5.24 TEFLUBENZURON (190)

TOXICOLOGY

Teflubenzuron is the ISO-approved common name for 1-(3,5-dichloro-2,4-difluorophenyl)-3-(2,6-difluorobenzoyl)urea (IUPAC), with the CAS number 83121-18-0. Teflubenzuron is an insect growth regulator belonging to the benzoyl urea group of compounds. It acts at the developmental stages of insect pests, primarily via ingestion, by interfering with chitin synthesis and the moulting process. It has an ovicidal effect in some insects.

Teflubenzuron was previously evaluated by JMPR in 1994, when an ADI of 0–0.01 mg/kg bw was established, based on a LOAEL for liver changes in the mouse carcinogenicity study at 2 mg/kg bw per day. There was no consideration of an ARfD. Teflubenzuron was evaluated by the present Meeting under the periodic review programme of CCPR.

In 2015, the eighty-first meeting of JECFA reviewed teflubenzuron for use as a veterinary drug and established an ADI of 0–0.005 mg/kg bw, based on a lower 95% confidence limit on the benchmark dose for a 10% response ($BMDL_{10}$) for hepatocellular hypertrophy in a mouse carcinogenicity study.

A number of additional studies have been made available to the Meeting since the 1994 review by JMPR. A search of the published literature was conducted, and no relevant publications were identified. All critical studies contained statements of compliance with GLP and met the minimum requirements of applicable national or international test guidelines.

Biochemical aspects

The toxicokinetics and biotransformation of teflubenzuron were investigated in rats administered ^{14}C-labelled teflubenzuron at a single dose of 25 or 750 mg/kg bw by gavage or 14 daily doses of 25 mg/kg bw per day of unlabelled teflubenzuron followed by a single labelled dose of 25 mg/kg bw. Following administration of a single oral dose of radiolabelled teflubenzuron at 25 mg/kg bw, approximately 20% of the radioactivity was absorbed, based on urinary and biliary excretion; only 4% was absorbed when rats were dosed at 750 mg/kg bw, suggesting a dose-dependent absorption. Peak plasma concentrations were reached within 1–2 hours post-dosing and were maintained at similar levels for up to 8 hours (low dose) or 24 hours (high dose). In repeatedly dosed animals, there was some evidence of a dose-dependent plateau in plasma concentration.

More than 90% of the radioactivity was excreted via faeces within the first 24 hours of dosing, most of which was unchanged compound. Only a small fraction (0.15–3%) of the radioactivity was excreted in the urine. There was no difference in excretion pattern between sexes or between animals dosed with a single or multiple low doses. Absorbed teflubenzuron was mostly excreted through bile (16% of the administered dose at 5 mg/kg bw). Only negligible residues of radioactivity were detected in tissues and organs (< 2% of the administered dose), with no evidence of accumulation. Metabolites identified in bile and urine were benzoyl or aniline ring hydroxylated teflubenzuron and conjugates of (3,5-dichloro-2,4-difluorophenyl)urea and 3,5-dichloro-2,4-difluoroaniline. Several polar metabolites were detected in faeces, but the only metabolite characterized was (3,5-dichloro-2,4-difluorophenyl)urea. Hydrolytic cleavage of the phenylurea bridge was identified as the predominant pathway of teflubenzuron metabolism in a study in which rats were gavaged once with approximately 55 mg/kg bw. The cleavage products were either excreted unmodified or further metabolized before being excreted.

Analyses of blood samples from a 28-day toxicity study and a 2-year study of chronic toxicity and carcinogenicity in rats indicated a plateau in plasma levels of teflubenzuron at doses equivalent to approximately 100 mg/kg bw per day. These results are in agreement with the findings in the routine absorption studies described above.

Toxicological data

Teflubenzuron was of low acute toxicity in rats and mice via the oral route (LD_{50} > 5000 mg/kg bw) and in rats via the dermal route (LD_{50} > 2000 mg/kg bw) and by inhalation (LC_{50} > 5.04 mg/L). Teflubenzuron was not irritating to the skin of rabbits, but was transiently and slightly irritating to the eyes of rabbits. Teflubenzuron was not a skin sensitizer in guinea-pigs in a maximization test.

In repeated-dose toxicity studies in mice, rats and dogs, the predominant effect was liver toxicity, characterized by increased organ weight, increased serum activities of marker enzymes of liver toxicity and histopathological changes.

In a 90-day study of toxicity in mice, dietary concentrations of teflubenzuron were 0, 100, 1000 and 10 000 ppm (equal to 0, 12, 115 and 1213 mg/kg bw per day for males and 0, 14, 143 and 1450 mg/kg bw per day for females, respectively). The NOAEL was 100 ppm (equal to 12 mg/kg bw per day), based on increased liver weights, hepatocellular swelling and fatty change at 1000 ppm (equal to 115 mg/kg bw per day).

In a 28-day study of toxicity in rats, dietary concentrations of teflubenzuron were 0, 1500, 5000 and 15 000 ppm (equal to 0, 133, 392 and 1302 mg/kg bw per day for males and 0, 119, 385 and 1284 mg/kg bw per day for females, respectively). The LOAEL was 1500 ppm (equal to 133 mg/kg bw per day), on the basis of increased serum activities of alkaline phosphatase and aspartate aminotransferase and increased bilirubin levels, outside the normal ranges, in males at all dose levels.

In a 90-day study of toxicity in rats, nominal dietary concentrations of teflubenzuron were 0, 100, 1000 and 10 000 ppm, but measured levels were typically 85% of the nominal values. Achieved intakes were reported as 0, 8.0, 81.6 and 809 mg/kg bw per day for males and 0, 9.1, 94.0 and 942 mg/kg bw per day for females, respectively. The NOAEL was 100 ppm (equal to 8.0 mg/kg bw per day), on the basis of significantly increased activities of alkaline phosphatase and lactate dehydrogenase in serum in males at 1000 ppm (equal to 81.6 mg/kg bw per day).

In a 90-day dietary study in which dogs were administered teflubenzuron at 0, 100, 1000 or 10 000 ppm (equal to mean intakes of 0, 3.2, 30.4 and 323 mg/kg bw per day, respectively), the NOAEL was 100 ppm (equal to 3.2 mg/kg bw per day), based on pathological findings in the stomach at 1000 ppm (equal to 30.4 mg/kg bw per day).

In a subsequent dietary study in which dogs were administered teflubenzuron at 0, 30 or 100 ppm (equal to mean intakes of 0, 1.15 and 4.1 mg/kg bw per day, respectively), there were no adverse effects of treatment. The NOAEL was 100 ppm (equal to 4.1 mg/kg bw per day), the highest dose tested.

In a 1-year study in dogs in which teflubenzuron was administered in the diet at 0, 30, 100 or 500 ppm (equal to 0, 1.0, 3.2 and 17 mg/kg bw per day for males and 0, 1.2, 4.0 and 18 mg/kg bw per day for females, respectively), the NOAEL was 500 ppm (equal to 17 mg/kg bw per day), the highest dose tested. The Meeting considered that the increase in absolute and relative liver weights in males at 500 ppm (equal to 17 mg/kg bw per day) was not adverse in the absence of associated histopathological or clinical chemistry changes.

The overall NOAEL for dogs was 500 ppm (equal to 17 mg/kg bw per day), and the overall LOAEL was 1000 ppm (equal to 30.4 mg/kg bw per day).

