5.36 TRIFLUMIZOLE (270)

TOXICOLOGY

Triflumizole is the common name provisionally approved by ISO for (*E*)-4-chloro-α,α,α-trifluoro-*N*-(1-imidazol-1-yl-2-propoxyethylidene)-*o*-toluidine (IUPAC), for which the CAS number is 68694-11-1. Triflumizole is a fungicide used for the control of powdery mildew. As a consequence of ergosterol biosynthesis inhibition, spore germination, mycelial growth and the spread of the fungi within the plants are inhibited.

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

All critical studies contained statements of compliance with GLP, unless otherwise specified.

Biochemical aspects

The absorption of (phenyl-U-^{14}C)-labelled triflumizole in rats was about 72% of the administered single dose at 10 and 300 mg/kg bw and about 80% of the applied repeated dose at 10 mg/kg bw. Absorption was considerably slower after the high dose than after the low dose, as evidenced by the much longer time to reach C_{max} (T_{max}). The radioactivity detected in tissues was generally low (~2%), with highest concentrations found in the liver. Excretion of triflumizole occurred rapidly and independently of sex. Most of the administered low dose (~90%) was recovered within 24 hours. At the single high dose of 300 mg/kg bw, 45–35% of the administered dose was excreted by 24 hours, increasing to 99–92% at 96 hours. The majority of the radiolabel was excreted via the urinary route (~75% of the administered dose compared with ~20% excreted via the faeces).

Triflumizole is extensively metabolized. A few differences in metabolite pattern were observed between males and females after repeated low and single high doses, but not after a single low dose. The major urinary metabolites are the sulfate conjugates of *N*-(4-chloro-2-trifluoromethyl-phenyl)-2-hydroxy-acetamidine (FM-8-1) and 2-amino-5-chloro-3-trifluoromethylphenol (FA-1-5). In faeces, *N*-(4-chloro-2-trifluoromethylphenyl)-2-hydroxy-acetamide (FD-2-1) is a major metabolite. Differences between dose regimens exist with respect to other major metabolites. 2-(4-Chloro-2-trifluoromethylphenylimino)-2-imidazol-1-yl-ethanol (FM-2-1) is the major metabolite after a single oral low dose. 4-Chloro-2-trifluoromethylphenylamine (FA-1-1) is a major metabolite after single and repeated low dosing, whereas *N*-(4-chloro-2-trifluoromethylphenyl)-2-propoxy-acetamide (FD-1-1) is the major metabolite after a single high dose The presence of the metabolite *N*-(4-chloro-2-trifluoromethylphenyl)-2-propoxy-acetamidine (FM-6-1) was confirmed in rat faeces and urine.

Toxicological data

Triflumizole has an oral LD_{50} of 1057 mg/kg bw in rats. The dermal LD_{50} is greater than 5000 mg/kg bw, and the inhalation LC_{50} is greater than 3.6 mg/L. No skin irritation and only mild eye irritation were observed. Based on a maximization test in guinea-pigs, triflumizole is considered a skin sensitizer. These studies were conducted prior to GLP, except for the acute inhalation study, but they were conducted to an acceptable standard.

In all short-term studies, decreased body weight gain combined with increased feed consumption and increased liver weights were observed. In a non-GLP 90-day dietary toxicity study, mice were exposed to 0, 20, 200 or 2000 ppm (equal to 0, 3.2, 33 and 381 mg/kg bw per day for males and 0, 4.2, 43 and 466 mg/kg bw per day for females, respectively). The NOAEL was 200 ppm (equal to 33 mg/kg bw per day), based on decreased body weight gain, increased feed consumption and liver effects (increased liver weight, swelling of cytoplasm) observed at 2000 ppm (equal to 381 mg/kg bw per day).

In a second non-GLP 90-day dietary toxicity study, rats were exposed to 0, 20, 200 or 2000 ppm (equal to 0, 1.4, 15 and 177 mg/kg bw per day for males and 0, 1.8, 17 and 218 mg/kg bw per day for females, respectively). Decreased body weight gain, increased feed consumption, liver effects (increased liver weight, fatty changes) and increased kidney weights were also observed at 2000 ppm in both sexes. Based on these effects at 2000 ppm (equal to 177 mg/kg bw per day), the NOAEL was 200 ppm (equal to 15 mg/kg bw per day).

In a 1-year oral toxicity study with dogs exposed to 0, 100, 300 or 1000 ppm (equal to 0, 3, 10 and 34 mg/kg bw per day for males and 0, 3, 11 and 35 mg/kg bw per day for females, respectively), the NOAEL was 300 ppm (equal to 10 mg/kg bw per day), based on liver effects (increased weights, macroscopic changes) and increased AP levels at 1000 ppm (equal to 34 mg/kg bw per day).

In a combined chronic toxicity and carcinogenicity study in mice, animals were exposed through the diet to triflumizole at a concentration of 0, 100, 400 or 1600 ppm (equal to 0, 16, 67 and 296 mg/kg bw per day for males and 0, 22, 88 and 362 mg/kg bw per day for females, respectively). At 400 ppm (equal to 67 mg/kg bw per day) and above, liver effects were observed, as demonstrated by increased organ weight and histopathological findings (nodules and fatty changes in both sexes as well as granulomatous inflammation, cytological alterations, pigmentation and necrosis in some males). Based on these liver effects, the NOAEL was 100 ppm (equal to 16 mg/kg bw per day).

In a combined chronic toxicity and carcinogenicity study in which rats were exposed through the diet to triflumizole at a concentration of 0, 100, 400 or 1600 ppm (equal to 0, 3.5, 14 and 59 mg/kg bw per day for males and 0, 4.5, 18 and 77 mg/kg bw per day for females, respectively), the liver was an important target organ, as demonstrated by increased organ weight and a wide range of histopathological findings at 400 ppm (equal to 14 mg/kg bw per day) and above. The highest dose group of females also showed an increased incidence of convulsive episodes and an increased incidence of ovarian follicular cysts. Based on the liver effects observed, the NOAEL was 100 ppm (equal to 3.5 mg/kg bw per day).

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

The genotoxic potential of triflumizole was tested in an adequate range of in vitro and in vivo studies. Triflumizole showed no evidence of genotoxicity in any assays.

The Meeting concluded that triflumizole is unlikely to be genotoxic.

Based on the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that triflumizole is unlikely to be carcinogenic in humans.

In a three-generation reproductive toxicity study, rats were exposed through the diet to triflumizole at a concentration of 0, 30, 70 or 170 ppm (equal to 0, 2.1, 4.8 and 12 mg/kg bw per day for males and 0, 2.5, 5.8 and 14 mg/kg bw per day for females, respectively). The NOAEL for parental toxicity was 70 ppm (equal to 4.8 mg/kg bw per day), based on increased placental weights and increased liver and kidney weights at the high dose (170 ppm, equal to 12 mg/kg bw per day). The NOAEL for reproductive toxicity was 70 ppm (equal to 4.8 mg/kg bw per day), based on reduced mating, fertility and litter size. The NOAEL for offspring toxicity was 170 ppm (equal to 12 mg/kg bw per day), the highest dose tested.

Two developmental toxicity studies were conducted in rats. In a non-GLP study, rats were exposed by gavage to 0, 10, 35 or 120 mg/kg bw per day, and in a GLP study, the dose levels were 0, 3, 7 and 35 mg/kg bw per day. Maternal toxic effects were similar in the two studies and comprised reduced body weight gain and feed consumption and increased placental weight at 35 mg/kg bw per day as well as increased liver and spleen weights at the same dose in the non-GLP study. Based on these effects, the overall NOAEL for maternal toxicity was 10 mg/kg bw per day, and the overall LOAEL was 35 mg/kg bw per day. The observed developmental effects were a reduction in the number of viable fetuses, a reduction in fetal weight and an increase in the number of late resorptions

at 35 mg/kg bw per day. The overall NOAEL for embryo and fetal toxicity was 10 mg/kg bw per day, with an overall LOAEL of 35 mg/kg bw per day.

