5.28 Triflumuron (317)

TOXICOLOGY

Triflumuron is the ISO-approved common name for 2-chloro-*N*-[[4-(trifluoromethoxy)phenyl] carbamoyl]benzamide (IUPAC), for which the CAS number is 64628-44-0.

Triflumuron is a synthetic insecticide from the active ingredient group of chitin biosynthesis inhibitors (chitin inhibitors) type 0. Triflumuron acts primarily as a feeding poison for biting and sucking pests. It disturbs the chitin biosynthesis of insects, particularly in immature life stages. It is used in a wide range of crops, including apple, pear, cabbage, citrus, cotton, potato and tea. It is also used as a veterinary drug.

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

The majority of the studies were conducted prior to the implementation of GLP regulation. GLP-compliant studies are identified in the monograph. Many studies were not conducted in accordance with national or international test guidelines since at the time the studies were performed no particular guideline had been agreed. However, the Meeting considered that overall the database was adequate for the risk assessment.

A search of the open literature did not reveal any relevant information additional to that submitted by the sponsor.

Biochemical aspects

Absorption, distribution and excretion of triflumuron[(4-trifluoromethoxy)aniline-UL-^{14}C] was studied in rats at a single gavage dose of 1.98 mg/kg bw (low-dose male), 318 mg/kg bw (high-dose male), unlabelled triflumuron at 3.74 mg/kg bw per day for 14 days, followed by a single oral dose of [^{14}C]triflumuron at 3.74 mg/kg bw by gavage (multiple dose) and 2.59 mg/kg bw in bile-cannulated rats. Oral absorption of triflumuron was estimated to be greater than 77% based on excretion of 41% in bile and 32% in urine, together with 4% in blood and carcass at 48 hours in bile-cannulated rats. The radioactivity was distributed within the body at low concentrations, with the highest levels found in the liver, kidney, spleen, lung and in fatty tissues. No significant differences were seen between the distribution pattern of [chlorophenyl-UL-^{14}C]-triflumuron and that of [(trifluoromethoxy)aniline-UL-^{14}C]-triflumuron.

Following a single oral administration of 2 mg/kg bw in males, the maximum plasma concentration of radioactivity was reached after 4.9 hours. Elimination was biphasic with half-lives of three and 13 hours in males. Excretion via urine and faeces was essentially complete 96 hours after dosing, with similar amounts excreted in urine and faeces, although female rats excreted slightly less of the radioactivity in urine over a longer period than males.

The half-life in the rat of radiolabelled [2-chlorophenyl-UL-^{14}C]triflumuron following oral dosing was relatively long in erythrocytes (ca 17 days); the radioactivity was primarily present in the globin fraction (76.2%). Triflumuron was rapidly metabolized in rats. A total of 17 components were detected in urine. Unchanged triflumuron was present at only low levels (1–2% of dose) in urine. The main metabolites in urine were identified as 2-hydroxy-4-(trifluoromethoxy)aniline (M09) and 3-hydroxy-4-(trifluoromethoxy)aniline (M10) and their sulfate conjugates (M16 and M17 respectively). A total of five components were observed in faecal extracts with the majority of the residue (19% at 3.7 mg/kg bw multiple doses; 91% at 318 mg/kg bw of the administered dose) remaining as unchanged triflumuron. A total of 26 components were observed in bile, with unchanged triflumuron present at only very low levels (< 1% of dose).

In rats, the major detoxification pathway proceeds initially through hydrolysis of triflumeron's urea moiety to yield 4-(trifluoromethoxy)aniline and chlorobenzoic acid. Minor metabolic pathways include hydrolysis of the 2-chlorobenzamide and direct hydroxylation of the trifluoromethoxyaniline ring prior to excretion. Parent and metabolites may also be conjugated.

Toxicological data

The acute LD_{50} by the oral and dermal routes in the rat was > 5000 mg/kg bw. The acute inhalation LC_{50} in rats was > 5.03 mg/L. Triflumuron is non-irritating to the skin and eyes of rabbits. Triflumuron was not sensitizing to the skin of guinea pigs, as determined by the Magnusson and Kligman test. In a single-dose oral toxicity study, rats were administered triflumuron via gavage at a dose of 0, 10, 70 or 500 mg/kg bw. The NOAEL was 500 mg/kg bw, the highest dose tested.

The main target organ of toxicity in short- and long-term studies in mice, rats and dogs was the haematopoetic system (erythrocyte damage). Compensation or regeneration processes (highly active bone marrow, extramedullary haematopoiesis in the spleen and frequent appearance of immature erythrocytes in the peripheral blood) were observed as a result of the erythrocyte damage. Enlarged spleen and haemosiderosis in spleen, liver and kidneys represented secondary effects.

In a 28-day toxicity study in rats, triflumuron was administered once daily via gavage at doses of 0, 30, 100 and 300 mg/kg bw per day. The NOAEL was 100 mg/kg bw per day based on decreases in erythrocytes and elevated reticulocytes and thrombocytes counts, and extramedullary haematopoiesis (splenic) seen in females at the LOAEL of 300 mg/kg bw per day.

In a 90-day toxicity study in rats, triflumuron was administered via diet at concentrations of 0, 50, 500 and 5000 ppm (equal to 0, 3.6, 35.5, and 349 mg/kg bw per day for males, 0, 4.5, 47.0 and 449 mg/kg bw per day for females). The NOAEL was 50 ppm (equal to 3.6 mg/kg bw per day) based on increased spleen weight in females, and slight declines in haemoglobin and erythrocytes seen at the LOAEL of 500 ppm (equal to 35.5 mg/kg bw per day) in both sexes.

In an another 90-day toxicity study in rats, triflumuron was administered via diet at concentrations of 0, 5, 15 and 45 ppm (equal to 0, 0.34, 1.02 and 3.12 mg/kg bw per day for males, 0, 0.39, 1.18 and 3.63 mg/kg bw per day for females), the NOAEL was 45 ppm (equal to 3.12 mg/kg bw per day), the highest dose tested.

In a separate 90-day toxicity study in rats, triflumuron was administered via diet at concentrations of 0, 20, 200 and 2000 ppm (equal to 0, 1.34, 13.9 and 142 mg/kg bw per day for males, 0, 1.52, 15.9 and 149 mg/kg bw per day for females), the NOAEL was 20 ppm (equal to 1.34 mg/kg bw per day) based on decrease in erythrocytes, haemoglobin, haematocrit, mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV) and increase in reticulocytes (females only) seen at the LOAEL of 200 ppm (equal to 13.9 mg/kg bw per day).

The overall NOAEL for triflumuron in 90-day toxicity studies in rats was 50 ppm (equal to 3.6 mg/kg bw per day), on the basis of haematological effects (decreased haemoglobin and erythrocytes) seen at 200 ppm (equal to 13.9 mg/kg bw per day).

In a 90-day toxicity study in dogs, triflumuron was administered in the diet at concentrations of 0, 100, 500 or 2500 ppm (equal to 0, 3.21, 17.3 or 85.2 mg/kg bw per day for males, 0, 3.66, 17.1 or 87.7 mg/kg bw per day for females). The NOAEL was 100 ppm (equal to 3.21 mg/kg bw per day) based on decreased haemoglobin and erythrocytes, increased methaemoglobin, reticulocytes and thrombocytes and histological findings (increase in bone marrow cells and extramedullary erythropoiesis in the spleen) at 500 ppm (equal to 17.1 mg/kg bw per day).