In a carcinogenicity study in mice, teflubenzuron was administered in the diet at 0, 15, 75 or 375 ppm (equal to 0, 2.1, 10.5 and 53.6 mg/kg bw per day for males and 0, 3.1, 15.4 and 71.7 mg/kg bw per day for females, respectively) for 78 weeks, with an interim kill at week 52. Several treatment-related, dose-dependent non-neoplastic hepatic changes were observed, which were more pronounced in males than in females. In particular, males had dose-dependent incidences of hepatocellular hypertrophy, single-cell necrosis, phagocytic cell foci and lipofuscin accumulation. In the low-dose group, the incidence, but not the severity, of these non-neoplastic hepatic changes was significantly higher when compared with the controls. Histopathological investigation of neoplastic lesions indicated an increased incidence of hepatocellular adenomas and nodular hepatocellular

hyperplasia in male mice treated at the middle and high doses compared with both concurrent and historical controls, but there was no difference in the incidence of hepatocellular carcinoma. Histopathological sections of liver from male mice in this study were subsequently re-evaluated by one independent pathologist, with a focus on nodular liver lesions. This pathologist concluded that there was a dose-related increase in the incidence of hepatocellular hyperplastic nodules and a slight, but statistically non-significant, increase in the incidence of hepatocellular adenomas.

Given that only benign hepatic adenomas were observed, the Meeting considered that teflubenzuron was not carcinogenic in mice. However, the Meeting concluded that teflubenzuron induced hyperplastic proliferation in liver of mice by an unknown mechanism. Based on the increased incidence of non-neoplastic hepatic changes observed in liver (e.g. hepatocellular hypertrophy, single-cell necrosis, phagocytic cell foci, lipofuscin accumulation) at all doses, no NOAEL could be identified. The lowest dietary concentration, 15 ppm (equal to 2.1 mg/kg bw per day), was identified as the LOAEL.

In the absence of a NOAEL, to better characterize the point of departure, the Meeting evaluated a dose–response analysis of these data performed by JECFA, using the benchmark dose (BMD) approach. Of several non-neoplastic hepatic changes identified, hepatocellular hypertrophy (diffuse plus centrilobular) was considered to be the most toxicologically relevant effect for dose–response modelling. The BMD for a 10% response (BMD_{10}) and the lower 95% confidence limit on the BMD_{10} ($BMDL_{10}$) were determined using nine different dichotomous models. The Meeting confirmed the conclusion of JECFA that the $BMDL_{10}$ of 0.54 mg/kg bw per day estimated by the multistage model was the most appropriate point of departure for this study.

In a dietary study of chronic toxicity and carcinogenicity, rats were administered teflubenzuron at 0, 20, 100 or 500 ppm (equal to 0, 1.0, 4.8 and 24.8 mg/kg bw per day for males and 0, 1.2, 5.9 and 29.9 mg/kg bw per day for females, respectively) for 120 weeks, with interim kills at weeks 53 and 107. Mortality, which was not influenced by treatment, ranged from 40% to 50% at week 120. Trend analysis identified increased incidences of haemangiomas in mesenteric lymph nodes and pancreatic exocrine carcinomas in the high-dose males. However, they were not significantly different when compared with historical controls. Also, the occurrence of pancreatic exocrine carcinoma was too infrequent (2/47 versus 0/50) to allow a meaningful comparison to be drawn. The NOAEL was 100 ppm (equal to 4.8 mg/kg bw per day), based on the changes in liver marker enzymes and liver weight at 500 ppm (equal to 24.8 mg/kg bw per day).

In a subsequent dietary study of carcinogenicity, rats were administered teflubenzuron at 0, 2500 or 10 000 ppm (equal to 0, 123 and 487 mg/kg bw per day for males and 0, 154 and 615 mg/kg bw per day for females, respectively) for 111 weeks, with an interim kill at week 104. Liver toxicity was evident, with findings including altered serum enzyme activities, increased liver weight and non-neoplastic microscopic changes noted in the liver of both sexes at both doses tested, lesions being more severe in males than in females. There was no compound-related increase in the incidence of any tumours observed in this study, including mesenteric lymph node haemangioma and pancreatic exocrine carcinoma in male rats. The results of this study confirm the lack of association between substance administration and incidences of tumours reported from the previous study.

Although no NOAEL could be identified in the second study owing to non-neoplastic microscopic hepatic changes and elevated liver enzyme activities in both treatment groups, the Meeting was able to identify an overall NOAEL of 100 ppm (equal to 4.8 mg/kg bw per day) from the two long-term toxicity and carcinogenicity studies in rats.

The Meeting concluded that teflubenzuron is not carcinogenic in mice or rats.

Teflubenzuron was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. All studies produced negative results. Teflubenzuron exhibited no potential to bind to the DNA from the livers of male NMRI mice.

The Meeting concluded that teflubenzuron is unlikely to be genotoxic.

In view of the fact that teflubenzuron is unlikely to be genotoxic, the absence of carcinogenicity in rats and the demonstration of a threshold for benign liver tumours in mice, the Meeting concluded that teflubenzuron is unlikely to pose a carcinogenic risk to humans from the diet.

In a two-generation study of reproductive toxicity in rats, with one litter per generation, dietary concentrations of teflubenzuron were 0, 20, 100 and 500 ppm (equal to mean intakes of 0, 1.5, 7.4 and 37 mg/kg bw per day for males and 0, 1.6, 7.9 and 39.5 mg/kg bw per day for females, respectively). The NOAEL for reproductive effects was 500 ppm (equal to 37 mg/kg bw per day), the highest dose tested. The NOAEL for parental toxicity was 500 ppm (equal to 37 mg/kg bw per day), the highest dose tested. The NOAEL for effects on offspring was 100 ppm (equal to 7.9 mg/kg bw per day), based on renal pelvis dilatation in F_1 pups at 500 ppm (equal to 39.5 mg/kg bw per day).[1]

In a study of developmental toxicity in rats dosed with teflubenzuron at 0, 10, 50 or 250 mg/kg bw per day by gavage in 0.5% carboxymethyl cellulose, there were no effects on any measured fetal or maternal parameters. An apparent decrease in fetal numbers was associated with fewer corpora lutea and hence unrelated to dosing with teflubenzuron. The NOAEL for maternal toxicity was 250 mg/kg bw per day, the highest dose tested. The NOAEL for embryo and fetal toxicity was 250 mg/kg bw per day, the highest dose tested.

In a subsequent study of developmental toxicity in rats dosed with teflubenzuron at 0, 100, 300 or 1000 mg/kg bw per day by gavage in 0.5% carboxymethyl cellulose, there were no effects on any measured fetal or maternal parameters. The NOAEL for maternal toxicity was 1000 mg/kg bw per day, the highest dose tested. The NOAEL for embryo and fetal toxicity was 1000 mg/kg bw per day, the highest dose tested.

In a study of developmental toxicity in rabbits dosed with teflubenzuron at 0, 10, 50 or 250 mg/kg bw per day by gavage, there were no effects on any measured maternal parameters. An apparent slight decrease in fetuses surviving for 24 hours at 250 mg/kg bw per day is considered to be an equivocal effect. The cause of death for these fetuses was not identified. Investigations for fetal abnormalities did not identify any malformations incompatible with initial survival. The Meeting concluded that the deaths of these fetuses was unlikely to have resulted from a single exposure of the dam. The NOAEL for maternal toxicity was 250 mg/kg bw per day, the highest dose tested. The NOAEL for embryo and fetal toxicity was 50 mg/kg bw per day, based on decreased survival at the highest dose.

In a subsequent study of developmental toxicity in rabbits dosed with teflubenzuron at 0 or 1000 mg/kg bw per day by gavage, there were no effects on any measured fetal parameters. In dams, a finding of granular livers of unknown toxicological significance was increased in the teflubenzuron-treated group. A NOAEL for maternal toxicity could not be determined based on the liver changes was 1000 mg/kg bw per day, the only dose tested. The NOAEL for embryo and fetal toxicity was 1000 mg/kg bw per day, the highest dose tested.

The Meeting concluded that teflubenzuron is not teratogenic.

The acute neurotoxicity of teflubenzuron was investigated in rats administered a dose level of 0, 125, 500 or 2000 mg/kg bw by gavage. No adverse effects were reported. The NOAEL for neurotoxicity was 2000 mg/kg bw, the highest dose tested.

In a subchronic (90-day) neurotoxicity study in rats, dietary concentrations of teflubenzuron were adjusted to give mean intakes of 0, 100, 300 and 1000 mg/kg bw per day. No adverse effects were reported. The NOAEL for neurotoxicity was 1000 mg/kg bw per day, the highest dose tested.