Two developmental toxicity studies were conducted in rabbits. In a non-GLP study, rabbits were exposed by gavage to 0, 50, 100 or 200 mg/kg bw per day, and in a GLP study, the dose levels were 0, 5, 25 and 50 mg/kg bw per day. Maternal toxic effects were reduced body weight gain and feed consumption, increased liver weights, decreased ovary weights and decreased placental weight at 200 mg/kg bw per day. The overall NOAEL for maternal toxicity was 100 mg/kg bw per day, with an overall LOAEL of 200 mg/kg bw per day. The observed developmental effects were a lower 24-hour pup survival rate and decreased pup weight at 200 mg/kg bw per day. Based on these effects, the overall NOAEL for embryo and fetal toxicity was 100 mg/kg bw per day, with an overall LOAEL of 200 mg/kg bw per day.

The Meeting concluded that triflumizole is not teratogenic in rats or rabbits.

The Meeting was aware of several mechanistic studies and unpublished reports that have been submitted to a regulatory authority. These studies aimed to clarify the effects seen in the reproductive and developmental toxicity studies in rats. These studies were not made available to the Meeting.

In an acute neurotoxicity study, rats were administered triflumizole by gavage at 0, 25, 100 or 400 (males)/200 (females) mg/kg bw. Based on the clinical findings and the functional and motor activity effects observed at the next higher dose (100 mg/kg bw), the NOAEL was 25 mg/kg bw.

In a 13-week neurotoxicity study, rats were exposed to triflumizole at 0, 70, 700 or 2000 ppm (equal to 0, 4.1, 41 and 117 mg/kg bw per day for males and 0, 4.9, 48 and 133 mg/kg bw per day for females, respectively). The systemic findings were similar to those obtained in the 90-day repeated-dose toxicity study, the liver clearly being the main target organ. Based on the liver effects at 700 ppm (equal to 41 mg/kg bw per day), the NOAEL for non-neurotoxic effects was 70 ppm (equal to 4.1 mg/kg bw per day). Observed effects on motor activity were considered not adverse because there was no dose-response relationship, there were no effects in females and the locomotor changes were within the normal range of behaviour. The NOAEL for neurotoxicity was 2000 ppm (equal to 117 mg/kg bw per day), the highest dose tested.

In an immunotoxicity study, triflumizole was administered for 28 days to female mice in diet containing concentrations of 0, 20, 200 and 2000 ppm (equal to 0, 4.4, 43 and 413 mg/kg bw per day, respectively). The NOAEL for systemic toxicity was 200 ppm (equal to 43 mg/kg bw per day), based on significantly reduced body weight gain at 2000 ppm (equal to 413 mg/kg bw per day). The NOAEL for immunotoxicity was 200 ppm (equal to 43 mg/kg bw per day), based on a significant reduction in anti–sheep red blood cell IgM in mice immunized with sheep red blood cells at 2000 ppm (equal to 413 mg/kg bw per day).

Toxicological data on metabolites and/or degradates

Acute oral toxicity studies were performed with a number of triflumizole metabolites. For metabolites FD-1-1, FD-2-1, FD-6-1, FM-2-1, FM-5-1, FM-6-1, FM-8-1 and FA-1-5, the oral LD_{50}s were similar to or higher than that of the parent (1057 mg/kg bw). Only metabolites FA-1-1 and FD-7-1 were slightly more toxic than the parent (LD_{50} = 771 mg/kg bw and ~1000 mg/kg bw, respectively).

Human data

A report on the health examination of production workers in the period May 1996 – May 2002 did not reveal any adverse health effects. No cases of acute poisoning or skin/eye irritation were observed in the same period.

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

Toxicological evaluation

An ADI of 0–0.04 mg/kg bw was established on the basis of the NOAEL of 3.5 mg/kg bw per day for hepatotoxicity (increased liver weight, macroscopic and microscopic hepatic changes) in the chronic toxicity study in the rat. A safety factor of 100 was applied. This is supported by the NOAEL of 4.8 mg/kg bw per day in the multigeneration study of reproductive toxicity in rats.

An ARfD of 0.3 mg/kg bw was established on the basis of the NOAEL of 25 mg/kg bw in the acute neurotoxicity study in the rat, based on clinical findings and effects on function and motor activity at 100 mg/kg bw. A safety factor of 100 was applied. The effects observed in developmental toxicity studies in rats were not considered to be a consequence of a single dose.

The ADI and the ARfD are also applicable to the metabolites containing the 4-chloro-2-(trifluoromethyl)phenyl group.

A toxicological monograph was prepared.

Levels relevant to risk assessment of triflumizole

Species	Study	Effect	NOAEL	LOAEL
Mouse	Ninety-day study of toxicity[a]	Toxicity	200 ppm, equal to 33 mg/kg bw per day	2000 ppm, equal to 381 mg/kg bw per day
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	100 ppm, equal to 16 mg/kg bw per day	400 ppm, equal to 67 mg/kg bw per day
		Carcinogenicity	1600 ppm, equal to 296 mg/kg bw per day[b]	—
Rat	Acute neurotoxicity study[c]	Neurotoxicity	25 mg/kg bw	100 mg/kg bw
	Ninety-day studies of toxicity[a,d]	Toxicity	200 ppm, equal to 15 mg/kg bw per day	700 ppm, equal to 41 mg/kg bw per day[d]
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	100 ppm, equal to 3.5 mg/kg bw per day	400 ppm, equal to 14 mg/kg bw per day
		Carcinogenicity	1600 ppm, equal to 59 mg/kg bw per day[b]	—
	Three-generation study of reproductive toxicity[a]	Parental toxicity	70 ppm, equal to 4.8 mg/kg bw per day	170 ppm, equal to 12 mg/kg bw per day
		Offspring toxicity	170 ppm, equal to 12 mg/kg bw per day[b]	—
		Reproductive toxicity	70 ppm, equal to 4.8 mg/kg bw per day	170 ppm, equal to 12 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
	Developmental toxicity studies[c,d]	Maternal toxicity	10 mg/kg bw per day	35 mg/kg bw per day
		Embryo and fetal toxicity	10 mg/kg bw per day	35 mg/kg bw per day
Rabbit	Developmental toxicity studies[c,d]	Maternal toxicity	100 mg/kg bw per day	200 mg/kg bw per day
		Embryo and fetal toxicity	100 mg/kg bw per day	200 mg/kg bw per day
Dog	One-year study of toxicity[a]	Toxicity	300 ppm, equal to 10 mg/kg bw per day	1000 ppm, equal to 34 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Two or more studies combined.

Estimate of acceptable daily intake

0–0.04 mg/kg bw

Estimate of acute reference dose

0.3 mg/kg bw

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

Results from epidemiological, occupational health and other such observational studies of human exposure

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

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid and extensive, 72–79%; 2-fold slower at 24 h at high dose than at low dose
Dermal absorption	No data
Distribution	Widely distributed
Potential for accumulation	No evidence for accumulation
Rate and extent of excretion	Rapid, ~90% excreted within first 24 h, mainly via urine (~75%)
Metabolism in animals	Extensively metabolized, less than 2% excreted as parent compound
Toxicologically significant compounds in animals, plants and the environment	Triflumizole and metabolites containing the 4-chloro-2-(trifluoromethyl)phenyl group
Acute toxicity	
Rat, LD_{50}, oral	1057 mg/kg bw