In a 12-month toxicity study in dogs, triflumuron was administered at concentrations of 0, 40, 200 or 1000 ppm in the diet (equal to 0, 1.42, 7.1 or 35.3 mg/kg bw per day for males, 0, 1.50, 7.3 or 37.9 mg/kg bw per day for females), the NOAEL was 40 ppm (equal to 1.42 mg/kg bw per day) based on haematological changes (increased reticulocytes), increased absolute spleen weight, pigmentation in liver, kidney and spleen seen at the LOAEL of 200 ppm (equal to 7.1 mg/kg bw per day).

In a separate 12-month toxicity study in dogs, triflumuron was administered at concentrations of 0 or 20 ppm in the diet (equivalent to 0 and 0.72 mg/kg bw per day) for a period of 12 months. The NOAEL was 20 ppm (equivalent to 0.72 mg/kg bw per day), the highest dose tested.

The overall NOAEL for 90-day and 12-month toxicity studies in dogs was 100 ppm (equal to 3.2 mg/kg bw per day). The LOAEL was 200 ppm (equal to 7.1 mg/kg bw per day).

Fluoride levels were elevated in the bones and teeth of rats and mice in chronic studies. No macroscopic or microscopic alterations of the bones or teeth were observed.

In a study of carcinogenicity in mice, triflumuron was administered via diet for 24 months at a concentration of 0, 20, 200 or 2000 ppm (equal to 0, 5.19, 49.0 and 523 mg/kg bw per day in males, 6.68, 67.9 and 692 mg/kg bw/day in females). The NOAEL for systemic toxicity was 20 ppm (equal to 5.19 mg/kg bw per day) based on haematological changes (reduced thrombocytes, increased Heinz bodies in males; reticulocytes, Heinz bodies, MCV and MCH values increased in females) and histopathological findings (increased haemosiderin pigment storage in the spleen in both sexes) seen at the LOAEL of 200 ppm (equal to 49.0 mg/kg bw per day). The NOAEL for carcinogenicity was 2000 ppm (equal to 523 mg/kg bw per day), the highest dose tested.

In a study of chronic carcinogenicity in rats, triflumuron was administered for 24 months via diet at a concentration of 0, 20, 200 or 2000 ppm (equal to 0, 0.82, 8.45 and 86.1 mg/kg bw per day in males, 0, 1.11, 11.2 and 110 mg/kg bw/day in the females). The NOAEL for systemic toxicity was 20 ppm (equal to 0.82 mg/kg bw per day) based on haematological effects (reticulocytes increased in males; leukocytes, erythrocytes, haemoglobin and haematocrit values reduced in females), and increased spleen weights seen at the LOAEL of 200 ppm (equal to 8.45 mg/kg bw per day). The NOAEL for carcinogenicity was 2000 ppm (equal to 86.1 mg/kg bw per day), the highest dose tested.

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

Triflumuron was tested for genotoxicity in a range of in vitro and in vivo assays. Although there were some deficiencies in the studies, no concerns were identified.

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

In view of the lack of carcinogenicity in mice and rats, and that it is unlikely to be genotoxic, the Meeting concluded that triflumuron is unlikely to pose a carcinogenic risk to humans from the diet.

In a multigeneration reproduction study in rats, triflumuron was administered via diet at a nominal dose of 0, 20, 200 or 2000 ppm (equivalent to 0, 1.32, 13.2 or 132 mg/kg bw per day) for three generations. The NOAEL for parental systemic toxicity, reproductive toxicity and offspring toxicity was 2000 ppm (equivalent to 132 mg/kg bw per day), the highest dose tested.

In a developmental toxicity study in rats, triflumuron was administered once daily by gavage at 0, 10, 30 or 100 mg/kg bw per day during GD 6–15. The NOAEL for maternal and embryo toxicity was 100 mg/kg bw per day, the highest dose tested.

In a separate developmental toxicity study in rats, triflumuron was administered once daily by gavage at 0, 100, 300 or 1000 mg/kg bw per day during GD 6–15. At 1000 mg/kg bw per day haematological effects were seen in maternal animals, however, a NOAEL for maternal toxicity could not be identified as no haematological measurements were conducted at 100 and 300 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 300 mg/kg bw per day based on a slight increase in skeletal variations (delayed ossifications) seen at the LOAEL of 1000 mg/kg bw per day, the highest dose tested.

In a developmental toxicity study in rabbits, triflumuron was administered once daily by gavage at 0, 10, 30 or 100 mg/kg bw per day during GD 6–18. The NOAEL for maternal and embryo/foetal toxicity was 100 mg/kg bw per day, the highest dose tested.

In a separate developmental toxicity study in rabbits, triflumuron was administered once daily by gavage at 0, 100, 300 or 1000 mg/kg bw per day during GD 6–18. At 1000 mg/kg bw per day haematological effects were observed in maternal animals, however, a NOAEL for maternal toxicity cannot be identified as no haematological measurements were conducted at 100 and 300 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 300 mg/kg bw per day based on increased resorption rate (late) seen at the LOAEL of 1000 mg/kg bw per day.

The Meeting concluded that triflumuron is not teratogenic.

No neurotoxicity studies are available, however, no evidence of neurotoxicity or neuropathology was observed in any of the studies of systemic toxicity.

The Meeting concluded that triflumuron is unlikely to be neurotoxic.

No evidence of direct immunotoxic effects were observed in the available toxicity studies.

The Meeting concluded that triflumuron is unlikely to be immunotoxic.

Toxicological data on metabolites and/or degradates

The compound 4-(trifluoromethoxy)aniline (M07; *p*-aminotrifluoroanisole; trifluoromethyl-4-aminophenyl ether; KLU 2996B) is a plant and rat metabolite. It was detected in a rat metabolism study at a trace level.

The LD_{50} of 4-(trifluoromethoxy)aniline in rats was 63 mg/kg bw. The acute dermal LD_{50} of 4-(trifluoromethoxy)aniline in rats was 25–50 mg/kg bw. The four hour inhalation LC_{50} in rats was 0.86–0.95 mg/L. It was non-irritating to the skin of rabbits and moderately irritating to the eyes of rabbits. In a limited study, cats were orally administered (gavage) 4-(trifluoromethoxy)aniline at 0, 0.5, 1.0 and 2.5 mg/kg bw (two cats/dose) and methaemoglobin formation was measured at 0, 3, 6, 24 and 48 hours post dosing. Methaemoglobin formation was observed at a single gavage dose of 1 mg/kg bw and above.

The compound 4-(trifluoromethoxy)aniline did not have any methaemoglobin-forming effect following single-dose administration of 500 mg/kg bw to male domestic cats.

Following administration of a 0.1 mg/kg bw per day gavage dose (total of 10 doses) no haemotoxic effects or methaemoglobin formation were detected in female domestic cats. After 2.5 mg/kg bw per day gavage dose (total of eight doses) 4-(trifluoromethoxy)aniline caused haemotoxic effects resulting in methaemoglobin formation and destruction of haemoglobin (Heinz body formation) in female domestic cats.