The Meeting concluded that teflubenzuron is not neurotoxic.

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[1] During the meeting, the Meeting became aware of the existence of a second multigeneration reproductive toxicity study from a different sponsor, but that study was not available for evaluation.

In a 28-day immunotoxicity study in male mice, dietary concentrations were 0, 200, 1000 and 5000 ppm (equal to 0, 44, 218 and 1059 mg/kg bw per day, respectively). No adverse effects were reported. The NOAEL for immunotoxicity was 5000 ppm (equal to 1059 mg/kg bw per day), the highest dose tested.

The Meeting concluded that teflubenzuron is not immunotoxic.

Toxicological data on metabolites and/or degradates

Data are available on two minor plant metabolites. 2,4-Difluoro-3,5-dichlorophenylurea has an acute oral LD_{50} of 700 mg/kg bw in rats and was not mutagenic in an Ames test. 2,4-Difluoro-3,5-dichloroaniline has an acute oral LD_{50} of 1759 mg/kg bw in rats and was not mutagenic in an Ames test.

Human data

No data were submitted on humans exposed to teflubenzuron.

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

Toxicological evaluation

The Meeting established an ADI for teflubenzuron of 0–0.005 mg/kg bw, on the basis of the $BMDL_{10}$ of 0.54 mg/kg bw per day for hepatocellular hypertrophy from the carcinogenicity study in mice. A safety factor of 100 was applied.

The Meeting concluded that it was not necessary to establish an ARfD for teflubenzuron in view of its low acute oral toxicity and the absence of any toxicological effects, including developmental toxicity, that would likely be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment of teflubenzuron

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity[a]	Toxicity	0.54 mg/kg bw per day ($BMDL_{10}$)	15 ppm, equal to 2.1 mg/kg bw per day
		Tumorigenicity	15 ppm, equal to 2.1 mg/kg bw per day	75 ppm, equal to 10.5 mg/kg bw per day
Rat	Two-year studies of toxicity and carcinogenicity[a,b]	Toxicity	100 ppm, equal to 4.8 mg/kg bw per day	500 ppm, equal to 24.8 mg/kg bw per day
		Carcinogenicity	10 000 ppm, equal to 487 mg/kg bw per day[c]	–
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	500 ppm, equal to 37 mg/kg bw per day[c]	–
		Parental toxicity	500 ppm, equal to 37 mg/kg bw per day[c]	–

Species	Study	Effect	NOAEL	LOAEL
		Offspring toxicity	100 ppm, equal to 7.9 mg/kg bw per day	500 ppm, equal to 39.5 mg/kg bw per day
	Developmental toxicity study[b]	Maternal toxicity	1 000 mg/kg bw per day[c]	–
		Embryo and fetal toxicity	1 000 mg/kg bw per day[c]	–
	Acute neurotoxicity study[b]	Neurotoxicity	2 000 mg/kg bw per day[c]	–
Rabbit	Developmental toxicity studies[b,d]	Maternal toxicity	250 mg/kg bw per day	1 000 mg/kg bw per day
		Embryo and fetal toxicity	50 mg/kg bw per day[c]	250 mg/kg bw per day
Dog	Thirteen-week and 1-year studies of toxicity[a,b]	Toxicity	500 ppm, equal to 17 mg/kg bw per day	1 000 ppm, equal to 30.4 mg/kg bw per day

[a] Dietary administration.

[b] Two or more studies combined.

[c] Highest dose tested.

[d] Gavage administration.

Acceptable daily intake (ADI)

0–0.005 mg/kg bw

Acute reference dose (ARfD)

Unnecessary

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 teflubenzuron

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Relatively rapid (peak plasma level 1–8 h); poorly absorbed, 20% at 25 mg/kg bw, 4% at 750 mg/kg bw (based on urine and bile)
Dermal absorption	No data submitted
Distribution	Limited information, highest levels in liver
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid, > 90% in 24 h
Metabolism in animals	Extensive; hydroxylation or cleavage followed by hydroxylation and conjugation

Toxicologically significant compounds in animals and plants	Teflubenzuron
Acute toxicity	
Rat, LD_{50}, oral	> 5 000 mg/kg bw
Rat, LD_{50}, dermal	> 2 000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.04 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Transiently and slightly irritating
Guinea-pig, dermal sensitization	Not sensitizing (maximization test)
Short-term studies of toxicity	
Target/critical effect	Clinical chemistry changes
Lowest relevant oral NOAEL	8.0 mg/kg bw per day (rat)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver: single-cell necrosis and hepatocellular hypertrophy (mice); hepatocellular adenomas (male mice)
Lowest relevant NOAEL	0.54 mg/kg bw per day ($BMDL_{10}$)
Carcinogenicity	Not carcinogenic in mice or rats[a]
Genotoxicity	
	No evidence of genotoxicity[a]
Reproductive toxicity	
Target/critical effect	Renal pelvis dilatation
Lowest relevant parental NOAEL	37 mg/kg bw per day, highest dose tested (rat)
Lowest relevant offspring NOAEL	7.9 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	37 mg/kg bw per day, highest dose tested (rat)
Developmental toxicity	
Target/critical effect	Mortality on postnatal day 1 for offspring; liver toxicity in dams (rabbit)
Lowest relevant maternal NOAEL	250 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	50 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity NOAEL	2 000 mg/kg bw, highest dose tested (rat)
Subchronic neurotoxicity NOAEL	1 000 mg/kg bw per day, highest dose tested (rat)
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	
Immunotoxicity NOAEL	1 059 mg/kg bw per day, highest dose tested (mouse)
DNA binding assay	No evidence of binding to mouse liver DNA

Human data
No data

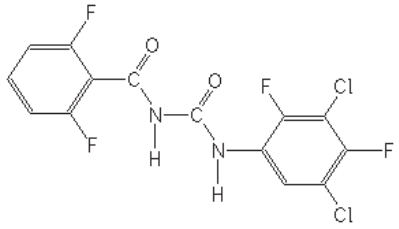
[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

Summary

	Value	Study	Safety factor
ADI	0–0.005 mg/kg bw	Eighteen-month toxicity and carcinogenicity study (mouse)	100
ARfD	Unnecessary	–	–

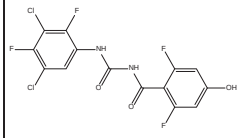
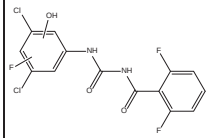
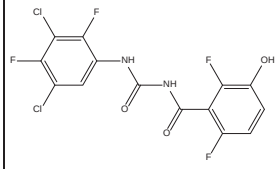
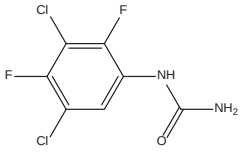
RESIDUE AND ANALYTICAL ASPECTS

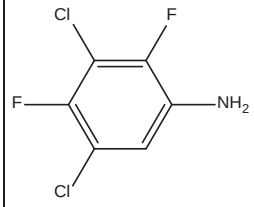
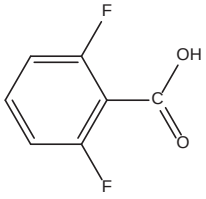
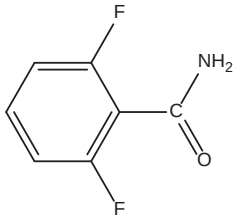
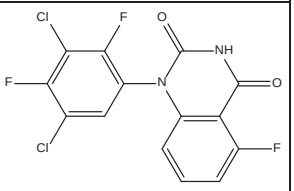
Teflubenzuron (1-(3,5-dichloro-2,4-difluorophenyl)-3-(2,6-difluorobenzoyl)urea) is a benzoylurea insecticide to control a range of insects including codling moth, leaf miners, whiteflies and caterpillars in a wide range of crops including fruit trees, vegetables, soya beans, oilseeds, maize, sugar cane and coffee. Teflubenzuron was first evaluated by JMPR in 1994 (toxicology) and in 1996 (residues). Teflubenzuron was scheduled at the 47th Session of the CCPR for Periodic Re-evaluation for residues and toxicology by the 2016 JMPR.