Rat, LD_{50}, dermal	> 5000 mg/kg bw
Rat, LC_{50}, inhalation	> 3.6 mg/L (4 h, nose only)
Rabbit, dermal irritation	Not a skin irritant
Rabbit, ocular irritation	Mild eye irritant
Guinea-pig, dermal sensitization	Sensitizer (maximization test)
Short-term studies of toxicity	
Target/critical effect	Liver
Lowest relevant oral NOAEL	15 mg/kg bw per day (rat)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (rat)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver
Lowest relevant NOAEL	3.5 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic
Genotoxicity	
	Not genotoxic
Reproductive toxicity	
Reproduction target/critical effect	Reduced fertility and litter size at parentally toxic doses
Lowest relevant parental NOAEL	4.8 mg/kg bw per day
Lowest relevant offspring NOAEL	12 mg/kg bw per day, the highest dose tested
Lowest relevant reproductive NOAEL	4.8 mg/kg bw per day
Developmental toxicity	
Developmental target/critical effect	Placenta, fetal viability and weight, number of late resorptions at maternally toxic doses
Lowest relevant maternal NOAEL	10 mg/kg bw per day (rat)
Lowest relevant embryo/fetal NOAEL	10 mg/kg bw per day (rat)
Neurotoxicity	
Acute neurotoxicity NOAEL	25 mg/kg bw per day (rat)
Subchronic neurotoxicity	177 mg/kg bw per day, the highest dose tested (rat)[a]
Other toxicological studies	
Immunotoxicity NOAEL	43 mg/kg bw per day (mouse)
Studies on metabolites	FD-1-1, FD-2-1, FD-6-1, FD-7-1FM-2-1, FM-5-1, FM-6-1, FM-8-1, FA-1-1, FA-1-5: oral LD_{50}s similar to or higher than that of parent
Medical data	
	No effects in manufacturing personnel, no cases of poisoning

[a] In the chronic study, possible neurotoxicity (convulsive periods) were observed in female rats from week 30 onwards.

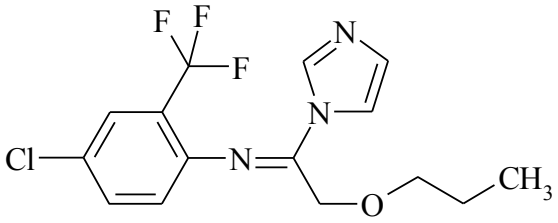
Summary

	Value	Study	Safety factor
ADI	0–0.04 mg/kg bw	Two-year study in rats	100
ARfD	0.3 mg/kg bw	Acute neurotoxicity study in rats	100

RESIDUE AND ANALYTICAL ASPECTS

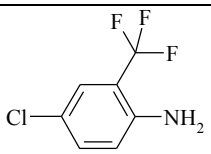
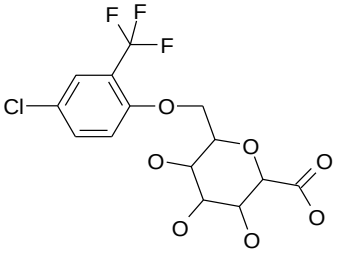
Residue and analytical aspects of triflumizole were considered for the first time by the present Meeting. The residue evaluation was scheduled for the 2013 JMPR by the Forty-fourth Session of the CCPR.

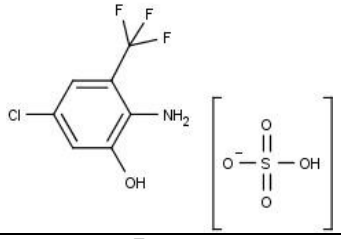
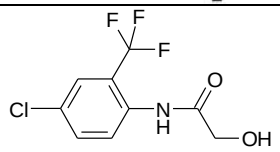
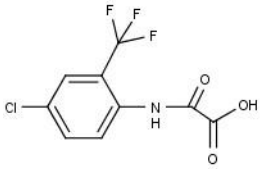
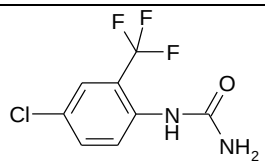
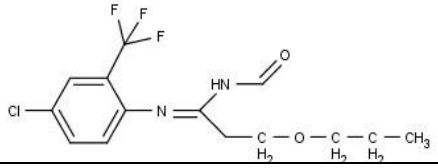
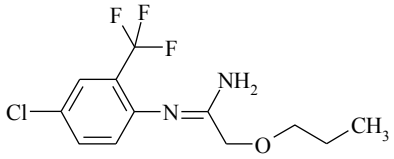
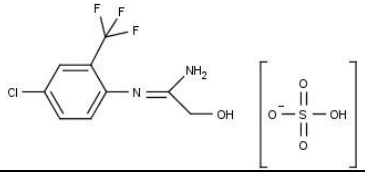
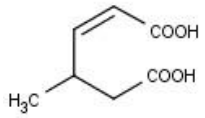
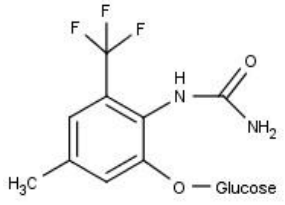
Triflumizole is a broad-spectrum foliar fungicide that controls a variety of fungal diseases in fruits and vegetables. It acts as a protectant and as an eradicant by preventing disease symptoms after infection has occurred. Triflumizole has anti-sporulant activity which reduces spores after lesions become visible. Triflumizole belongs to the demethylation inhibitor (DMI) group of fungicides classified as Group 3 by the Fungicide Resistance Action Committee (FRAC). Triflumizole has protective and curative action, and acts as an inhibitor of chitin biosynthesis. The product is mixed with water and applied as a foliar spray using ground equipment equipped for conventional spraying on crops. The Meeting received information on identity, animal and plant metabolism, environmental fates in soil, rotational crops, analytical methods, storage stability, use patterns, supervised trials, dairy cattle feeding studies, and fates of residues in processing.



(E)-4-chloro-α,α,α-trifluoro-N-(1-imidazol-1-yl-2-propoxyethylidene)-o-toluidine

In this appraisal, the following abbreviated names were used for metabolites.

Identifier	Chemical Structure
FA-1-1	
FA-1-glucuronide	

Identifier	Chemical Structure
FA-1-5 (Free and sulphate conjugate)	
FD-2-1	
FD-7-1	
FD-9-1	
FM-5-1	
FM-6-1	
FM-8-1 (Free and sulphate conjugate)	
XIV	
XXVI	

Animal metabolism

The Meeting received animal metabolism studies with triflumizole in rats, lactating goat and laying hens. The metabolism and distribution of triflumizole in animals were investigated using triflumizole universally labelled in the phenyl ring.

In the metabolism studies, rats were dosed at 10 mg/kg bw per day (single and multiple dose studies) or at 300 mg/kg bw per day (single dose study). Metabolite identification in tissues was not provided. The metabolite profile indicates that triflumizole is extensively metabolized in rats: less than 2% of the radiolabel recovered from urine or faeces was identified as parent compound. A few differences in metabolite pattern were observed between males and females after repeated low and single high doses, but not after a single low dose. The major urinary metabolites are the sulphate conjugates of N-(4-chloro-2-trifluoromethylphenyl)-2-hydroxy-acetamidine (FM-8-1) and 2-amino-5-chloro-3-trifluoromethylphenol (FA-1-5). In faeces, N-(4-chloro-2-trifluoromethylphenyl)-2-hydroxy-acetamide (FD-2-1) is a major metabolite. Differences between dose regimens exist with respect to other major metabolites. 2-(4-Chloro-2- trifluoromethylphenylimino)- 2-imidazol- 1-yl-ethanol (FM-2-1) is the major metabolite after a single oral low dose, 4-Chloro-2-trifluoromethylphenylamine (FA-1-1) is a major metabolite after single and repeated low dosing, whereas N-(4-chloro-2-trifluoromethylphenyl)-2-propoxy-acetamide (FD-1-1) is the major metabolite after a single high dose. The presence of the metabolite N-(4-chloro-2-trifluoromethylphenyl)- 2-propoxy-acetamidine (FM-6-1) was confirmed in rat faeces and urine.

Lactating goat was dosed with [^{14}C]triflumizole at a dose equivalent to approximately 280 ppm in the diet twice daily for 5 consecutive days. Gelatine capsules containing [^{14}C]triflumizole were administered orally via a balling gun. The majority of the dose was rapidly excreted in urine (56% of the TAR) and faeces (19.9% TAR).

