meeting also concluded that the acute dietary exposure to pyflubumide from the consumption of apple processed commodities and tea infusion is unlikely to present a public health concern.