The Meeting received information from the manufacturer on physical and chemical properties, metabolism studies on plants and animals, rotational crop studies, environmental fate in soil, analytical method and stability in stored analytical samples, use patterns and supervised residue trials, processing studies, and livestock feeding studies.

The metabolism and distribution of teflubenzuron in plants and animals was studied using the aniline or benzoyl ^{14}C-labelled compound. The following abbreviations are used for the metabolites or degradation products discussed below:

3379	3380 ; E114	3381 ; E115; CL902374	CL902374; E15; CFPU
			
N-((3,5-dichloro-2,4-difluorophenyl)carbamoyl)-	1-(3,5-dichloro-2-fluoro-4-hydroxy-phenyl)-3-	N-((3,5-dichloro-2,4-difluorophenyl)carbamoyl)-	3,5-dichloro-2,4-difluorophenyl urea

2,6-difluoro-4-hydroxybenzamide;	(2,6-difluorobenzoyl)urea Or 1-(3,5-dichloro-4-fluoro-2-hydroxy-; phenyl)-3-(2,6-difluorobenzoyl)urea	2,6-difluoro-3-hydroxybenzamide	
E14; CL902373; EMD	CL245508	CL 211558	E30
			
3,5-dichloro-2,4-difluoroaniline;	2,6-difluorobenzoic acid;	2,6-difluorobenzamide;	N-(2,4-difluoro-3,5-dichlorobenzene)-5-fluoro[3H]-dihydroquinazoline-2,4-dione;

Plant metabolism

The metabolism of teflubenzuron has been studied with [^{14}C]teflubenzuron on apples, potatoes and spinach. The study designs of the plant uptake parts reflect the registered use patterns with several foliar applications.

Following foliar applications, there was little translocation from treated foliage to other parts of the plants, which is consistent with its properties (log P_{ow}> 4). In the studies on apples, the teflubenzuron residues remained predominantly associated with the peel (98–99% TRR), low residues (1.2–2.0% of TRR) were extracted from the pulp. In foliage, > 99% TRR was extracted from the surface of leaves. Teflubenzuron was identified as the major component in fruits and leaves (97–99% TRR).

In the studies on potatoes, more than 99% TRR was extracted from treated potato tops at harvest after foliar application. Low radioactive residues (< 0.001 mg/kg) were detected in the tubers. Almost all extracted residues in surfaces of leaves and stems (99% and 98% TRR) were identified as parent teflubenzuron. Radioactive residues in potato tops and tubers after soil drench were 0.001–0.003 mg/kg. Identification of these radioactive residues was not conducted.

In studies on spinach, no significant metabolism of teflubenzuron was observed. The TRR levels in spinach leaves were highest immediately after foliar application at 12–14 mg eq/kg, and decreased to 0.88–0.90 mg eq/kg and 0.08–0.26 mg eq/kg in the 15 and 30 DAA. Most radioactive residues (99–100% TRR) were extracted in leaves, of which 96–100% TRR was identified as parent teflubenzuron in samples from 30 days after application. Minor unidentified metabolites (< 3.2% of the TRR) were detected at 30 DAA.

Plant metabolism studies in apples, potatoes and spinach show that most of teflubenzuron residue remains on the surface of plants and is not readily translocated into the pulp of apple fruit (< 2.2% of TRR translocated into apple pulp) or from potato leaves to tubers (> 98% TRR remaining in potato leaves and stems). A very high level of the radioactivity was attributed to parent compound (> 97% TRR in apple peel, 96–100% TRR in spinach leaves and 99% TRR in potato tops) with no indication of the presence of metabolites or cleavage products.

Confined rotational crop studies

Two studies on confined rotational crops with [^{14}C]teflubenzuron radiolabelled either in the aniline or benzoyl moiety were provided to the Meeting. [^{14}C]teflubenzuron was applied at a rate of 0.5 kg ai/ha to a sandy loam soil in indoor plots, which covered most application scenarios. The TRR in the crop samples at harvest declined with longer plant back intervals. The TRRs in lettuce after 30, 120, and 360 days of plant back interval were 0.007–0.001 mg eq/kg, 0.026–0.001 mg eq/kg in carrot roots, 0.24–0.007 mg eq/kg in wheat straw and 0.012–0.002 mg eq/kg in wheat grain. The TRR in the crops at harvest were low (< 0.01 mg eq/kg) with the exception of wheat straw. Characterisation of the radioactive residues in wheat straw after 30 and 120 days of plant back intervals showed several polar unknowns at concentrations < 0.05 mg/kg. Neither teflubenzuron, nor the two known soil metabolites 3, 5-dichloro-2, 4-difluorophenyl urea and 3,5-dichloro-2,4-difluoroaniline were detected in the plants at levels > 0.01 mg/kg.

The Meeting concluded that due to the very low levels of radioactive residues of teflubenzuron and metabolites detected in confined rotational crops studies, no residues above the limit of quantitation (LOQ) would be expected in rotational crops.

Animal metabolism

Studies were submitted on the metabolism of teflubenzuron in lactating goats. The aniline labelled [^{14}C]teflubenzuron was administered orally to two lactating goats twice daily for 7.5 days at a dose of 1 mg/kg bw/day (equivalent to 25 ppm diet, based on a daily feed intake of 2 kg). More than 93% of the total radioactivity administered was excreted via faeces and urine. Highest levels of total radioactivity were found in liver (0.49 mg eq/kg) corresponding to 0.14% of the total administered dose. Levels in kidney and fat were 0.03 and 0.08 mg eq/kg, respectively. Levels in muscle and skin were at or below the limit of detection. 58% of TRR in liver was extracted. Identification of radioactive residues in liver showed that the major components (81% TRR) were the polar unknowns, along with low levels of metabolite 3379 (3.7% TRR), parent compound (1.6% TRR) and metabolite 3381(1.5% TRR). The TRR in milk was close to the limit of detection; the highest levels of total radioactivity in milk were found in Day 5 evening milk (0.01–0.015 mg eq/kg) and accounted for 0.002–0.005% of the cumulative administered dose. Analysis of milk extracts showed the presence of teflubenzuron (6.5% TRR), metabolite 3381 (1.5% TRR) and polar unknowns (82.5% TRR). Further attempts to separate compounds produced no interpretable results due to the low amounts (< 0.015 mg eq/kg) of radioactivity.

A study on identification of metabolites in laying hens was available to the Meeting. The aniline-labelled [^{14}C]teflubenzuron was administered orally to eighteen laying hens twice daily for 7.5 days at a dose of 1.25 mg/kg bw /day (equivalent to 25 ppm diet, based on a daily feed intake of 100 g). 88% of the total administered radioactivity was excreted, with less than 0.01% in the eggs and less than 0.4% in the tissues. The radioactive residues in egg yolk reached a maximum of 0.99 mg eq/kg on Day 9. 92% TRR in egg yolk was extracted with methanol, and more than 62% TRR was identified as parent teflubenzuron. Low levels of metabolite E15 (5.4% TRR) and 3381(7.1% TRR) were observed in yolk extracts. The radioactive residues in the tissues (expressed as parent equivalent) were 0.33 mg eq/kg in liver, 0.17 mg eq/kg in kidney, 0.95–1.1 mg eq/kg in fat, 0.45 mg eq/kg in skin, and 0.026–0.066 mg eq/kg in muscle. 70% TRR in liver, 90% TRR in kidney and 94% TRR in fat were extracted with methanol; 35% TRR in liver, 30.1% TRR in kidney and 79% TRR in fat were identified as parent teflubenzuron. Metabolites 3381 and E15 were observed at low levels in liver (6.8% TRR, 3.4% TRR) and kidney (4.5% TRR, 13% TRR). The radioactive residues in muscle were not sufficiently high to enable characterisation.