In a toxicity study in rats, 4-(trifluoromethoxy)aniline was administered as a single oral gavage dose at concentrations of 0, 0.5, 2 and 10 mg/kg bw per day. Animals from one group were killed 24 hours post-dosing and another group at five days post-dosing. The NOAEL of 0.5 mg/kg bw was based on clinical signs, chocolate brown coloration of the blood, higher methaemoglobin levels in both sexes, a slight increase in mean absolute reticulocyte counts in females (not statistically significant), observed one hour post-dosing, and increases in both absolute and relative weight in females and a slightly higher severity grade of diffuse extramedullary haematopoiesis in the spleen of females (termination) seen at the LOAEL of 2 mg/kg bw.

Investigations using the Ames test, an in vitro DNA test and an in vivo micronucleus test 4-(trifluoromethoxy)aniline was negative for genotoxicity.

N,*N'*-bis(trifluoromethoxyphenyl)urea (technical impurity) has an acute oral LD_{50} to rats of 133 mg/kg bw. The acute oral LD_{50} to domestic cats was > 1000 mg/kg bw and no haemotoxic effects were observed.

The Meeting concluded that metabolite M02 and metabolite M03 are major rat metabolites and would be covered by the toxicity of the parent compound. No data are available for metabolite M01 and M04 and these metabolites were not detected in rat metabolism studies, therefore the Meeting concluded that the genotoxic TTC value is appropriate for M01 and M04 for dietary exposure assessment. The Meeting also concluded that metabolite M08 would be covered by the toxicity of metabolite M07.

Microbiological data

No data are available.

Human data

Occupational medical surveillance of workers exposed to triflumuron during manufacturing indicate no health hazard to workers.

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

Toxicological evaluation

The Meeting established an ADI for triflumuron of 0–0.008 mg/kg bw, based on the NOAEL of 20 ppm (equal to 0.82 mg/kg bw per day) based on haematological effects and increase in spleen weights seen at the LOAEL of 200 ppm (equal to 8.45 mg/kg bw per day), observed in the two-year carcinogenicity study in rats and using a safety factor of 100.

The Meeting concluded that it was not necessary to establish an ARfD for triflumuron in view of its low acute oral toxicity, lack of systemic toxicity in a single-dose study at doses up to 500 mg/kg bw, lack of methaemoglobin formation in cats at doses up to 500 mg/kg bw and the absence of any other toxicological effects, including developmental toxicity, that are likely to be elicited by a single dose.

The Meeting established an ADI and ARfD of 0.02 mg/kg bw for 4-(trifluoromethoxy)aniline (M07) on the basis of the NOAEL of 0.5 mg/kg bw based on clinical signs, chocolate brown coloration of the blood, higher methaemoglobin levels in both sexes, and a slight increase in mean absolute reticulocyte counts in females, observed one hour post-dosing, and increase in both absolute and relative spleen weight in females and a slightly higher severity grade of diffuse extramedullary haematopoiesis in the spleen in females (termination) seen at the LOAEL of 2 mg/kg bw observed in single dose oral (gavage) toxicity study. A safety factor of 25 was used as the effect was C_{max}-dependent. The Meeting concluded that the ADI and ARfD also cover the toxicity of metabolite M08.

A toxicological monograph was prepared.

Levels relevant to risk assessment of triflumuron

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	20 ppm, equal to 5.19 mg/kg bw per day	200 ppm, equal to 49.0 mg/kg bw per day
		Carcinogenicity	2000 ppm, equal to 523 mg/kg bw per day[c]	-
Rat	Single-dose studies of toxicity[b]	Toxicity	500 mg/kg bw[c]	-
	90-day studies of toxicity[d]	Toxicity	50 ppm, equal to 3.6 mg/kg bw per day	200 ppm, equal to 13.9 mg/kg bw per day
	Two-year studies of toxicity and carcinogenicity[a]	Toxicity	20 ppm, equal to 0.82 mg/kg bw per day	200 ppm, equal to 8.45 mg/kg bw per day
		Carcinogenicity	2000 ppm, equal to 86.1 mg/kg bw per day[c]	-
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	2000 ppm, equal to 132 mg/kg bw per day[c]	-
		Parental toxicity	2000 ppm, equal to 132 mg/kg bw per day[c]	-
		Offspring toxicity	2000 ppm, equal to 132 mg/kg bw per day[c]	-
	Developmental toxicity study[b]	Maternal toxicity	-	1000 mg/kg bw per day[f]
		Embryo and fetal toxicity	300 mg/kg bw per day	1000 mg/kg bw per day
Rabbit	Developmental toxicity study[b]	Maternal toxicity	-	1000 mg/kg bw per day[f]
		Embryo/fetal toxicity	300 mg/kg bw per day	1000 mg/kg bw per day
Dog	13-week and one-year studies of toxicity[d,e]	Toxicity	100 ppm, equal to 3.2 mg/kg bw per day	200 ppm, equal to 7.1 mg/kg bw per day
Metabolite M07				
Rat	Single dose study of toxicity	Toxicity	0.5 mg/kg bw	2.0 mg/kg bw

[a] Dietary administration

[b] Gavage administration

[c] Highest dose tested

[d] Two or more studies combined

[e] Capsule administration

[f] NOAEL for maternal toxicity could not be identified as no haematological measurements were taken at lower doses

Acceptable daily intake (ADI), applies to triflumuron, M02, M03, expressed as triflumuron

0–0.008 mg/kg bw

Acute reference dose (ARfD), applies to triflumuron, M02, M03, expressed as triflumuron

Unnecessary

Acceptable daily intake (ADI) applies to 4-(trifluoromethoxy)aniline (M07) and M08, expressed as M07

0–0.02 mg/kg bw

Acute reference dose (ARfD), applies to 4-(trifluoromethoxy)aniline (M07) and M08, expressed as M07

0–0.02 mg/kg bw

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

Results from epidemiological, occupational health and other such observational studies of human exposure. Toxicity studies on plant metabolites and new genotoxicity studies on triflumuron.

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapidly absorbed and eliminated in urine and faeces, oral absorption ≥ 77% within 48 hours (based on urine, bile and carcass)
Dermal absorption	No data provided
Distribution	Widely distributed (fatty tissue, blood, liver, kidney, lung and spleen)
Potential for accumulation	No potential for accumulation
Rate and extent of excretion	Almost completely excreted via urine and faeces within 72 h
Metabolism in animals	In rats, metabolites were formed through hydrolysis followed by subsequent conjugation, or by hydroxylation of the parent compound followed by hydrolysis and/or conjugation
Toxicologically significant compounds in animals and plants	Triflumuron, M07, M08, M01, M02, M03 and M04
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw
Rat, LD_{50}, dermal	> 5000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.03 mg/L
Rabbit, dermal irritation	Not irritant
Rabbit, ocular irritation	Not irritant
Guinea pig, dermal sensitization	Not a sensitizer (Magnusson and Kligman test)
Short-term studies of toxicity	
Target/critical effect	Haematopoietic system (reduced erythrocytes count, haemoglobin and haematocrit)
Lowest relevant oral NOAEL	3.6 mg/kg bw per day (rat) 3.21 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	100 mg/kg bw per day
Lowest relevant inhalation NOAEC	0.0045 mg/L (rat, three-week study)
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Haematopoietic system (haemolytic anaemia)
Lowest relevant NOAEL	0.82 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic in mice and rats[a]
Genotoxicity	Unlikely to be genotoxic[a]
Reproductive toxicity	
Target/critical effect	None
Lowest relevant parental NOAEL	132 mg/kg bw per day, highest dose tested
Lowest relevant offspring NOAEL	132 mg/kg bw per day, highest dose tested
Lowest relevant reproductive NOAEL	132 mg/kg bw per day, highest dose tested
Developmental toxicity	
Target/critical effect	Delayed ossification (rat) and late resorptions (rabbit)
Lowest relevant maternal NOAEL	None (no assessment of haematological parameters at lower doses)
Lowest relevant embryo/fetal NOAEL	300 mg/kg bw per day (rat, rabbit)