Total radioactive residues (TRR) in the milk accounted for 0.18% TAR. Tissues contained approximately 0.65% TAR. Total material balance was 76.7% TAR, with an additional 5–12% TAR estimated to be in the bladder, digestive tract and carcass; $^{14}CO_2$ was not monitored.

Levels of radiolabel material reached a plateau in milk within approximately 24 hours and account for approximately 0.16% TAR. TRR was highest in liver and kidney (11.3 and 3.4 mg eq/kg, respectively) and approximately an order of magnitude lower in muscle (0.3 mg eq/kg) and fat (0.66 mg eq/kg). The residue in liver accounted for 0.4% TAR.

Triflumizole was not detected in any matrix. Major residues in liver were FA-1-1 (79.2% TRR, of which 54.8% TRR was bound) and FA-1-5-sulphate (12.4% TRR). In milk, major residues were FA-1-5-sulphate (29.1% TRR), FA-1-5-glucuronide (11.8% TRR), FD-2-1 (10.4% TRR), and FM-8-1-sulphate (12.6% TRR). No other individual compounds accounted for more than 10% of the TRR. The study noted that residues in other matrices were not identified due to low radioactivity; however, it is unclear why further characterization/identification was not done in muscle and liver given the level of residues in those tissues (0.3 and 0.66 mg eq/kg, respectively).

Laying hens were orally dosed with [^{14}C]triflumizole at a dose equivalent to 39 (3 hens) or 53 (2 hens) ppm in the diet twice daily for 5 consecutive days. The majority of the dose was rapidly eliminated in the excreta. Average radioactive residues in the excreta and cage wash accounted for 85.3% of the total administered dose.

Total ^{14}C residues in eggs did not plateau during the dosing period. Egg yolk and white were assayed separately for the eggs from hens treated at 53 ppm. Initially, TRR levels were greater in egg white than in the yolk; however, by Day 3 of dosing residues in yolk were much greater than in the egg white. On Day 5, residues in whole eggs from hens treated at 39 ppm ranged from 0.215 to 0.431 mg eq/kg. Residues ranged from 0.899 to 2.312 mg eq/kg in egg yolk and from 0.074 to 0.408 mg eq/kg in egg white. Residues in tissues from hens treated at the lower rate were consistently lower than those from hens treated at the higher rate. At the lower rate, residue ranges (mg eq/kg) were 0.989–1.232 in liver, 0.537–0.677 in kidney, 0.050–0.067 in fat, 0.017–0.047 in leg muscle, and 0.026–0.049 in breast muscle. At the higher rate, residues (mg eq/kg) were 0.781 and 1.115 in kidney,

0.312 and 0.358 in fat, 0.066 and 0.073 in leg muscle, and 0.054 and 0.087 in breast muscle; liver samples were used for metabolite identification and were not assayed for total radioactivity.

Major residues identified in egg white/yolk consisted of triflumizole (13.4/3.7% TRR), FD-6-1 or FD-4-1 (12.6/3.0% TRR), and FA-1-1 (35.3/22.1% TRR). Volatility of FA-1-1 resulted in some evaporative losses of that analyte. Unextracted residues accounted for 17.2 and 39.8% TRR in egg white and yolk, respectively. All other identified or characterized residues were less than approximately 4% TRR. Analysis of the liver samples indicated that the only metabolite was FA-1-1 or a compound convertible to FA-1-1 during proteolytic digestion.

In animal metabolism studies, triflumizole was metabolized to several compounds. The majority of the dosed radioactivity was excreted and radioactive residues in tissues were generally low. Triflumizole was identified as a residue in egg whites only. Metabolite FA-1-1 was the most prominent component in liver and egg. Sulphur- and glucuronide-conjugated FA-1-5 was the most prominent residue in milk.

Plant metabolism

The Meeting received plant metabolism studies performed on apple, pear, grape, and cucumber with triflumizole universally labelled in the phenyl ring.

In the apple metabolism study, trees were grown in a greenhouse and treated by spotting clusters of leaves with the test substance (approximately 0.127 mg/4-leaf cluster). Branches were harvested at 0, 1, 3, 7, 14, 21, 31, 60, and 90 DAT; fruits were not harvested.

Over the 90-day time span, the overall residue decreased from 51.65 mg eq/kg to 3.03 mg eq/kg, with an initial half-life of approximately 4 days, and was associated primarily with the treated leaves. Radioactive residue in the surface wash of treated leaves accounted for the majority of the residue until 14-DAT sampling. By the 14-DAT sampling, over half of the radioactivity in treated leaves was accounted for as extracted residues or associated with the post-extraction solids (PES). Radioactivity in untreated leaves above the treatment location remained relatively constant throughout the study, ranging from 0.04–0.07 mg eq/kg. Residues in untreated leaves below the treatment location showed a small increase in levels with time, with a maximum of 0.24 mg eq/kg at the 21-DAT sampling. In treated leaves, the only major (> 10% TRR) identified compounds that appeared consistently in the residue profile were triflumizole (0.02–0.12 mg eq/kg) and FM-6-1 (1.2–31% TRR, 0.01–0.02 mg eq/kg); FD-2-1 accounted for 12.6% TRR (< 0.01 mg eq/kg) at the 90-DAT sampling. As overall residues of radiocarbon declined with increasing time after treatment FD-2-1, unidentified metabolites and the contribution from PES became more prominent in the residue profile in terms of %TRR.

In the pear metabolism study, pear trees grown in a greenhouse were treated with test substance by spotting leaves (approximately 1 mg/4-leaf cluster) or the surface of pear fruits (approximately 0.166 mg/fruit) with radiolabelled test substance. Branches from leaf-treated trees were harvested at 0, 1, 3, 7, 14, 21, 31, 60, and 90 DAT and were divided into treated leaves, untreated leaves, and fruit. Treated fruits were harvested 0, 1, 3, 7, and 14 DAT.

Data from the leaf-treatment samples showed very little movement of radioactivity away from the treated leaves. Radioactivity reached maxima of 0.98% TAR in untreated leaves and 0.18% TAR in untreated fruit. In treated leaves, the majority of the radioactivity was associated with the surface wash through the 31-DAT sampling, at which point extractable residues and PES-associated residues, combined, constitute more than half of the TRR (56% TRR, 5.6 mg eq/kg). As with the apple study, the data show a rapid decline in radiocarbon residues, with an initial half-life of approximately 4 days.

For treated fruit, the vast majority (> 95%) of the radioactive residue was confined to the peel, with very little movement into the flesh or core of the pear. For peel, residues in surface wash were the majority at the 0- and 1-DAT sampling times, after which extractable residues became the

most prominent. The data also show a rapid decline in radiocarbon residues, with an initial half-life of between 1 and 3 days, and a slower rate of decline between 3 and 14 DAT.

In leaves, triflumizole and FM-6-1 were the only residues > 10% TRR. After 3 days and for the remainder of the study, FM-6-1 occurred at levels greater than triflumizole, peaking at 0.25 mg eq/kg at 3 DAT. In fruit, major residues were triflumizole (maximum = 93.56% TRR, 1.11 mg eq/kg, 0 DAT), FM-6-1 (maximum = 30.0% TRR, 0.14 mg eq/kg, 7 DAT) and FD-1-1 (10.51% TRR, 0.06 mg eq/kg, 3 DAT).

In the grape metabolism study, grape vines were grown in a greenhouse. Treatments were with triflumizole, uniformly labelled with ^{14}C in the phenyl ring, applied either to a branch of approximately 10 leaves and blossoms approximately 67 days prior to harvesting mature fruit, or to a bunch of young fruits 35 days before harvesting mature fruit. For both treatments, the rate was equivalent to 0.280 kg ai/ha. Treated branches were harvested 0, 3, 7, 14, 31, and 67 DAT and were divided into treated leaves and fruit; treated fruits were harvested 0, 3, 7, 14, and 35 DAT.