Metabolism studies performed on goats and hens have shown that teflubenzuron is poorly absorbed and metabolised with more than 88% of total administered radioactivity excreted. The major residues in milk and goat liver were polar unknowns. The most prominent residue in egg yolk and hen tissues (liver and kidney) was parent teflubenzuron. The main metabolites found were

metabolite E15 with highest amounts in kidneys of hens (13% TRR) and metabolite 3381 with highest amounts in livers of goats (30% TRR).

Environmental fate

Studies on the degradation of aniline and benzoyl labelled [^{14}C]teflubenzuron under aerobic conditions, field dissipation, hydrolysis and photolysis were received. The [^{14}C]teflubenzuron was applied to sandy loam soil at a rate of 5 mg/kg and silty clay loam at rate of 0.5 mg/kg. The major part of the radioactive residues in soil was from parent teflubenzuron (97% AR on Day 0 to > 48% AR on Day 30) under aerobic conditions. Major metabolites identified were 3,5-dichloro-2,4-difluoroaniline (maximum of 28% AR after 14 days), 3,5-dichloro-2,4-difluorophenylurea (CL902374, maximum of 10% AR after 29 days). Up to 52% AR was mineralized to CO_2 in silty clay soil after 150 days. Cleavage of the [^{14}C-benzoyl]-teflubenzuron into 2,6-difluorobenzoic acid was not observed under aerobic conditions.

Four field dissipation trials at a rate of 0.36 kg ai/ha showed DT_{50} and DT_{90} values of 17–24 and 55–78 days for teflubenzuron. Degradation of teflubenzuron in the humic sand was relatively fast with a half-life of approximately 2 weeks, and significantly slower in the sandy loam where a half-life of around 6 weeks was calculated.

The hydrolysis of aniline or benzoyl labelled [^{14}C]teflubenzuron was studied in buffered solutions of 0.04 mg/L at pH 5, 7 and 9 in the absence of light at 25 °C. The teflubenzuron is stable to hydrolysis at pH 5–7 after 30 days at 25 °C. At pH 9, teflubenzuron was extensively hydrolysed with a half-life of 10 days. The major metabolites identified after 30 days at pH 9 were 3,5-dichloro-2,4-difluorophenylurea (61% from the aniline labelled), 3,5-dichloro-2,4-difluoroaniline (12% from the aniline labelled), 2,6-difluorobenzoic acid (62% from the benzoyl labelled) and 2,6-difluorobenzamide (12% from the benzoyl labelled). No other metabolites were at levels above 10% AR.

The study on photo-degradation of aniline labelled [^{14}C]teflubenzuron on soil estimated a photolytic half-life time of approximately 10 days. The only metabolite identified was N-(2,4-difluoro-3,5-dichlorobenzene)5-fluoro[3H]-dihydroquinazoline-2,4-dione (32% AR after 15 days).

The Meeting concluded that teflubenzuron is stable to hydrolysis under neutral and acidic conditions, and photolysis might contribute significantly to degradation of teflubenzuron. In soil its degradation is moderately quick, indicating no potential for accumulation.

Methods of analysis

The Meeting received descriptions and validation data for analytical methods for residues of teflubenzuron in plant matrices (avocadoes, peppers, cucumbers, tomatoes, cherry tomatoes, oats, sugar cane, citrus, cauliflowers, maize, sunflowers, wheat and rye) and animal commodities (milk, liver, muscle, fat and egg). The homogenized samples were extracted with acetone and purified with silica gel for cucumbers, tomatoes, oats, sugar cane, citrus and cauliflowers; extracted with methanol and purified with PSA for maize grain; and extracted with isohexane and acetonitrile purified with formic acid for sunflower seeds. Samples of animal tissues, egg and milk were extracted with acetonitrile and purified with PSA. The determination of teflubenzuron used LC-MS/MS for plants and animal matrices. Typical LOQs achieved for plant and animal commodities were 0.01 mg/kg. The recoveries were within the range of 70–120%, and RSD was within 20%. Methods have been subjected to independent laboratory validation. Multiple residue method of QuEChERS was validated for analysis of teflubenzuron in plant commodities and animal commodities.

Stability of pesticide residues in stored analytical samples

Information was received on the freezer storage stability of teflubenzuron in plant commodities. Studies on stability showed that teflubenzuron residues were stable under freezer condition (-20 °C)

in spiked samples of apples, pears, potatoes and cabbage for at least 36 months, and in samples of tomatoes, oranges, cotton seeds, soya bean, maize and sunflower seeds for at least 24 months. No information on storage stability of animal commodities were available.

Definition of the residue

In plant metabolism studies performed on fruits (apples), leafy crops (spinach) and tuber crops (potatoes) similar metabolic behaviour was observed. The parent compound teflubenzuron is the dominant component of the residues in plant commodities and ranged from 96–99% TRR in apples, potato tops and spinach leaves. No individual metabolite occurred at a level of > 0.05 mg eq/kg.

The Meeting concluded that teflubenzuron was the major residue in all primary treated plants. No significant residues are expected in rotational crops following application of the active substance. Analytical single- and multi-residue methods are available to measure teflubenzuron in plant matrices. The Meeting decided that the residue definition for plants (compliance with MRLs and dietary intake purposes) is parent teflubenzuron.

Low levels of TRR were detected in milk (< 0.01 mg eq/kg) and tissues of goats (< 0.01 in muscle to 0.49 mg eq/kg in liver). The major components (81% TRR) of radioactive residues in liver were polar unknowns. Minor levels of teflubenzuron (1.6% TRR), metabolite 3379 (3.7% TRR) and 3381 (1.5% TRR) were observed in livers of goats.

Teflubenzuron was the major compound observed in eggs (66% TRR), livers (35% TRR), kidneys (30%TRR), and fat (79%) of hens. TRR levels in muscles were too low to be characterized. Minor metabolites 3381and E15 were observed in livers (6.8% TRR, 3.4% TRR) and kidneys (4.5% TRR, 13% TRR). The parent teflubenzuron serves as a suitable marker for poultry commodities.

The Meeting concluded that teflubenzuron was the major residue in poultry tissues and eggs and present in goat matrices at levels sufficient for identification. No other compounds were suitable for markers in animal commodities. The Meeting decided that the residue definition for animals (compliance with MRLs and dietary intake purposes) is parent teflubenzuron.

Teflubenzuron has a log P_{ow} of 4.2. In feeding studies on hens, the teflubenzuron residues in fat were 8.3–18 times higher than residues in muscle. The Meeting decided that the residue of teflubenzuron is fat soluble.

Definition of the residue (for compliance with the MRL and for estimation of dietary intake) for plant and animal commodities: *Teflubenzuron.*

The residue is fat soluble.

Results of supervised residue trials on crops

The Meeting received supervised residue trial data for citrus fruits, apples, grapes, mangoes, papaya, pineapples, broccoli, cauliflower, melons, cucumbers, gherkins, tomatoes, sweet peppers, pulse, maize and coffee. If two field samples were taken or results of two replicate plots were submitted, the mean value was calculated. When two or more trials were carried out side-by-side, the higher residue was chosen.

Oranges, Sweet, Sour

The critical GAP in Brazil is two foliar applications on citrus at a rate of 0.09 kg ai/ha with a PHI of 28 days. No trials matched GAP.

Field trials conducted at 2 × 0.12 kg ai/ha were taken into account by applying the proportionality principle (scaling factor of 0.75; 0.09 kg ai/ha ÷ 0.12 kg ai/ha). In 11 supervised trials conducted on oranges in Brazil at a rate of 2 × 0.12 kg ai/ha in Brazil, teflubenzuron residues in whole fruit of oranges at 28 DALA were: 0.02, 0.02, 0.03, 0.04, 0.12, 0.14, 0.22, 0.23, 0.24, 0.25 and

0.26 mg/kg (n = 11). The residues in pulp were: < 0.01 mg/kg (n = 3). The residues in whole fruits after scaling according to the factor of 0.75 were: 0.015, 0.015, 0.023, 0.03, 0.09, 0.11, 0.17, 0.17, 0.18, 0.19 and 0.20 mg/kg (n = 11).