Neurotoxicity	
Acute neurotoxicity NOAEL	No specific studies, no evidence of neurotoxicity in the database
Subchronic neurotoxicity NOAEL	No specific studies, no evidence of neurotoxicity in the database
Developmental neurotoxicity NOAEL	No specific studies, no evidence of developmental neurotoxicity in the database
Immunotoxicity	No data provided

Studies on toxicologically relevant metabolites

Acute toxicity	
4-(trifluoromethoxy)aniline (metabolite M07)	
Rat, LD_{50}, oral	63 mg/kg bw
Rat, LD_{50}, dermal	25–50 mg/kg bw
Rat, LC_{50}, inhalation	0.008–0.009 mg/L
Rabbit, dermal irritation	Not irritant
Rabbit, ocular irritation	Moderately
Genotoxicity	
4-(trifluoromethoxy)aniline (metabolite M07)	Negative for genotoxicity in the Ames test, DNA damage test and in vivo micronucleus test
Human data	No adverse effects in workers

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

Summary

	Value	Study	Safety factor
ADI	0–0.008 mg/kg bw[a]	Two-year study of toxicity and carcinogenicity (rat)	100
ARfD	Unnecessary		
4-(trifluoromethoxy)aniline (metabolite M07)			
ADI	0.02 mg/kg bw[b]	Single dose study of toxicity (rat)	25
ARfD	0.02 mg/kg bw[b]	Single dose study of toxicity (rat)	25

[a] Applies to triflumuron, and M02, M03, expressed as triflumuron

[b] Applies to 4-(trifluoromethoxy)aniline (M07), and M08, expressed as M07

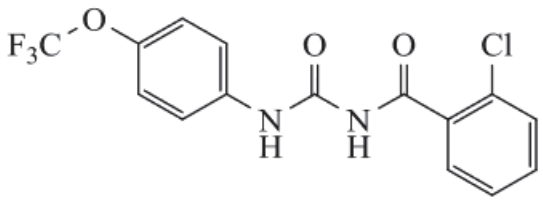
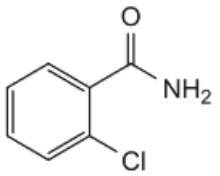
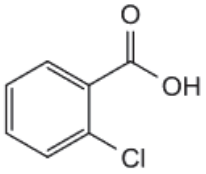
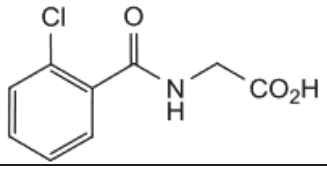
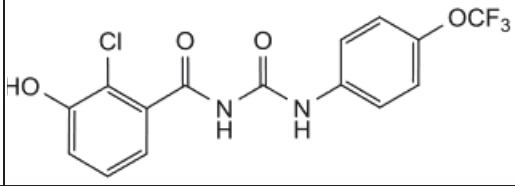
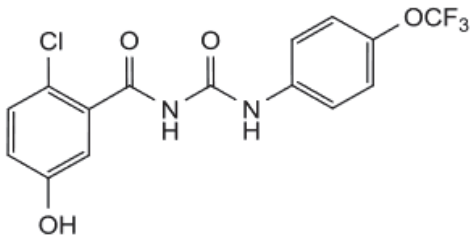
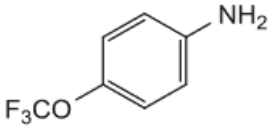
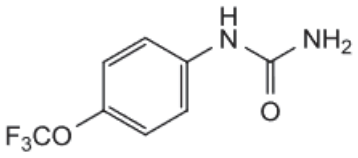
RESIDUE AND ANALYTICAL ASPECTS

Triflumuron is a benzoylurea insecticide. The mode of action is insect growth regulation by inhibiting the synthesis of chitin in insect larvae that are about to moult and interfering with the moulting hormone system. The IUPAC name for triflumuron is 1-(2-chlorobenzoyl)-3-[4-trifluoromethoxyphenyl]urea.

Triflumuron was scheduled at the Fiftieth Session of CCPR (2018) for evaluation as a new compound by the 2019 JMPR. The Meeting received information on identity, physical and chemical properties, plant and animal metabolism, environmental fate, methods of analysis, use pattern and supervised trials on soya bean, fate of residues in storage and processing and an animal feeding study.

The code numbers, chemical names and chemical structures of the compounds are as follows:

Table 1 Triflumuron and its metabolites referred to in this appraisal

Compound Code number, Chemical name	Structure
Triflumuron	
M01 2-Chlorobenzamide	
M02 2-Chlorobenzoic acid	
M03 2-Chlorohippuric acid	
M04 1-(2-chloro-3-hydroxybenzoyl)-3-[4-trifluoromethoxyphenyl]urea	
M05 1-(6-chloro-3-hydroxybenzoyl)-3-[4-trifluoromethoxyphenyl]urea	
M07 4-Trifluoromethoxyaniline	
M08 4-Trifluoromethoxyphenyl urea	

With respect to the physical and chemical properties that may impact on residues in crops, triflumuron is not regarded as volatile and the log P_{ow} is 3.5–3.6.

Plant metabolism

The Meeting received information on the fate of triflumuron in apples after direct treatment or soaking and in tomatoes, soya beans and potatoes after foliar applications. In the studies, triflumuron labelled with ^{14}C at the chlorophenyl group ([2-chlorophenyl-UL-^{14}C] triflumuron) and the 4-trifluoromethoxyaniline group ([4-trifluoromethoxy-phenyl-UL-^{14}C] triflumuron) were used. In the metabolism studies, total radioactive residues (TRR) are expressed in mg triflumuron equivalents/kg.

In a translocation study on apples, shoots cut from apple tree were placed into a beaker filled with an aqueous solution of labelled triflumuron. The apple cuttings absorbed 7.5–7.7% of the labelled triflumuron over a 13-day period. In another treatment, ten leaves of apple trees were treated with labelled triflumuron and, 13 days after treatment 0.05% of the applied radioactivity was translocated into upper plant parts.