Following treatment of leaves, the % TAR decreased from 99% TAR to 15% TAR at 67 DAT. Most of the radioactivity in leaves was recovered from the surface wash, with < 2% TAR being translocated to fruits. Triflumizole was the major residue out to 31 DAT (51% TRR, 8.8 mg eq/kg). The only other major residue was FM-6-1 (11.1% TRR, 0.76 mg eq/kg at 67 DAT). Post-extraction residues in leaves gradually increased from 3.1% TRR (1.73 mg eq/kg) to 26.02% TRR (1.79 mg eq/kg) over the course of the study. Minor metabolites and those remaining at the origin increased to 39% TRR at 67 DAT, with no individual component exceeding 8% TRR.

In treated fruit over the 35-day period of the study, overall radioactivity decreased from 100% TAR (7.79 mg eq/kg) to 24.8% TAR (1.93 mg eq/kg). The majority of the radioactivity in treated fruit was recovered from the surface wash for the 0-, 3-, and 7-DAT samples; at the 14- and 35-DAT sampling points. More of the total residue was associated with extracted and bound residues. At all of the sampling times, the only major residue was triflumizole. FM-6-1 reached a maximum of 7.59% TRR (0.07 mg eq/kg) at 35 DAT, at which point triflumizole constituted 31% TRR (0.31 mg eq/kg).

The cucumber study was conducted under greenhouse conditions. Three types of treatment were made: Foliar treatment to investigate metabolism (0.13 mg/plant), fruit treatment to investigate metabolism (0.041 mg/plant), and foliar treatment to investigate translocation (0.16 mg/plant). In the case of the foliar treatment for metabolism, whole plants were harvested 1, 3, 7, 14, 21, and 45 days after treatment (DAT). For the fruit metabolism and translocation investigations, fruits were harvested 1 (metabolism only), 3, 7, and 14 DAT.

Results from all three lines of investigation demonstrated that the majority of the radioactivity (65–76% of applied) remained on the surface of the harvested material and that there was very little movement of radioactivity within the cucumber plants. Triflumizole accounted for most of the radioactivity through 14 DAT; at 21 DAT and 45 DAT, FM-6-1 residues were approximately equal to those of triflumizole and at 45 DAT, residues of F-8-1 were greater than either triflumizole or FM-6-1 on a % TRR basis. No metabolite exceeded 10% of the TRR except for FM-6-1approximately 12% TRR, < 0.01 mg eq/kg) at the 7- and 14-DAT sampling times in the cucumber fruit study. In those samples, FM-6-1 was associated with the peel and flesh of the fruit and not the surface wash.

The metabolic profile observed in these studies was similar across all four crops. Over the time course of the studies, triflumizole and FM-6-1 account for the majority of the radioactivity. Generally triflumizole decreased rather rapidly (half-life on the order of 3 days), with the exception of grapes where metabolism was slower (half-life approximately 14 days). Loss of triflumizole was accompanied by an increase in the FM-6-1 metabolite, which was the only metabolite to consistently occur at $\geqslant$ 10% TRR.

Environmental fate in soil

The Meeting received information on soil-surface photolysis, soil dissipation, aerobic soil metabolism, and confined and field rotational crop studies.

Under aerobic conditions in soil, the imidazole ring of triflumizole is opened to yield FM-5-1, FD-1-1, and FM-6-1. The resulting amide or amine moiety is then hydrolysed to form the FA-1-1 metabolite, which then becomes associated with bound residues or is oxidized to CO_2. The DT_{50} was 16–22 days at 20 °C with indoor studies and 7.1–22 days with outdoor studies.

In the soil photolysis study, triflumizole degraded significantly. On average after 11 days of exposure, triflumizole had declined to 30.0% of the AD. This was accompanied by formation of FM-6-1, which reached a maximum of 21.8% TAR after 7 days of exposure to simulated sunlight and then dissipated to 15.6% TAR at Day 11. The metabolites FD-1-1 (3.6% TAR at Day 11), FM-8-1 (1.8% TAR, Day 11), FD-7-1 (8.6% TAR, Day 11), and CO_2 (3.5% TAR, Day 11) were also observed. Bound residues increased over the time course of the study and averaged 18.7% TAR by the end of the 11-day period.

The results of both the aerobic soil and soil photolysis study indicate that triflumizole is not likely to be persistent in the environment.

In the confined rotational crop study, radiolabelled triflumizole was applied to bare soil at approximately 1.4 kg ai/ha (1× GAP; 6 plots) or approximately 12.7 kg ai/ha (10× GAP; 2 plots) and rotational crops of lettuce, radish, and wheat were planted into each. Plant-back intervals (PBIs) were 30, 120, and 365 days for the 1× plots and 30 days for the 10× plots. Radish was sampled for roots and tops, and wheat was sampled for forage, grain, hay, and straw. The 1X plots were used to determine % TRR only and the 10× plots were used to make metabolite identifications (except for 1× samples for wheat forage).

Quantifiable levels of TRR occurred for all crop matrices at all PBIs. Highest values were for wheat straw, starting at 1.65 mg eq/kg at the 30-day PBI and declining to 0.478 mg eq/kg at the 365-day PBI. The lowest values were for lettuce (0.086 to 0.021 mg eq/kg at the 120- and 365-day PBI, respectively). For each crop matrix, the TRR declined when going from shorter to longer PBIs with the exception of lettuce which had a maximum at the 120-day PBI (0.086 mg eq/kg) and wheat grain for which the 365-day PBI TRR (0.067 mg eq/kg) was greater than the 120-day PBI TRR (0.055 mg eq/kg).

Triflumizole underwent extensive metabolism in the confined rotational crop study. Forty-nine metabolites were identified, four of which were > 10% TRR and > 0.01 mg eq/kg in at least one matrix. No triflumizole was identified in any crop and no single metabolite was consistently the predominant residue. Two of the major metabolites were identified as glucose conjugates of FM-6-1 and FM-8-1, which constituted 22.9% TRR in lettuce and 16.1% TRR in wheat forage, respectively. The other major metabolites in the confined rotational crop study (XIV and XXVI) were not significant residues in either the crop or livestock metabolism profiles.

Field rotational crop studies were conducted with lettuce, turnip, cabbage, cotton, onion, tomato and wheat. Triflumizole was applied to squash at approximately 30 days prior to harvest or to cucumbers at the vining stage. In both studies, the initial application was followed by four subsequent applications at 7 ± 1 day intervals. All applications were 0.28 kg ai/ha for a total rate of 1.4 kg ai/ha. For all commodities except wheat fodder, forage, and hay, residues of triflumizole, analysed by the common-moiety method, were < 0.01 mg/kg, or in a few cases slightly above 0.01 mg/kg, at plant-back intervals (PBIs) of 30, 60, 90, 120, 180, and 270 days (not all crops were sampled at all intervals). In wheat animal forage, hay, and straw, quantifiable residues persisted throughout all of the plant-back intervals with no particular trend related to PBI. Residue ranges were < 0.01–0.20 mg/kg in wheat forage, < 0.01–0.144 mg/kg in wheat hay, and < 0.01–0.134 mg/kg in wheat straw.

The field rotational crop study indicates that residues are generally not expected (< 0.01 mg/kg) in food crops planted in rotation following treatment to the previous crop. When residues do occur, they are not expected to be much above 0.01 mg/kg. In contrast, readily quantifiable residues in forage/fodder, hay, and straw commodities from cereal grains are expected when such crops are planted in rotation following a treated.

Methods of analysis

The Meeting received description and validation data for analytical methods for residues of total triflumizole (all residues convertible to the FA-1-1 metabolite, expressed as triflumizole) as well as methods for specific residues (e.g., triflumizole, FM-6-1, FA-1-5). Recovery data were provided for raw and processed agricultural commodities as well as animal commodities.