Based on residues after scaling, the Meeting estimated an STMR of 0.11 mg/kg, an HR of 0.2 mg/kg, and a maximum residue level of 0.5 mg/kg for teflubenzuron on oranges. The Meeting noted that the residues in orange pulp from three trials and lemon pulps from three trials were < 0.01 mg/kg. Based on the residues in pulp of oranges and lemons, the Meeting estimated an STMR of 0.01 mg/kg and an HR of 0.01 mg/kg for teflubenzuron on oranges for dietary estimation.

The Meeting noted that the GAP in Brazil is for citrus, and agreed to extrapolate the estimation from orange to the subgroups of oranges (sweet and sour).

The Meeting estimated an STMR of 0.01 mg/kg, an HR of 0.01 mg/kg and recommended a group maximum residue level of 0.5 mg/kg for teflubenzuron on the sub-group of oranges (sweet and sour).

Lemons

The critical GAP for citrus in Brazil is two foliar applications at a rate of 0.09 kg ai/ha with a PHI of 28 days. No trials on lemons matched GAP. Five trials on lemons conducted in Brazil at 2 ×0.12 kg ai/ha were taken into account by applying the proportionality principle. The teflubenzuron residues in whole fruit of lemons were: 0.06, 0.09, 0.12, 0.36 and 0.36 mg/kg, the residues in pulp were < 0.01 mg/kg (n = 3). The residues after scaling according to the factor of 0.75 were: 0.045, 0.068, 0.09, 0.27 and 0.27 mg/kg.

The Meeting recommended the maximum residue level of 0.5 mg/kg for teflubenzuron on lemons. Based on the residues in pulps of lemons and oranges, the Meeting estimated an STMR of 0.01 mg/kg and an HR of 0.01 mg/kg for teflubenzuron on lemons for dietary estimation.

The Meeting noted that the GAP in Brazil is for citrus, and agreed to extrapolate the estimation from lemon to the sub-groups of lemons and limes.

The Meeting estimated an STMR of 0.01 mg/kg, an HR of 0.01 mg/kg and recommended a group maximum residue level of 0.5 mg/kg for teflubenzuron on the sub-groups of lemons and limes.

Apples

Teflubenzuron is registered for foliar spray application on apples in Brazil at a rate of 3 × 0.045–0.060 kg ai/ha with a PHI of 1 day. In 12 supervised trials conducted in Brazil at a rate of 4 × 0.045 kg ai/ha at 10 days interval, the teflubenzuron residues in whole fruits at 1 DALA were: 0.06, 0.08, 0.09, 0.11, 0.14, 0.14, 0.17, 0.18, 0.21, 0.21, 0.22 and 0.29 mg/kg (n = 12).

The Meeting noted that the application number in supervised trials is one more than the GAP. The Meeting also noted that the total application rate in field trials was 0.18 kg ai/ha, same as the maximum rate for GAP. Metabolism studies and decline trials indicated no decrease of teflubenzuron, which is expected to be a stable surface residue. Therefore, the Meeting agreed that the supervised trials with four applications approximately matched the Brazilian GAP.

The Meeting estimated an STMR of 0.16 mg/kg, and recommended a maximum residue level of 0.5 mg/kg for teflubenzuron on apples. The previous recommendation of 1 mg/kg for Pome fruits is withdrawn, as no supporting data was provided.

Plums

The Meeting agreed the previous recommendation of a maximum residue level of 0.1 mg/kg for plums (FS 0014) should be withdrawn as no supporting data was provided.

Grapes

The GAP for grapes in Brazil is three foliar applications of up to 0.048 kg ai/ha with a PHI of 7 days. No trials matching GAP were submitted. However, in 12 supervised trials conducted on grapes in Brazil at rates of 3× 0.075 kg ai/ha at 6–7 days interval, the teflubenzuron residue in berries at 7 DALA were: 0.02, 0.04, 0.06, 0.11, 0.12, 0.15, 0.15, 0.26, 0.31, 0.37, 0.49 and 0.62 mg/kg. The Meeting agreed to use the proportionality approach according to the scaling factor of 0.64 (0.048 kg ai/ha/0.075 kg ai/ha). The rank order of scaled residues was: 0.013, 0.026, 0.038, 0.07, 0.077, 0.096, 0.096, 0.17, 0.20, 0.24, 0.31 and 0.40 mg/kg (n = 12).

The Meeting estimated an STMR of 0.096 mg/kg, and recommended a maximum residue level of 0.7 mg/kg for teflubenzuron on grapes.

Assorted tropical and sub-tropical fruit-inedible peel

Mango

Teflubenzuron is registered for one foliar spray application on mangoes in Brazil at a rate of 0.015 to a maximum of 0.24 kg ai/ha with a PHI of 7 days. There were no supervised trials provided (3 × 0.30 kg ai/ha) matching GAP.

Papaya

Teflubenzuron is registered for foliar application on papaya in Brazil at a rate of 3 × 0.06 kg ai/ha with a PHI of 7 days. In four supervised trials conducted in Brazil at a rate of 3 × 0.075 kg ai/ha at 6–8 days interval, teflubenzuron residues in fruit at 7 DALA were: 0.04, 0.13, 0.18 and 0.19 mg/kg.

The Meeting agreed to estimate an STMR of 0.16 mg/kg, and recommended a maximum residue level of 0.4 mg/kg for teflubenzuron on papaya.

Pineapples

The registered use of teflubenzuron on pineapples in Brazil is one foliar application of 0.24 kg ai/ha with a PHI of 7 days. There were no supervised trials provided (3 × 0.3 kg ai/ha) matching GAP.

Brassica (cole or cabbage) vegetables, Head cabbages, Flowerhead cabbages

Broccoli

Teflubenzuron is registered for three foliar applications on broccoli in Brazil at rate of 0.0375 kg ai/ha with a PHI of 14 days. No trials were provided that matched GAP.

Cauliflower

Teflubenzuron is registered for foliar spray applications on cruciferae (Brassicae) in Central America (Guatemala, El Salvador, Honduras, Nicaragua and Panama） at a rate of 0.0225 kg ai/ha with a PHI of 21 days. In seven supervised trials conducted in Guatemala, Costa Rica and Honduras at a rate of 3 × 0.0225 kg ai/ha with 6–8 days interval, teflubenzuron residues in the inflorescence at 21 days after the last application were < 0.01 mg/kg (n = 7).

The Meeting noted that the number of applications is not specified in the GAP in Central America. However, since three treatments in the supervised field trials did not result in residues above the LOQ in cauliflower, the additional previous applications are considered unlikely to contribute significantly to the terminal residues. Therefore, the Meeting agreed that the supervised trials matched the GAP irrespective of the number of applications.

The Meeting estimated an STMR of 0.01 mg/kg, and recommended a maximum residue level of 0.01* mg/kg for teflubenzuron on cauliflowers.

Brussels sprouts

The current MRL of 0.5 mg/kg for Brussels sprouts (VB 0402) should be withdrawn as no supporting data was provided.

Cabbages, Head

The current MRL of 0.1 mg/kg for cabbages, head (VB 0041) should be withdrawn as no supporting data was provided.

Potatoes

The current MRL of 0.05 mg/kg for potatoes (VR 0589) should be withdrawn as no supporting data was provided.

Fruiting vegetables, Cucurbits

Melon

Teflubenzuron is registered for three foliar applications on melons in Brazil at a rate of up to 0.06 kg ai/ha with a PHI of 7 days. In eight supervised trials conducted in Brazil at rates of 3 × 0.075 kg ai/ha at 7 days interval, teflubenzuron residues in whole fruit at 7 DALA were: 0.04, 0.05, 0.06, 0.07, 0.09, 0.09, 0.11 and 0.19mg/kg (n = 8), the teflubenzuron residues in pulp were: < 0.01, < 0.01, 0.02 and 0.02 mg/kg.