In a metabolism study on apples conducted over two years, chlorophenyl-label or 4-trifluoromethoxyaniline-label triflumuron was applied topically to three individual apples on a tree under outdoor conditions, at rates equivalent to spray concentrations of 10 g ai/L in the first year and 0.2 or 1.0 g ai/L in the second year. Harvested apples 5–35 DAT were washed with acetone (acetone wash) and peeled. Peel and pulp were extracted with acetone. Surface wash accounted for 90–99% TRR. Most of the radioactivity in apples was present as triflumuron (≥ 98% of TRR at 31 DAT).

In a metabolism study on tomatoes, chlorophenyl-label or 4-trifluoromethoxyaniline-label triflumuron was applied to tomato plants grown in a greenhouse, with two foliar applications (21-day interval) at 0.38–0.39 kg ai/ha. Tomatoes were harvested 7 DALA and thereafter. Ripe tomatoes were washed with dichloromethane and then homogenized and extracted with acetonitrile/water (80:20) and then acetonitrile. Of the total radioactivity for whole tomatoes (1.1–1.4 mg/kg), 97–98% was found in surface wash. Almost 100% TRR in tomato was present as triflumuron.

In a translocation study on soya bean, labelled triflumuron was painted on the leaf surface of soya bean. About 0.02% of the AR was recovered in mature soya beans harvested 101 DAT. When 5 mg of labelled triflumuron was injected into the stem, 0.10–0.11% of the applied radioactivity was recovered in mature soya beans 101 DAT.

In a metabolism study on soya bean, chlorophenyl- or 4-trifluoromethoxyaniline-label triflumuron was applied to soya beans under field conditions at full bloom, with a foliar spray at an application rate of 1.12 kg ai/ha. Radioactive residues in foliage decreased over time during the study period (84 mg eq/kg at 0 DAT to 5.8 mg eq/kg at 77 DAT for the chlorophenyl-label; 41 mg eq/kg at 0 DAT to 11 mg eq/kg at 70 DAT for the 4-trifluoromethoxyaniline-label). TRR were higher in foliage (5.8–84 mg eq/kg, 0–77 DAT) and pods (0.4–9.0 mg eq/kg, 0–77 DAT) than in mature beans (0.21–0.31 mg eq/kg, 60–77 DAT).

In mature soya bean seed (60–77 DAT), 29–55% TRR was extracted by methanol, of which 14–15% TRR was partitioned into hexane and 13–41% TRR was in the aqueous phase. The majority of radioactivity was unextracted (45% or 71%). In the hexane phase, triflumuron was predominant (14% TRR, 0.03–0.04 mg eq/kg), followed by M01 (0–0.4% TRR, 0–0.001 mg eq/kg) and M02 (0–0.4% TRR, 0–0.001 mg eq/kg). Acid hydrolysis (6 M HCl, reflux for 16 hours) of PES released further parent triflumuron (2.1% of TRR, 0.004 mg eq/kg) and M02 (30% of TRR, 0.063 mg eq/kg) for the chlorophenyl-label and M07 (33% of TRR, 0.10 mg eq/kg) for the 4-trifluoromethoxyaniline-label.

In foliage and pods of soya bean (0–77 DAT), the major portion of radioactivity was extracted by methanol (73–99% TRR), of which 72–99% TRR and 58–98% TRR, respectively, was partitioned into hexane and 0.4–17% TRR and 2.1–17% TRR, respectively, in the aqueous phase. Triflumuron accounted for the majority of the residue in the hexane phase of foliage and pods at 72–99% TRR and 69–98% TRR, respectively. M01, M02 and M08 were also found (≤ 1.3% TRR). TRR in the water phase was not identified. Acid hydrolysis (6 M HCl, reflux for 16 hours) of the unextracted residue of foliage (60 DAT) released M07 (0.4% TRR).

In a translocation study on potatoes, the leaf surface of four potato plants was treated with chlorophenyl- or 4-trifluoromethoxyaniline-label triflumuron. The potato tubers harvested 42 days post-

treatment contained 0.005–0.008% of the AR. Another treatment with chlorophenyl- or 4-trifluoromethoxyaniline-label triflumuron was injected into the stems of two potato plants. Stem injection resulted in low levels of residue in the tubers (up to 0.7% AR, 12 DAT).

In a metabolism study on potatoes, chlorophenyl- or 4-trifluoromethoxyaniline-label triflumuron was applied to potatoes grown outdoors or in the greenhouse, respectively, at bloom as a foliar spray at an application rate of 1.12 kg ai/ha. Radioactive residues in tubers after application of 2-chlorophenyl-label increased from 0.01 mg eq/kg (7 DAT) to 0.08 mg eq/kg (42 DAT) and TRR in foliage or pods (23–98 mg eq/kg between 0–42 DAT) was always higher than that in tubers.

After treatment with 2-chlorophenyl-label triflumuron, in mature potato tubers (42 DAT), acetone and dichloromethane extracted 46–78% TRR, with a further 14% extracted by water. In the organic-solvent extract, triflumuron and M02 accounted for 26% TRR (0.037 mg eq/kg) and 14% TRR (0.011 mg eq/kg), respectively. Hydrolysis of the organic-solvent extract with HCl (1 M, reflux for 6 hours) released further triflumuron (8.3% TRR, 0.007 mg eq/kg). Acid hydrolysis (1 M HCl, reflux for 6 hours) of PES released additional parent triflumuron (15% TRR, 0.012 mg eq/kg), M01 (2.9% TRR, 0.002 mg eq/kg) and M02 (14% TRR, 0.011 mg eq/kg).

After treatment with 4-trifluoromethoxyaniline-label triflumuron, 0.01 mg eq/kg TRR was found in mature potato tubers (42 DAT), from which 78% TRR was extracted with methanol (0.008 mg eq/kg). In the methanol extract, triflumuron (42% TRR, 0.004 mg eq/kg) and M08 (14% TRR, 0.001 mg eq/kg) was identified. Further extraction or hydrolysis was not conducted.

Summary of plant metabolism

Translocation studies on apples, soya bean and potatoes indicated limited translocation of triflumuron within the plant.

When triflumuron was applied to apples and tomatoes, most residues were at the surface of the fruits (> 96% TRR in surface wash). When triflumuron was applied to soya beans and potatoes, residues were at lower concentrations in edible parts of the plants than inedible parts. In all of the plants tested, the majority of the triflumuron remained unmetabolized.

Triflumuron is the main residue in apples (> 98% TRR, free), tomatoes (> 99% TRR, free), soya bean foliage and pods (> 69% TRR, free and conjugated), soya bean seeds (16% TRR, 0.03–0.04 mg/kg, free and conjugated), and potato tubers (42 DAT, 42–49% of TRR, free and conjugated).

Major metabolites in soya bean seeds were M02 (30% TRR, 0.063 mg eq/kg) and M07 (33% TRR, 0.10 mg eq/kg), and in potato tubers M08 (14% TRR, 0.001 mg eq/kg) and M02 (14% TRR, 0.011 mg eq/kg) (all metabolites were totals of free and conjugated).

The Meeting concluded that the metabolic profiles between the species were qualitatively similar. All of the plant metabolites identified are also observed in the metabolism in rat.

Environmental fate

Aerobic degradation in soil

Triflumuron is not persistent in soil (DT_{50} 1.7–19 days).