Methods that analyse total triflumizole in crops involve an initial extraction with water. Hydrolysis is accomplished by refluxing in concentrated acetic acid and sodium acetate followed by distillation in the presence of sodium hydroxide into hexane. Residues are cleaned up by column chromatography, and analysed by GC-NPD, GC-MSD, or HPLC-UV.

Methods for the analysis of specific residues in crops use solvent extraction (methanol or acetonitrile), clean-up by solid-phase partitioning and liquid/liquid partitioning, and analysis by GC-NPD, GC-MSD, HPLC-UV, or LC-MS/MS.

Recoveries for the common-moiety method averaged 80.8% and recoveries for the specific-residue method averaged 86.5%. Recoveries for both methods were generally within the range of 70–120%. Limits of quantitation are reported as being of 0.01 mg/kg for most matrices, 0.02 mg/kg for hops, and 0.05 mg/kg for nutmeats.

Data describing multi-residue method testing for residues of triflumizole were not provided.

In animals, the common-moiety method uses 20% NaOH and a Bleidner extractor to digest/distil/extract residues into hexane. The terminal residue is the FA-1-1 metabolite and analysis is by GC-NPD. Recoveries for this method ranged from 78 to 92%.

In the procedure for determining residues containing FA-1-5, the sample was extracted using an acidic digestion followed by clean up and concentration using solid phase extraction (SPE) on reversed phase C18 columns. Final separation and quantification was conducted by HPLC on a C18 column and electrochemical detection. Recoveries for this method averaged 85%.

All of the submitted methods are adequate for the analysis of triflumizole residues.

Stability of residues in stored analytical samples

The Meeting received data on the stability of residues of triflumizole and its metabolites in crops (apple, grape, strawberry, cucumber, cherry, muskmelon, squash, lettuce, and wheat forage) and livestock. The test compound was added to homogenized test matrix. Samples were placed into frozen storage and analysed by the common-moiety or analyte-specific method(s) used in the supervised residue trial.

For the following commodities, stability of residues during storage was demonstrated for at least 3 months in hazelnut, 4 months in wheat forage, 6 months in animal commodities, 12 months in cherries and grapes, and 18 months in papaya.

For the following commodities, stability of residues during storage was demonstrated for no longer than 2 months in lettuce, 3 months in muskmelon and summer squash, and 6 months in apple, cucumber, and strawberry.

For the following commodities, stability of residues during storage was not demonstrated for any time period: cabbage, mustard greens, Swiss chard, and tomato.

Definition of the residue

In the lactating goat metabolism study, TRR were significantly higher in liver than in any other matrix, including milk. Triflumizole was not detected in liver or milk. In liver, free and conjugated FA-1-1 constituted nearly 80% of the residue, with FA-1-5-sulphate making up an additional 12%. In milk, sulphate and glucuronide conjugates of FA-1-5 account for 40% of the residue; the only other major residues were FD-2-1 (10.4% TRR) and FM-8-1-sulphate (12.6% TRR).

In the laying hen metabolism study, TRR were highest in liver, kidney, and egg. Liver contained only FA-1-1 (or a metabolite converted to FA-1-1 during proteolytic digestion). In egg, major residues were triflumizole (13.4% TRR in whites), FD-6-1 or FD-4-1 (12.6% TRR in white), and FA-1-1 (up to 35% TRR in white and 22% TRR in yolk). Hen kidney was not subjected to analysis for residue identification.

In the lactating cattle feeding study, samples were analysed using a common-moiety method, which would have captured all of the major residues observed in the lactating goat and laying hen metabolism studies except for FA-1-5-sulphate, which was the major metabolite in milk observed in the metabolism study. However, in the feeding study, residues of FA-1-5-sulphate were < 0.01 mg/kg in milk and < 0.03 mg/kg in liver and kidney.

Analytical methods for animal matrices are available for the analysis of residues convertible to FA-1-1 or for analysis of FA-1-5-sulphate.

The Meeting agreed that residues converted to 4-chloro-2-(trifluoromethyl)aniline (FA-1-1) and expressed as parent triflumizole are suitable for enforcement and dietary risk purposes in animal commodities.

The log P_{OW} of the residues in animal commodities will be determined by the composition and relative amounts of the metabolite residues in the various matrices. In the lactating cattle feeding study, total residues of triflumizole in fat were, on average, approximately 3.5 times greater than those in muscle.

The Meeting concluded that the residue is fat soluble.

In metabolism studies with apple (leaves only), pear, cucumber, and grape, triflumizole and FM-6-1 constitute the vast majority of the identified residues, and no other residues consistently occur at greater than 10% TRR. The FM-6-1 metabolite was observed in the rat.

The analytical method for plant matrices is a common-moiety method that quantifies all residues convertible to FA-1-1, including FM-6-1.

The Meeting agreed that residues converted to 4-chloro-2-(trifluoromethyl)aniline (FA-1-1) and expressed as parent triflumizole are suitable for enforcement and dietary risk purposes in plant commodities.

The Meeting recommended the following residue definition:

For plants and animals:

Definition of the residue (for compliance with the MRL and for estimation of dietary intake):

Residues analysed as 4-chloro-2-(trifluoromethyl)aniline and expressed as parent triflumizole.

Results from supervised residue trials on crops

The Meeting received supervised trial data for the foliar application of triflumizole on apple, pear, cherry, grape, strawberry, papaya, broccoli, cabbage, cucumber, muskmelon, squash, tomato, lettuce (head and leaf), mustard green, Swiss chard, turnip green, hazelnuts and hops. Residue trial data were made available from the USA for all crops as well as Japan (cucumber, apple and pear), Netherlands (cucumber and tomato), and Belgium (tomato).

Labels for end-use products containing triflumizole were available from the USA and the Netherlands (glasshouse use on tomato and cucumber only) describing the registered uses of triflumizole.

For most crops, the residues were determined by the common-moiety method and reflect the sum of all residues convertible to the aniline moiety, expressed as triflumizole. For the trials in Japan (cucumber), the Netherlands (cucumber and tomato) and Belgium (tomato), the reported residues are the sum of triflumizole and FM-6-1. Side-by-side data reflecting analysis by both common-moiety and residue-specific (triflumizole + FM-6-1) methods are available for hops. In those samples, residues from the common-moiety method were considerably greater than those from the residue-specific method. As the residue definition is for residues convertible to the FA-1-1 metabolite, only residues determined as total triflumizole are suitable for making residue estimates.

Pome fruits

The GAP in the USA on pome fruit is foliar application at a maximum rate of 0.56 kg ai/ha and a PHI of 14 days. Applications may be made at a 7- to 10-day interval with a maximum seasonal rate of 2.24 kg ai/ha.

Apple

Data were available from supervised trials on apple in the USA. Data were also provided from Japan; however, there is no GAP in Japan.

Eighteen supervised trials were conducted in the USA at GAP and residues were obtained by the common-moiety method. Using trials with a supported storage interval, the Meeting selected the following data for consideration (n=3): < 0.02, 0.26, 0.30 mg/kg.

The meeting agreed that the data for apple were insufficient to make a recommendation.

Pear

Data were available from supervised trials on pear in the USA. Data were also provided from Japan; however, there is no GAP in Japan.

Seven supervised trials were conducted in the USA at GAP and residues were obtained by the common-moiety method. Using trials with a supported storage interval, the Meeting selected to following datum for consideration (n=1): 0.28 mg/kg.

The Meeting agreed that the data for pear were insufficient to make a recommendation.

Cherry

The GAP in the USA on cherry is foliar application at a maximum rate of 0.56 kg ai/ha and a PHI of 1 day. Applications may be made at a 7- to 14-day interval with a maximum seasonal rate of 3.36 kg ai/ha.

Eight supervised trials were conducted in the USA at GAP and residues were obtained by the common-moiety method. The residue results are supported by the available storage stability data. The

trials resulted in the following eight independent residue values: 0.59, 0.96, 1.1, 1.1, 1.2 (2), 1.3, 1.5 mg/kg.