The Meeting recommended a maximum residue level of 0.3 mg/kg for teflubenzuron on melons. The Meeting estimated an STMR of 0.01 mg/kg based on residues in pulp for dietary estimation.

Cucumber

Teflubenzuron is registered for three foliar applications on cucumbers (field and greenhouse) in the Netherlands, at a rate of up to 0.225 kg ai/ha with a PHI of 3 days.

In three supervised trials conducted in France and Greece matching the critical GAP, the residues in fruit were: 0.05, 0.06 and 0.33 mg/kg.

In five trials conducted in the Netherland at a rate of two applications of 0.27 kg ai/ha, the residues in fruit were: 0.05, 0.10, 0.10, 0.12 and 0.16 mg/kg.

The Meeting noted that the first application of GAP was 20 days before last application. As cucumbers in greenhouses grow quickly from flowering to harvest, the Meeting concluded that the fruits are unlikely to ever receive three treatments. The Meeting agreed that two applications in trials approximated the GAP.

The residues in eight trials were: 0.05, 0.05, 0.06, 0.10, 0.10, 0.12, 0.16 and 0.33 mg/kg (n = 8).

The Meeting estimated an STMR of 0.10 mg/kg, and recommended a maximum residue level of 0.5 mg/kg for teflubenzuron on cucumbers.

Gherkins

Teflubenzuron is registered for three foliar applications on gherkins in the Netherlands at a rate of 0.225 kg ai/ha with a PHI of 3 days.

The teflubenzuron residues in whole fruit from four supervised trials conducted in France, Poland and Spain matching GAP were: 0.08, 0.23, 0.42 and 0.55 mg/kg (n = 4).

The Meeting estimated an STMR of 0.33 mg/kg, and recommended a maximum residue level of 1.5 mg/kg for teflubenzuron on gherkins.

Fruiting vegetables, other than Cucurbits

Tomato

The critical GAP of teflubenzuron for tomatoes (field and greenhouse) in the Netherlands with three foliar applications, at a rate of 0.225 kg ai/ha and a PHI of 3 days.

The teflubenzuron residues in whole fruit (field) from two supervised trials conducted in the Netherlands matching the critical GAP were (n = 2): 0.32 and 0.49mg/kg.

The teflubenzuron residues in whole fruit (greenhouse) from 10 supervised trials on tomatoes conducted in France, the Netherlands and Spain matching the critical GAP were (n = 10): 0.07, 0.07, 0.07, 0.09, 0.26, 0.33, 0.35, 0.36, 0.42 and 0.88 mg/kg

Based on tomatoes grown in greenhouses, the Meeting estimated an STMR of 0.30 mg/kg, and recommended a maximum residue level of 1.5 mg/kg for teflubenzuron on tomatoes.

Sweet pepper

The critical GAP of teflubenzuron for peppers (bell) in the Netherlands with three foliar spray applications, at a rate of 0.225 kg ai/ha and a PHI of 3 days.

In trials conducted in the Netherlands at the rate of 3 × 0.27 kg ai/ha, the teflubenzuron residues in whole fruit were: 0.46, 0.46 and 0.61 mg/kg.

The Meeting considered three trials to be insufficient to make any recommendations for sweet peppers.

Soya bean

Teflubenzuron is registered for foliar applications on soya beans in Central America (Guatemala, El Salvador, Honduras, Nicaragua and Panama) at a rate of 0.025–0.03375 kg ai/ha with a PHI of 21 days.

The teflubenzuron residues at 21 DALA in soya beans from 10 supervised trials conducted at a rate of 3× 0.034 kg ai/ha with 10 days interval in Argentina and Brazil were (n = 10): < 0.01(4), 0.01(3), 0.02 (2) and 0.03 mg/kg. The Meeting noted that the GAP in Central America did not specify the application number, and the early applications are unlikely to contribute significantly to residues at harvest. Therefore, The Meeting agreed that the trials approximated the GAP of Central America.

The Meeting estimated an STMR of 0.01 mg/kg and recommended a maximum residue level of 0.05 mg/kg for teflubenzuron on soya beans.

Maize

Teflubenzuron is registered for two foliar spray applications on maize in Bolivia at a rate of 0.018–0.0225 kg ai/ha with a PHI of 45 days.

In nine trials conducted at a rate of 1–4 × 0.0225 kg ai/ha, the teflubenzuron residues in grain at 30 or 45 DALA were (n = 9) all < 0.01 mg/kg.

The Meeting estimated an STMR of 0.01 mg/kg and recommended a maximum residue level of 0.01* mg/kg for teflubenzuron on maize.

Sugar cane

Teflubenzuron is registered for two foliar spray applications on sugar cane in Brazil at a rate of 0.0225 kg ai/ha with a PHI of 40 days.

In four trials conducted at a rate of 3× 0.0225 kg ai/ha, the teflubenzuron residues in stalks at 40 DALA were (n = 4) < 0.01 mg/kg.

The Meeting estimated an STMR of 0 mg/kg, and recommended a maximum residue level of 0.01* mg/kg for teflubenzuron on sugar cane.

Sunflower

Teflubenzuron is registered for two foliar spray applications on sunflowers in Brazil at a rate of 0.0075–0.01125 kg ai/ha with a PHI of 7 days.

In eight trials conducted at rate of 2× 0.01275–0.0132 kg ai/ha, the teflubenzuron residues in seeds at 7 DALA were (n = 8): < 0.01(6), 0.08 and 0.13 mg/kg.

The Meeting estimated an STMR of 0.01 mg/kg and recommended a maximum residue level of 0.2 mg/kg for teflubenzuron on sunflower seeds.

Coffee

Teflubenzuron is registered for two foliar spray applications on coffee in Brazil at a rate of 0.0375 kg ai/ha with a PHI of 30 days.

The teflubenzuron residues in dry beans from one supervised trial conducted in Brazil matching the GAP was < 0.01 mg/kg. The Meeting noted that coffee cherries were mechanically pulped and dried at room temperature for about 2 weeks in trials on dry beans.

Since one trial is insufficient for estimation, the Meeting took into consideration seven trials conducted at a rate of 0.075 kg ai/ha using the proportionality approach. The teflubenzuron residues in dry beans were: < 0.01, < 0.01, 0.01, 0.01, 0.08, 0.29 and 0.29 mg/kg. The scaled (using the factor of 0.0375/0.075 = 0.5) residue data was: < 0.005(2), 0.005(2), 0.004, 0.15 and 0.15 mg/kg (n = 7).

The data set available for estimation was: < 0.005(2), 0.005(2), < 0.01, 0.004, 0.15 and 0.15 mg/kg (n = 8).

Based on the data above, the Meeting estimated an STMR of 0.01 mg/kg and recommended a maximum residue level of 0.3 mg/kg for teflubenzuron on coffee beans.

Fate of residues during processing

The Meeting received information on hydrolysis studies and on the fate of teflubenzuron residues during the processing of oranges to juice, oil and dry pulp; of apples to juice, puree, dried pomace and wet pomace; of grapes to juice, must, wine, dry pomace and wet pomace; of tomatoes to juice, canned tomatoes, puree and wet pomace; of soya beans to meal and oil; of sunflowers to meal and oil; of maize to grits, meal, flour, oil and starch; of sugar cane to bagasse, molasses and sugar; and of coffee to roasted beans and instant coffee.

Studies on hydrolysis in solutions simulating pasteurization and sterilization (pH 6, incubation for 25 minutes at 120 °C) showed that teflubenzuron is stable under hydrolysis conditions

representing sterilisation and pasteurisation (recoveries of 89% and 94% remained as unchanged parent).

The processing factors obtained in the processing studies and estimated STMR-P and HR-P values are summarized below.