Hydrolysis

Triflumuron is stable to hydrolysis at pH 5 and 7. It is hydrolysed at pH 9 (DT_{50} = 57 days at 25 °C) resulting in M02 at 29% AR after 30 days.

Soil photolysis

Triflumuron is stable to photolysis.

Rotational crop studies (confined)

All the metabolites of triflumuron found in succeeding crops (kale, red beet and wheat) were also found in the plant metabolism studies. At an application rate 7.3 times higher than the maximum seasonal rate in the Colombian GAP, TRR were 0.25–0.66 mg eq/kg at 1-month PBI and decreased to ≤ 0.08 mg eq/kg at longer PBI (4 or 9 months). At 1-month PBI, M02 (13–20% TRR, 0.03–0.12 mg eq/kg) was predominant, followed by M01 (1.1–20% TRR, 0.01–0.11 mg eq/kg) and triflumuron (1.4–5.7% TRR, < 0.01–0.02 mg eq/kg). The Meeting, however, concluded that it was unlikely that triflumuron used according to the GAP rate would carry over to follow-on crops at longer PBI (4 or 9 months).

Animal metabolism

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

In lactating goats, the metabolic fate of triflumuron was investigated using chlorophenyl- or 4-trifluoromethoxyaniline-label triflumuron.

For the chlorophenyl-label, triflumuron was administered once orally at 3.0 mg/kg bw and then 56 hours later at 25.1 mg/kg bw (equivalent to 170 ppm in the feed, dry matter basis (DM)). The goat was sacrificed 20 hours after the last dose. Following the first dose, approximately 60% of AR was excreted in faeces (54% AR) and urine (6.2% AR) within 56 hours.

The TRR in edible tissues was the highest in liver (3.3 mg eq/kg), followed by fat (1.8 mg eq/kg), kidney (0.87 mg eq/kg) and muscle (0.30 mg eq/kg). In milk, the TRR was 0.43 mg eq/kg.

The tissues and milk were extracted with dichloromethane (milk), hexane (fat) or methanol (liver, kidney and muscle). In milk and fat, 96–99% TRR was extracted. In liver, kidney and muscle, extractability with methanol was 31, 71 and 83% TRR, respectively. Water extracted an additional 4.2, 50, 21 and 7.1% TRR for milk, liver, kidney and muscle.

Parent triflumuron was a major component of the residue representing 75% TRR (0.32 mg eq/kg) in milk, 15% TRR (0.51 mg eq/kg) in liver, 20% TRR (0.18 mg eq/kg) in kidney, 58% TRR (0.18 mg eq/kg) in muscle and 96% TRR (1.8 mg eq/kg) in fat. The following metabolites were identified: M01 (free) in milk, liver, kidney, muscle and fat (0.9–20% TRR, 0.02–0.15 mg eq/kg); M03 (free and conjugated) in milk (6.2% TRR, 0.03 mg eq/kg) and kidney (36% TRR, 0.31 mg eq/kg); M04 (free and conjugated) in milk (4.1% TRR, 0.02 mg eq/kg) and kidney (0.8% TRR, 0.01 mg eq/kg); and M05 (free and conjugated) in liver (4.0% TRR, 0.13 mg eq/kg).

For the 4-trifluoromethoxyaniline-label, triflumuron was administered orally at 18 mg/kg bw (equivalent to 440 ppm in the feed (DM)) for 3 consecutive days with sacrifice 20 hours after the final dose.

The TRR in edible tissues was the highest in liver (6.1 mg eq/kg), followed by fat (4.8 mg eq/kg), kidney (1.6 mg eq/kg) and muscle (0.18 mg eq/kg). In milk collected 20 hours after first application, the TRR was 0.76 mg eq/kg.

The tissues and milk were extracted with dichloromethane (milk), hexane (fat) or methanol (liver, kidney and muscle). In milk, kidney, muscle and fat, 86–98% TRR was extracted. In liver, 52% TRR was extracted. Additional radioactivity was extracted with water (3.0–8.8% TRR in milk, liver, kidney and muscle).

Parent triflumuron was a major component of the residue at 60% TRR (0.45 mg eq/kg) in milk, 20% TRR (1.2 mg eq/kg) in liver, 27% TRR (0.43 mg eq/kg) in kidney, 80% TRR (0.14 mg eq/kg) in muscle and 95% TRR (4.6 mg eq/kg) in fat. The following metabolites were identified: M04 (free and conjugated) in milk (11% TRR, 0.08 mg eq/kg), liver (8.2% TRR, 0.50 mg eq/kg), kidney (28% TRR, 0.45 mg eq/kg), muscle (1.6% TRR, < 0.01 mg eq/kg) and fat (0.9% TRR, 0.04 mg eq/kg); and M08

(free and conjugated) in milk (4.8% TRR, 0.04 mg eq/kg), liver (1.5% TRR, 0.09 mg eq/kg), kidney (2.4% TRR, 0.04 mg eq/kg) and muscle (0.9% TRR, < 0.01 mg eq/kg).

In laying hens, the metabolic fate of triflumuron was investigated using chlorophenyl-label triflumuron. Three hens received daily oral doses of 8.0 mg/kg bw (equivalent to 100 ppm in the feed (DM)) for five consecutive days. Animals were sacrificed 3 hours after the last treatment.

The TRR in edible tissues was the highest in fat (27 mg eq/kg), followed by skin (14 mg eq/kg), liver (7.3 mg eq/kg), kidney (3.1 mg eq/kg) and muscle (0.80 mg eq/kg). In eggs, the TRR consistently increased from 24 to 96 hours after application (0.61–0.98 mg eq/kg) and no plateau was reached. Only eggs collected 96 hours after the last application were used for extraction.

Extractability with the solvents used was > 78% TRR; methanol for liver and kidney, acetone and dichloromethane for muscle and eggs, and hexane and acetonitrile for fat and skin.

Parent triflumuron was a major component of the residue and was found at 86% TRR (0.57 mg eq/kg) in eggs, 91% TRR (0.73 mg eq/kg) in muscle, 97% TRR (26 mg eq/kg) in fat, 97% TRR (13 mg eq/kg) in skin, 59% TRR (1.8 mg eq/kg) in kidney and 86% TRR (6.2 mg eq/kg) in liver. The following metabolites, free and conjugated, were identified: M01 in eggs (7.6% TRR, 0.05 mg eq/kg), muscle (6.3% TRR, 0.05 mg eq/kg), fat (0.3% TRR, 0.08 mg eq/kg), skin (0.5% TRR, 0.07 mg eq/kg), kidney (4.4% TRR, 0.14 mg eq/kg) and liver (8.9% TRR, 0.65 mg eq/kg); and M02 (free and conjugated) in muscle (0.3% TRR, < 0.01 mg eq/kg), fat (< 0.1% TRR, < 0.03 mg eq/kg), skin (0.1% TRR, 0.1 mg eq/kg), kidney (26% TRR, 0.81 mg eq/kg) and liver (0.3% TRR, 0.02 mg eq/kg) (absent in eggs).

Five other hens received a single oral dose of the chlorophenyl-label at 2.5 mg/kg bw (equivalent to 33 ppm in the feed (DM)). Eggs were collected within 96 hours after dosing and the TRR in eggs (96 hours after application) was 0.075 mg eq/kg with 92% TRR extracted with acetone and then dichloromethane. Parent triflumuron was found at 85% TRR (0.064 mg eq/kg) and the only identified metabolite was M01 (3.3% TRR, 0.002 mg eq/kg).