The Meeting estimated a maximum residue level, STMR, and HR for triflumizole residues in cherries (Subgroup 003A) of 4 mg/kg, 1.2 mg/kg, and 1.5 mg/kg, respectively.

Berries and other small fruits

The GAP in the USA on grapes and strawberries is foliar application at a maximum rate of 0.28 kg ai/ha and a PHI of 7 days for grapes and 1 day for strawberry. Applications may be made at a minimum interval of 14 days, with a maximum seasonal rate of 1.12 kg ai/ha.

Grape

Nineteen supervised trials were conducted in the USA at GAP for grapes and residues were obtained by the common-moiety method. The residue results are supported by the available storage stability data. The trials resulted in the following ten independent residue values: 0.09, 0.1, 0.15, 0.16, 0.18, 0.21, 0.31, 0.50, 0.90, 0.94, 1.4, and 2.0 mg/kg.

Based on these data, the Meeting estimated a maximum residue level, STMR, and HR for triflumizole residues in grapes of 3 mg/kg, 0.26 mg/kg, and 2.0 mg/kg, respectively.

Strawberry

Eight supervised trials were conducted in the USA. The residue data for strawberry are not supported by the available storage stability data.

The Meeting agreed not to make a recommendation for strawberry.

Papaya

The GAP in the USA on papaya is foliar application at a maximum rate of 0.35 kg ai/ha on a 14-day interval, with a PHI of 0 days. The maximum seasonal rate is 0.84 kg ai/ha.

Four supervised trials were conducted in the USA. Each treated plot received five applications at approximately 0.42 kg ai/ha on a 12- to14-day interval for a total rate of approximately 2.1 kg ai/ha. Papaya were harvested 0 DAT.

The Meeting agreed that although application in the papaya field trials reflects an over dosing relative to GAP due to the number of applications, the retreatment interval (12 to14 days) combined with residue decline and the rapid growth of the papaya fruit which would be occurring during the first two applications, the early applications are unlikely to have contributed significantly to the residue level at harvest. Therefore, the available trials are suitable for estimation of residue levels resulting from GAP applications. The residue data (n=4) are: 0.22, 0.53, 0.88, and 0.89 mg/kg.

Based on the trials for papaya in the USA, the Meeting estimated a maximum residue level, STMR, and HR for triflumizole residues in papaya of 2 mg/kg, 0.71 mg/kg, and 0.89 mg/kg, respectively.

Brassica (Cole or Cabbage) Vegetables, Head Cabbages, Flowerhead Cabbages

The GAP in the USA on Brassica vegetables is foliar application at a maximum rate of 0.28 kg ai/ha, at a 14-day interval, and a PHI of 1 day. The maximum seasonal rate is 0.63 kg ai/ha.

Broccoli

Ten supervised trials were conducted in the USA. The residue data for broccoli are not supported by the available storage stability data.

The Meeting agreed not to make a recommendation for broccoli.

Cabbage

Nine supervised trials were conducted in the USA. The residue data for cabbage are not supported by the available storage stability data.

The Meeting agreed not to make a recommendation for cabbage.

Fruiting vegetables, Cucurbits

The GAP in the USA on cucurbit vegetables is foliar application at a maximum rate of 0.28 kg ai/ha at a 7- to 14-day interval, and a PHI of 0 days. The maximum seasonal rate is 1.4 kg ai/ha.

The GAP in the Netherlands on cucumber and summer squash is foliar application at a maximum rate of 0.225 kg ai/ha and a PHI of 1 day. One to six applications may be made per season at a 7-day interval.

Cucumber-Outdoor Crops

Six supervised trials were conducted in the USA at GAP and residues were obtained by the common-moiety method. The residue results supported by the available storage stability data are as follows (n=4): 0.13 (2), 0.17, and 0.18 mg/kg.

The Meeting agreed that the data from field-grown cucumber were insufficient to make a recommendation.

Cucumber-Indoor Crops

Four supervised trials were conducted in the USA at GAP and residues were obtained by the common-moiety method. The residue results supported by the available storage stability data are as follows (n=3): 0.10, 0.11, and 0.21 mg/kg.

An additional four trials were conducted in the Netherlands according to the Netherlands GAP. The trials measured only triflumizole and FM-6-1; therefore the residues did not match the residue definition.

The Meeting agreed that the data from indoor-grown cucumber were insufficient to make a recommendation.

Residues from the indoor and outdoor trials on cucumbers from the USA matching the USA GAP are from the same population (Mann-Whitney U test). Using the combined data set (n=7): 0.10, 0.11, 0.13 (2), 0.17, 0.18 and 0.21 mg/kg, the Meeting estimated a maximum residue level, STMR, and HR for triflumizole residues in cucumber of 0.5 mg/kg, 0.13 mg/kg, and 0.21 mg/kg, respectively.

Melon

Six supervised trials were conducted on muskmelon in the USA at GAP. The residue data for muskmelon are not supported by the available storage stability data.

The Meeting agreed not to make a recommendation for muskmelon.

Summer squash

Five supervised trials were conducted in the USA at GAP at GAP and residues were obtained by the common-moiety method. The residue data for summer squash are not supported by the available storage stability data.

The Meeting chose not to make a recommendation for summer squash.

Tomato

The GAP in the USA on tomato is foliar application at a maximum rate of 0.28 kg ai/ha at a 7- to 14-day interval and a PHI of 0 days. The maximum seasonal rate is 1.4 kg ai/ha. The USA GAP is the Critical GAP.

Four supervised trials were conducted in the USA at GAP and residues were obtained by the common-moiety method. The residue data for tomato are marginally supported by the storage stability data and are as follows (n=4): < 0.5 (2), 0.59, and 0.76 mg/kg.

The Meeting agreed that the data for tomato from the USA were insufficient to make a recommendation.

The GAP in the Netherlands on tomato is foliar application at a maximum rate of 0.015 kg ai/hL and a PHI of 1 day. One to five applications may be made per season at a 7-day interval.

Four supervised trials were conducted in each of the Netherlands and Belgium. Treated plot received three applications each at 0.016 kg ai/hL on a 7-day interval and fruits were harvested 3 DAT.

The trials in the Netherlands and Belgium were conducted according to the Netherlands GAP. The Netherlands trials measured only triflumizole and FM-6-1; therefore the residues do not reflect the residue definition.

The Meeting agreed not to make a recommendation for tomato.

Leafy vegetables (including Brassica leafy vegetables)

The GAP in the USA on leafy vegetables is foliar application at a maximum rate of 0.28 kg ai/ha at a 14-day interval and a PHI of 0 days. The maximum seasonal rate is 0.63 kg ai/ha.

Lettuce

Data were available from supervised trials on lettuce in the USA.

Seventeen supervised trials were conducted in the USA on lettuce (head lettuce = seven field trials; leaf lettuce = seven field trials + two greenhouse trials; unspecified = one field trial). In 16 trials, treated plot received four applications each at approximately 0.28 kg ai/ha on a 6- to 9-day interval. The total application rate was approximately 1.12 kg ai/ha. In the remaining trial on the unspecified lettuce variety, five applications were made at approximately 0.57 kg ai/ha, for a total rate of approximately 2.85 kg ai/ha. Lettuce was harvested 0 DAT.

The Meeting agreed that in both the number and interval of applications, the residue trials for lettuce did not match the GAP for lettuce in the USA, and that the proportionality concept could not be used.

The Meeting agreed not to make a recommendation for lettuce.

Mustard greens

Ten supervised trials were conducted in the USA on mustard greens at GAP. The residue trials are not supported by the available storage stability data.

The Meeting agreed not to make a recommendation for mustard greens.

Swiss chard

Data were available from supervised trials on Swiss chard in the USA at GAP. The residue trials are not supported by the available storage stability data.

The meeting agreed not to make a recommendation for Swiss chard.