Raw agricultural commodity (RAC)		Processed commodity			
Name	STMR (mg/kg)	Name	Processing factor	(median or best estimate)	STMR-P (mg/kg)
Oranges	0.11	Juice	< 0.03, 0.05	< 0.04	0.0044
		Oil	413, 91	252	28
		Dry pulp	1.4, 0.7	1.1	0.12
Apples	0.16	Juice	< 0.15, < 0.035, < 0.08	< 0.035	0.0056
		Dried pomace	6, 6.9,	6.5	1.0
		Wet pomace	1.8, 3.83	2.4	0.38
		Apple puree	0.25	0.25	0.04
		Dry apple	12	12	1.9
Grapes	0.096				
		Must	1.3, 0.4	1.3	0.12
		Wet pomace	1.8, 1.7	1.8	0.17
		Dry pomace	1.4, 1.5	1.4	0.13
		Young wine	0.02, 0.03, < 0.03, < 0.04	0.03	0.0029
Tomatoes	0.30				
		Peeled tomatoes	0.08		0.024
		Juice	0.17		0.051
		Wet pomace	1.78		0.534
		Puree	0.45		0.135
		Canned tomatoes	0.07		0.021
Soya bean	0.01	Hull	6.4, 2.7	4.6	0.046
		Meal	< 0.1, 0.04	0.1	0.001
		Oil	0.3, 0.6	0.5	0.005
Sunflower	0.01	meal	< 0.1, < 0.2	< 0.2	0.002
		Oil (refined)	< 0.1, < 0.1	< 0.1	0.001
Maize	0.01	Grits	< 0.5, n/a	< 0.5	0.005
		Meal	< 0.5, n/a	< 0.5	0.005
		Flour	1.0, n/a	1.0	0.01
		Starch	< 0.5, n/a	< 0.5	0.005
		Refined oil (dry milling)	1.5, n/a	1.5	0.015
		Refined oil (wet milling)	1.0, n/a	1.0	0.01
Sugar cane	0	Bagasse	1.0, n/a	1.0	0
		Molasses	< 0.5, n/a	< 0.5	0
		Sugar	< 0.5, n/a	< 0.5	0
Coffee	0.01	Roasted beans	< 0.1		0.001
		Liquor extract	< 0.1		0.001
		Instant coffee	< 0.1		0.001

The Meeting noted that teflubenzuron concentrated during processing in orange pomace and oil. Based on the recommended MRL of 0.5 mg/kg for teflubenzuron residues in oranges and the processing factor of 252, the Meeting estimated a maximum residue level of 126 mg/kg for orange oil ($252 \times 0.5 = 126$).

The Meeting noted that teflubenzuron concentrated during processing in hulls of soya beans. The Meeting estimated a maximum residue level of 0.2 mg/kg for soya bean hulls based on the processing factor of 4.6 and recommended a MRL of 0.05mg/kg for soya beans.

The Meeting noted that teflubenzuron concentrated during processing in refined oil (dry milling) of maize. Based on the recommended MRL of 0.01 mg/kg for teflubenzuron residues in maize and the processing factor of 1.5, the Meeting estimated a maximum residues level of 0.015 mg/kg for maize oil.

Residues in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of teflubenzuron in farm animals on the basis of the diets listed in Appendix XIV of the 2016 Edition of the JMPR Manual. The calculations were made according to the livestock diets from Australia, the EU, Japan and US-Canada in the OECD Table. Because the calculation is mainly based on the STMR-P values of the processed by-products, the maximum and mean burden is identical. The dietary burden calculated for the beef cattle, dairy cattle, broilers and laying poultry are summarized below.

Summary of livestock dietary burden (ppm of dry matter diet)								
	US-Canada		EU		Australia		Japan	
	max	mean	max	mean	max	mean	max	mean
Beef cattle	0.027	0.027	0.51	0.51	0.54 [A]	0.54 [C]	0.01	0.01
Dairy cattle	0.26	0.26	0.026	0.026	0.36 [B]	0.36 [D]	0.01	0.01
Poultry-broiler	0.011	0.011	0.015 [E]	0.015 [F]	0.004	0.004	0.008	0.008
Poultry-layer	0.011	0.011	0.012 [G]	0.012 [H]	0.004	0.004	0.009	0.009

[A] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian meat

[B] Highest maximum dairy cattle dietary burden suitable for MRL estimates for mammalian milk

[C] Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat

[D] Highest mean dairy cattle dietary burden suitable for STMR estimates for mammalian milk

[E] Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs

[F] Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs

[G] Highest mean poultry dietary burden suitable for MRL estimates for poultry eggs

[H] Highest mean poultry dietary burden suitable for STMR estimates for poultry eggs

For beef and dairy cattle, the calculated maximum and mean dietary burden is 0.54 ppm and 0.36 ppm dry weight of feed respectively. For poultry, the calculated maximum and mean dietary burden is 0.015 ppm and 0.012 ppm dry weight of feed respectively.

Farm animal feeding studies

The Meeting received feeding studies on dairy cows and laying hens. It was noted that the storage period for milk, egg and tissues samples was about 2.5 months.

Lactating dairy cows were orally fed with teflubenzuron at levels of 10, 30 and 100 ppm in the feed for 4 weeks. Cows were sacrificed at 29–30, 36 and 43 days after first dosing. No teflubenzuron residues above LOQ (0.01 mg/kg) were found in any of the milk samples. Since occasional residues up to 0.026 mg/kg found in tissues of animals in the control group were unrelated to doses, no teflubenzuron residues above LOQ (0.01 mg/kg) were expected in tissues (muscle, liver, kidney and fat).

The Meeting note that the highest animal burden (0.54 ppm) is much less than the lowest feed level (10 ppm), and estimated the maximum residue levels of 0.01* mg/kg and STMRs of 0.01 mg/kg for milk and milk fat, mammalian meat, edible offal and mammalian fat (other than fat from milk).

Laying hens were treated with teflubenzuron orally via the diet at 0.5, 1.5 and 5 ppm for 28 days. Birds without withdrawal periods were sacrificed at the end of 28 days, birds with withdrawal periods were sacrificed at 35 and 42 days (7 and 14 days after treatment end). Residues of teflubenzuron in eggs were found at the highest level (0.34 mg/kg) in the 5 ppm dose group on Day 26. Highest residues of teflubenzuron in tissues were found in the 5 ppm dose group with 0.70 mg/kg in abdominal fat, 0.32 mg/kg in skin and subcutaneous fat, 0.081 mg/kg in liver, 0.036 mg/kg in kidney and 0.038 mg/kg in muscle.

The calculation used to estimate highest total residues for use in estimating maximum residue levels, STMR and HR values for poultry matrices is shown below.

	Feed level ppm) for egg residues	Residues (mg/kg) in eggs	Feed level (ppm) for tissue residues	Residues (mg/kg)			
				kidney	liver	Muscle	Fat
MRL (mg/kg)							
Feeding study	0.5	0.04	0.5	0.021	0.058	0.011	0.086
Dietary burden and high residue estimation	0.015	0.0012	0.015	0.0063	0.0017	0.0033	0.0026
STMR (mg/kg)							
Feeding study	0.5	0.04	0.5	0.015	0.041	< 0.01	0.077
Dietary burden and median residue estimated	0.012	0.00096	0.012	0.00036	0.00098	< 0.00024	0.0018

The Meeting noted that the LOQ for egg and poultry tissues is 0.01 mg/kg. The Meeting estimated maximum residue levels and an STMR of 0.01* mg/kg respectively for eggs, poultry meat, fat and edible offal.

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 and for estimation of dietary intake) for plant and animal commodities: *teflubenzuron.*

The residue is fat soluble.

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The International Estimated Dietary Intakes (IEDIs) of teflubenzuron were calculated for the 17 GEMS/Food cluster diets using STMRs and STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.005 mg/kg bw and the calculated IEDIs were 1–30% of the maximum ADI. The Meeting concluded that the long-term exposure to residues of teflubenzuron resulting from the uses considered by the current JMPR is unlikely to present a public health concern.

Short-term dietary exposure

The 2016 JMPR decided that ARfD for teflubenzuron was unnecessary. The Meeting therefore concluded that the short-term dietary exposure to residues of teflubenzuron, resulting from uses that have been considered by the present Meeting, is unlikely present a public health concern.