Summary

Parent triflumuron is the major component of the residue. Major metabolites were M03 and M04 in kidney of goats and M02 in kidney of hens. The Meeting concluded that the metabolic profiles were qualitatively similar between goats and hens.

Methods of analysis

The Meeting received methods of analysis for supervised field trials and animal feeding studies.

Method 00722/M002 was for analysis of triflumuron, M07 and M08 in sunflower seeds, soya beans and its processed commodities and aspirated grain fractions. In general, triflumuron, M07 and M08 were extracted with acetonitrile or acetonitrile/hexane (3:2, v/v) and filtered. Determination was by LC-MS/MS using external matrix-matched standards. The method was validated for triflumuron in sunflower seeds, soya beans and processed commodities of soya beans (soya bean oil, cold pressed; soya bean oil, solvent extracted; soya bean flour; soya bean hulls; soya bean meal; and soya bean milk) (LOQ=0.01 mg/kg), and aspirated grain fractions (LOQ=0.1 mg/kg) with mean recovery ranges of 83–108%. The method was also validated for M07 and M08 in soya beans and soya bean products with a LOQ of 0.005 mg/kg (equivalent to 0.01 mg/kg triflumuron) with mean recovery ranges of 82–105%.

Method 73295 was for analysis of triflumuron residues in animal commodities. Residues of triflumuron were extracted with acetone (milk) or dichloromethane/methanol (9:1, v/v; muscle, liver, kidney or fat), filtered, and cleaned up. Determination was by HPLC-UV (240 nm). The LOQs for triflumuron in milk, certain tissues (muscle, liver and kidney) and fat were 0.01 mg/kg, 0.05 mg/kg and 0.1 mg/kg, respectively. The mean recoveries (76–96%) were within the acceptable range. The Meeting confirmed that the method is suitable for analysis of triflumuron in milk, muscle, liver, kidney and fat.

Method 00757 was for analysis of triflumuron residues in animal commodities. Residues of triflumuron are extracted with acetonitrile/n-hexane (3:2 v/v) and filtered. Determination is by LC-

MS/MS using external matrix-matched standards. The method was validated for determination of triflumuron in animal commodities with LOQs of 0.005 mg/kg in fat, kidney, liver, meat and milk and the mean recoveries (84–101%) were within the acceptable range. The Meeting confirmed that the method is suitable for milk, muscle, liver, kidney and fat.

Stability of residues in stored analytical samples

A stability study on triflumuron residues in fortified sunflower seed (high oil content crop) was available. The Meeting concluded that triflumuron in high oil content commodities stored at ≤ -18 °C was stable for at least 23 months.

Based on a stability study on M07 stored at ≤-20 °C in fortified soya bean seed, the Meeting concluded that M07 in soya bean seed was stable for up to 3.3 months.

M08 stored at ≤-20 °C in fortified soya bean seed was stable for at least 12 months.

In animal commodities, a stability study on triflumuron residues in fortified liver, muscle and milk stored at ≤ -18 °C was available. No significant degradation was observed for at least 3.4 months in liver and muscle and up to 3.0 months for milk. The Meeting concluded that triflumuron residues in animal commodities stored at ≤ -18 °C are stable for at least 3.0 months.

Definition of the residue

Plant commodities

In the plant metabolism studies on apple, tomato, soya bean and potato, the predominant residue in solvent extracts was parent triflumuron (> 98% TRR in apple and tomato fruits; 16% TRR in soya bean seeds and 42–49% TRR in potatoes). Triflumuron was found in all primary crop commodities tested. The Meeting noted that suitable analytical methods exist to measure triflumuron in plant commodities. The Meeting considered that parent triflumuron was suitable marker for enforcement.

In deciding which compounds should be included in the residue definition for dietary risk assessment, the Meeting noted that no metabolites exceeded 10% TRR or 0.01 mg eq/kg in the metabolism studies on apples and tomatoes. In the metabolism study on soya bean, M02 and M07 exceeded 10% TRR and 0.01 mg eq/kg after acid hydrolysis of the unextracted residue. In the plant metabolism study on potatoes, M02 exceeded 10% TRR and 0.01 mg/kg after acid hydrolysis of the unextracted residue.

For M02, similar toxicity to parent triflumuron was assumed and the ADI for triflumuron (0–0.008 mg/kg bw) should apply to M02. The Meeting noted that the level of M02 in the soya bean metabolism study (DAT 77, free: 0.001 mg eq/kg, released by HCl hydrolysis: 0.063 mg eq/kg) was significant (total: 0.064 mg eq/kg), but that M02 (free and conjugated) was not analysed in the supervised trials. Considering the residue of the parent compound was 0.030 mg eq/kg in the same plant metabolism study at the same DAT, it was likely that the residue of M02 would be higher than that of the parent compound and it was necessary to estimate the residue level of M02 for dietary risk assessment. The Meeting concluded that the concentration of M02 in soya bean could be estimated to be 2.1 times (0.064 / 0.030) higher than parent triflumuron.

The Meeting established a separate ADI of 0–0.02 mg/kg bw and ARfD of 0.02 mg/kg bw to be applicable to M07 and M08 (expressed as M07). According to the plant metabolism study (DAT 60), free M07 was not found but the level of conjugated M07 (0.10 mg eq/kg) was higher than the parent compound (0.04 mg eq/kg). In the supervised field trials, free M07 was analysed, but conjugated M07 (released by HCl hydrolysis) was not. Considering the residue of the parent compound in the same plant metabolism study at the same DAT was 0.040 mg eq/kg, it was likely that the residue of M07 would be higher than that of the parent compound. Thus, it was necessary to estimate the residue level of conjugated M07 for dietary risk assessment. The Meeting concluded that the concentration of conjugated M07 in soya bean could be estimated to be 2.5 times (0.10 / 0.040) higher than parent.

In the plant metabolism study, triflumuron was released by HCl from the unextracted residue at a low concentration (0.004 mg eq/kg) where the application rate was 7.2 times higher than that of the maximum seasonal application rate in the Columbian GAP. The Meeting decided not to include conjugated triflumuron in the residue definition.

In the hydrolysis study simulating conditions of pasteurisation, baking/brewing/boiling, and sterilization, M07 and M08 were identified. In the processing study on soya bean (hulls, meal, flour, soya milk, solvent extracted oil and cold pressed oil), M07 and M08 were <LOQ (0.005 mg/kg). The Meeting concluded that further consideration of M07 and M08 in processed commodities was not necessary.

Animal commodities

In the animal metabolism studies on lactating goat and laying hen, the predominant residue was parent triflumuron. Triflumuron is found in all animal commodities tested. The Meeting noted that suitable analytical methods exist to measure triflumuron in animal commodities. The Meeting considered parent triflumuron to be a suitable marker compound for enforcement.

In the animal metabolism study, the triflumuron residues were much higher in fat than in muscle (6–27 times higher in lactating goat and 27–85 times higher in laying hen). While no information was available on the partition of residues in milk or eggs, the Meeting considered triflumuron to be fat-soluble.