Turnip greens

The GAP in the USA for triflumizole on turnip greens is foliar application at a maximum rate of 0.28 kg ai/ha and a PHI of 1 day. Two to three applications may be made per season at a 14-day interval with a maximum seasonal rate of 0.63 kg ai/ha.

In one trial conducted in USA, where five applications of 0.27–0.3 kg ai/ha triflumizole were made on a 7-day schedule, total residues in turnip greens 1 day after the last application were 7.1 mg/kg.

The Meeting agreed that the supporting data for turnip greens did not match the GAP in USA and are of insufficient quantity. The Meeting agreed not to make a recommendation for turnip greens.

Hazelnuts/Filberts

The GAP in the USA on hazelnut is foliar application at a maximum rate of 0.21 kg ai/ha and a PHI of 18 days. Four to six applications may be made per season at a 10- to 14-day interval with a maximum seasonal rate of 0.84 kg ai/ha.

All of the field trials in the USA (n=3) were conducted at an exaggerated rate of 6.25× GAP. Per-trial average triflumizole residues (via common moiety) were < 0.05 mg/kg for all samples. The Meeting noted that all three trials were conducted in the same year and in the same orchard complex.

The Meeting noted that the trials are not independent and agreed not to make a recommendation for hazelnuts.

Hops

The GAP in the USA on hops is foliar application at a maximum rate of 0.42 kg ai/ha and a PHI of 7 days. Three applications may be made per season at a 14-day interval with a maximum seasonal rate of 1.26 kg ai/ha.

Data were available from supervised trials on hops in the USA.

Four supervised trials were conducted in the USA at GAP and residues were obtained by the common-moiety method. The residue results are supported by the available storage stability data. The trials resulted in the following 4 independent residue values for dried hops: 7.0, 7.8, 10, and 11 mg/kg.

Based on the trials for hops in the USA, the Meeting estimated a maximum residue level, STMR, and HR for triflumizole residues in hops, dried of 30 mg/kg, 8.9 mg/kg, and 11 mg/kg, respectively.

Fate of residues during processing

The Meeting received data depicting the effects of processing on residue levels in apple (juice, sauce, and wet/dry pomace) and grape (juice, raisins (and related commodities), stems, and wet/dry pomace). The estimated processing factors for grape commodities are 0.42 for juice; 0.22 for grape, dried; and 4.3 for wet pomace.

The Meeting estimated an STMR and HR for grapes of 0.41 mg/kg and 2.0 mg/kg, respectively. Application of the estimated processing factors results in an estimated STMR-P and HR-P, respectively, of 0.09 mg/kg and 0.44 mg/kg for grape, dried; an STMR-P of 0.17 mg/kg for grape juice; and an STMR-P of 1.2 mg/kg for wet grape pomace.

Residue in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of triflumizole in farm animals on the basis of the diets listed in Appendix IX of the FAO Manual 2009. Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Appendix IX of the FAO manual. The calculations were made according to the animal diets from US-Canada, EU, Australia and Japan in the Table (Appendix IX of the FAO manual). The diets are based on residues in wet grape pomace.

Livestock dietary burden, triflumizole, ppm of dry matter diet [a]								
	US-Canada		EU		Australia		Japan	
	Max	Mean	Max	Mean	Max	Mean	Max	Mean
Beef cattle	–	–	–	–	1.49 [a]	1.49 [c]	–	–
Dairy cattle	–	–	–	–	1.49 [b]	1.49 [d]	–	–
Poultry—broiler	–	–	–	–	–	–	–	–
Poultry—layer	–	–	–	–	–	–	–	–

[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 milk.

Farm animal feeding studies

The Meeting received lactating dairy cow feeding studies, which provided information on likely residues resulting in animal commodities and milk from triflumizole residues in the animal diet.

Lactating dairy cows

Lactating dairy cows were dosed with triflumizole for 28 days at the equivalent of 10 or 50 ppm in the diet. Analysis was for residues convertible to FA-1-1 and FA-1-5 (high-dose group only). Residues for all analyses and tissues were < 0.02 for control animals.

From the high-dose group, milk samples from even-numbered treatment days (except Day 24) were analysed. Residues of FA-1-5 were < 0.01 mg/kg in all milk samples and < 0.03 mg/kg in liver and kidney, which were the only tissue analysed for this compound. Total triflumizole residues were < 0.02 mg/kg in milk on Day 0 and were then rather consistent, ranging from, on average, 0.03 to 0.06 mg/kg. In the low- and high-dose tissue samples, respectively, average residues were 0.06 to 0.33 mg/kg in fat, 0.31 to 1.55 mg/kg in kidney, 0.48 to 4.25 mg/kg in liver, < 0.02 to 0.94 in muscle, and < 0.02 to 0.04 mg/kg in milk.

Animal commodities maximum residue levels

For MRL estimation, the residue in the animal commodities is residues analysed as 4-chloro-2-(trifluoromethyl)aniline and expressed as parent triflumizole.

Residues in tissues and milk at the expected dietary burden for beef cattle in Australia are shown in the Table below. The residue in milk was relatively consistent from Day 2 through Day 28 and the mean estimated residue in milk was calculated using the residue values from Day 4 to the final day.

Triflumizole feeding study	Feed level (ppm) for milk residues	Residues (mg/kg) in milk	Feed level (ppm) for tissue residues	Residues (mg/kg) in			
				Muscle	Liver	Kidney	Fat
MRL beef or dairy cattle							
Feeding study [a]	10 50	< 0.02 0.041	10 50	< 0.02 0.106	0.496 4.602	0.460 1.717	0.115 0.478
Dietary burden and high residue	1.49	< 0.02	1.49	< 0.02	0.07	0.69	0.03
STMR beef or dairy cattle							
Feeding study [b]	10 50	< 0.02 0.041	10 50	< 0.02 0.094	0.484 4.248	0.307 1.552	0.056 0.330
Dietary burden and residue estimate	1.49	< 0.02	1.49	< 0.02	0.072	0.046	0.008

[a] Highest residues for tissues and mean residues for milk

[b] Mean residues for tissues and mean residues for milk

The Meeting estimated the following maximum residue levels: Milk = 0.02(*) mg/kg, meat = 0.03 (fat) mg/kg and edible offal = 0.1 mg/kg.

The Meeting estimated the following STMR levels: Milk = 0 mg/kg, meat = 0 mg/kg, fat = 0.008 mg/kg and edible offal = 0.072 mg/kg.

The Meeting estimated the following HR levels: Milk = 0mg/kg, meat = 0 mg/kg, fat = 0.017 mg/kg and edible offal = 0.074 mg/kg.

RECOMMENDATIONS

On the basis of the data from supervised trials, the Meeting concluded that the residue levels listed below are suitable for estimating maximum residue limits and for IEDI and IESTI assessments.

Plant and animal commodities:

Definition of the residue for plant and animal commodities (for compliance with the MRL and for estimation of dietary intake): *Residues analysed as 4-chloro-2-(trifluoromethyl)aniline and expressed as parent triflumizole.*

The residue is fat soluble

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDIs) of triflumizole were calculated for the 13 GEMS/Food cluster diets using STMRs/STMR-Ps estimated by the current Meeting. The ADI is 0–0.04 mg/kg bw and the calculated IEDIs were 0–2% of the maximum ADI (0.04 mg/kg bw). The Meeting concluded that the long-term intakes of residues of triflumizole, resulting from the uses considered by the current JMPR, are unlikely to present a public health concern.

Short-term intake

The International Estimated Short-Term Intakes (IESTI) of triflumizole were calculated for food commodities and their processed commodities using HRs/HR-Ps or STMRs/STMR-Ps estimated by the current Meeting. The ARfD is 0.3 mg/kg bw and the calculated IESTIs were ≤ 100% of the ARfD for all commodities. The Meeting concluded that the short-term intake of residues of triflumizole, when used in ways that have been considered by the JMPR, is unlikely to present a public health concern.