In deciding which compounds should be included in the residue definition for risk assessment, the Meeting noted that among the animal commodities tested, the residues that exceeded 10% TRR and 0.01 mg eq/kg were: in lactating goat, M03 and M04 (free and conjugated) in kidneys, and in laying hens, M02 in kidneys.

For M02, significant levels were only found in kidneys of hens and not found in lactating goats. The Meeting decided that it was not necessary to include M02 in the residue definition for animal commodities.

For M03, similar toxicity to parent triflumuron was assumed. M03 was found only in milk and kidney from lactating goat in the metabolism study. The estimated levels of M03 in animal commodities based on the calculated animal dietary burden were very low (0.012 mg/kg in kidney and 0.001 mg/kg in milk). The Meeting decided not to include M03 in the residue definition for dietary risk assessment.

No toxicity data were available for M04. Based on its structure, the Meeting concluded that it was appropriate to apply the TTC approach for a potentially genotoxic compound. The Meeting estimated that long-term dietary exposure to M04 from animal commodities (0.0041 µg/kg bw per day) was higher than the threshold of toxicological concern for potential genotoxic compounds (0.0025 µg/kg bw per day).

TTC consideration of M01

Metabolite M01 was found in soya bean (seed and forage) in the metabolism study, tissues and milk from lactating goats, eggs and kidney from hens in the animal metabolism studies and kale, beet (tops and roots) and wheat (forage, heads and straw) in the confined rotational crop study. As no toxicity information was available for M01, based on its structure, the Meeting concluded that it was appropriate to apply the TTC approach for a potentially genotoxic compound.

The Meeting noted that the estimated long-term dietary exposure to M01 from soya bean, rotational crops (leafy vegetables, root and tuber vegetables and cereal grains) and animal commodities were higher (0.046 µg/kg bw per day) than the threshold of toxicological concern for potential genotoxic compounds (0.0025 µg/kg bw per day).

Conclusion

The Meeting decided that the residue definition for compliance with the MRL for plant and animal commodities was triflumuron. The residue is fat-soluble.

The Meeting was unable to conclude on residue definitions for dietary risk assessment for plant and animal commodities.

Results of supervised residue trials on crops

Soya beans

The critical GAP for triflumuron on soya bean in Colombia is two applications at 0.077 kg ai/ha with a minimum interval between sprays of 15 days and a PHI of 21 days. In trials matching the Colombian GAP, residues of triflumuron in soya beans were (n = 9): < 0.01 (3), 0.011, 0.014 (2), 0.048, 0.051 and 0.055 mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg.

As the residue definitions for dietary risk assessment were not established, the Meeting could not estimate an STMR for soya bean or complete a dietary risk assessment. .

Fates of residues during processing

High temperature hydrolysis

Triflumuron was shown to be hydrolytically stable for the simulated conditions of pasteurisation (> 97% of AR, 90 °C, pH 4, 20 min). Under simulated baking/brewing/boiling conditions (100 °C, pH 5, 60 min), 89% of the AR remained as triflumuron and M07 was formed (3.4% AR). Under the simulated sterilization condition (120 °C, pH 6, 20 min), 51% of triflumuron remained and compounds derived from hydrolysis, M07 (17% of AR) and M08 (16% of AR), were formed. Further characterization was not conducted.

Processing

The Meeting received information on the fate of triflumuron residues during the processing of soya beans. The Meeting estimated processing factors for parent triflumuron of 3.4 for soya bean hulls and 0.1 for soya bean meal, flour, soya milk, solvent extracted oil (RBD) and cold pressed oil (RBD).

Residues in animal commodities

Farm animal feeding studies

The Meeting received a dairy cow feeding study. Triflumuron in gelatine capsules was administered orally once daily to two groups of dairy cows (three animals in each group) for 29 days at levels equivalent to 5.9 ppm or 12 ppm in the feed (DM; 0.3 or 0.6 mg/kg bw). The residue levels of triflumuron in milk, liver, kidney, muscle and fat were < 0.01, < 0.05, < 0.05, < 0.05 and < 0.1 mg/kg, respectively, at both dose levels.

Farm animal dietary burden

The OECD diets include soya bean, hulls, meal, soya bean hay and fodder. In the supervised trials for soya bean, only seed was analysed. The levels of triflumuron in soya bean hay and forage were estimated using plant metabolism study.

Dietary burdens were calculated for beef cattle, dairy cattle, broilers and laying poultry based on feed items evaluated by the Meeting. The dietary burdens, estimated using the 2018 OECD Feed diets listed in Appendix XIV Electronic attachments to the 2016 edition of the FAO manual[19], are presented in Annex 6 and summarized below.

[19] http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmpr/jmpr-docs/en/

Table 2 Animal dietary burden for triflumuron

	Animal dietary burden of triflumuron, ppm of dry matter diet							
	US-Canada		EU		Australia		Japan	
	Max	Mean	max	mean	max	mean	max	mean
Beef cattle	0.009	0.009	0.008	0.008	13[a]	13[c]	0.012	0.012
Dairy cattle	3.1	3.1	0.009	0.09	6.1[b]	6.1[d]	0.011	0.011
Poultry – broiler	0.007	0.007	0.013	0.013	0.008	0.008	0.005	0.005
Poultry – layer	0.007	0.007	1.5[e g]	1.5 [f h]	0.008	0.008	0.005	0.005

[a] Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian tissues

[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 tissues.

[d] Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.

[e] Highest maximum poultry dietary burden suitable for MRL estimates for poultry tissues.

[f] Highest mean poultry dietary burden suitable for STMR estimates for poultry tissues.

[g] Highest maximum poultry dietary burden suitable for MRL estimates for poultry eggs.

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

Animal commodity maximum residue levels

Cattle

The Meeting noted that no residues were detected in milk at 2× the dietary burden for dairy cattle or in tissues at the approximate dietary burden for beef cattle. The Meeting estimated maximum residue levels of 0.01(*) mg/kg for milks, 0.05(*) mg/kg for mammalian offal, 0.1(*)(fat) for meat, mammalian and 0.1(*) mg/kg for mammalian fat.

Table 3 Maximum residue levels of triflumuron in poultry commodities

	Feed Level (ppm) for eggs residues	Triflumuron (mg /kg) in eggs	Feed Level (ppm) for tissue residues	Triflumuron (mg /kg)			
				Muscle	Liver	Kidney	Fat
HR Determination (broiler or laying hen)							
Feeding Study	100	0.57	100	0.73	6.2	1.8	26
Dietary burden and estimate of highest residue	1.5	0.0085	1.5	0.011	0.093	0.027	0.39

The Meeting noted that no feeding study for laying hen was available. The Meeting considered the metabolism study where hens were administered triflumuron for 5 days at rates 67× the estimated dietary burdens. In the absence of a poultry feeding study no maximum residue levels were estimated for poultry.

RECOMMENDATIONS

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

Definition of the residue for dietary risk assessment for animal and plant commodities: a conclusion could not be reached.

DIETARY RISK ASSESSMENT

No maximum residue levels are recommended, nor are levels estimated for use in long-term and acute dietary exposure assessments as the Meeting could not reach a conclusion on the residue definitions for dietary risk assessment.