

5.13 FLUTRIAFOL (248)

TOXICOLOGY

Flutriafol is the International Organization for Standardization (ISO)–approved name for (*RS*)-2,4'-difluoro- α -(1H-1,2,4-triazol-1-ylmethyl)benzhydryl alcohol (International Union of Pure and Applied Chemistry), which has the Chemical Abstracts Service No. 76674-21-0. Flutriafol is a contact and systemic fungicide belonging to the triazole class. It is used on a wide range of cereal crops and as a seed treatment. Its fungicidal mechanism of action is the inhibition of ergosterol biosynthesis and thus disruption of fungal cell wall synthesis.

Flutriafol was reviewed for the first time by the Joint FAO/WHO Meeting on Pesticide Residues at the request of the Codex Committee on Pesticide Residues. All critical studies contained statements of compliance with good laboratory practice.

Biochemical aspects

Flutriafol is rapidly and extensively absorbed following oral administration to the rat at dose levels of 5 or 250 mg/kg body weight (bw) in polyethylene glycol 600. Based on values for urinary and biliary excretion, oral absorption is greater than 90%. Flutriafol and/or its metabolites are widely distributed, with highest levels of radioactivity associated with red blood cells. Data from studies with repeated administration indicate that there is unlikely to be any bioaccumulation. Flutriafol is extensively metabolized in the rat, with only trace levels of unchanged parent detected in excreta following oral administration. The initial stage of metabolism is oxidation of the 2-fluorophenyl ring, followed by conjugation. Excretion was predominantly within 24 hours at 5 mg/kg bw, with similar amounts of radiolabel present in the urine and faeces. Biliary excretion was extensive (~80%), with evidence for enterohepatic circulation.

Toxicological data

Flutriafol has acute oral median lethal dose (LD₅₀) values of 1140–1480 mg/kg bw in the rat. Acute oral toxicity was higher in the mouse, rabbit and guinea-pig (LD₅₀s 179–400 mg/kg bw). Lower acute toxicity was seen via the dermal (LD₅₀ > 2000 mg/kg bw in rabbits) and inhalation (median lethal concentration [LC₅₀] > 5.2 mg/L) routes. Flutriafol was not irritating to rat or rabbit skin but was a mild irritant to rabbit eyes; all ocular effects had resolved within 72 hours. Flutriafol did not produce any evidence of skin sensitization in a Magnusson and Kligman assay in guinea-pigs or in a local lymph node assay in mice.

The red blood cell and liver were identified as targets of flutriafol toxicity in short-term oral toxicity studies in the rat, mouse and dog. Increases in hepatocyte hypertrophy and liver weight with no other effects were considered to be adaptive and not treated as adverse effects; other histopathological findings in the liver, such as fatty vacuolation or necrosis, were treated as adverse. Reduced body weights, weight gains and/or feed consumption were also seen at high dose levels in all three species. Effects on haematological parameters consistent with mild microcytic anaemia were seen in the rat and mouse; such effects were less marked in the dog. In a 29-day study, the majority of mice exposed at 1500 ppm died. Increased liver weights and hepatocytic vacuolation were seen at intermediate doses. Hepatocytic lipid accumulation was seen at all dose levels; the lowest-observed-adverse-effect level (LOAEL) was 50 ppm (equivalent to 7.5 mg/kg bw per day). Hepatotoxicity in the rat at high dose levels was characterized by elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, the disruption of lipid metabolism, increased liver weight, altered pigmentation and granulation, centrilobular hepatocyte hypertrophy and vacuolation, fatty change, focal necrosis and hydropic degeneration. At lower dose levels, findings of increased liver weight, centrilobular hepatocyte hypertrophy, elevated hepatic aminopyrine-*N*-demethylase activity and proliferation of the smooth endoplasmic reticulum are consistent with an adaptive effect. The no-

observed-adverse-effect level (NOAEL) in the 90-day rat study was 200 ppm (equal to 13 mg/kg bw per day). In the dog, hepatotoxicity was characterized by elevated serum alkaline phosphatase activity, perturbation of lipid metabolism, increased liver weight and (in the 1-year study) granular, swollen liver, hepatocytic vacuolation and lipid accumulation. The NOAELs for the 90-day and 1-year dog studies were both 5 mg/kg bw per day.

In a 28-day dermal toxicity study in rats, there were no systemic effects; the NOAEL was 1000 mg/kg bw per day. The NOAEL for local effects was 250 mg/kg bw per day, based on erythema and flaking of the skin at the application site.

The liver was identified as the target organ of flutriafol toxicity following chronic administration to the rat and mouse. Hepatotoxicity in the 2-year mouse study was characterized by increased liver weight and fatty change; the incidence of liver adenoma was marginally increased in males at the top dose level, but was within the historical control range. The NOAEL in the 2-year mouse study was 10 ppm (equal to 1.2 mg/kg bw per day), based on centrilobular fatty changes in the liver at 50 ppm (equal to 6 mg/kg bw per day). Flutriafol was not carcinogenic in mice.

Toxicity in the chronic rat study was characterized by clinical chemistry findings (reduced serum triglycerides and alkaline phosphatase activity and increased ALT activity in males; increased serum cholesterol in females) at 2000 ppm and increased liver weight and fatty change at 200 ppm and above. Incidences of liver adenoma and carcinoma were slightly increased at the top dose level, but were within historical control ranges. Evidence of anaemia was seen at the high dose level; effects on red blood cell parameters were accompanied in females by reduced serum iron concentration, elevated total iron binding capacity and haemosiderin accumulation in the spleen and liver. The NOAEL in the 2-year rat study was 20 ppm (equal to 1.0 mg/kg bw per day), based on increased fatty change and weight of the liver in males at 200 ppm (equal to 10 mg/kg bw per day). Flutriafol was not carcinogenic in rats.

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

Flutriafol has been tested for genotoxicity in an adequate range of in vitro and in vivo studies. Equivocal results were seen in two reverse mutation assays with mouse lymphoma L5178Y cells. The remaining in vitro and all the in vivo tests were negative.

The Meeting concluded that flutriafol is unlikely to be genotoxic.

Based on the absence of genotoxicity and absence of treatment-related carcinogenicity in mice and rats, the Meeting concluded that flutriafol is unlikely to be carcinogenic in humans.

Two reproductive toxicity studies in rats are available. Evidence of reproductive toxicity was seen in the first two-generation rat study; mean litter size was lower at the top dose level of 1000 ppm, and there was a reduced fertility index at the mating for the F_{1a} litter. The NOAEL for reproduction was 240 ppm (equal to 14 mg/kg bw per day). Minor maternal body weight effects and hepatotoxicity (fatty change) were seen at 240 ppm in both sexes. The NOAEL for parental toxicity was 60 ppm (equal to 3.5 mg/kg bw per day). Fatty changes in the liver were also seen in pups at the top dose level. The NOAEL for offspring toxicity was 240 ppm (equal to 14 mg/kg bw per day). Similar findings were seen in the range-finding component of the more recent rat reproductive toxicity study. Post-implantation losses (13%) were increased at doses causing mild to moderate maternal toxicity in the preliminary reproduction study at 240 ppm (equal to 13 mg/kg bw per day) and above. NOAELs for parental, pup and reproductive effects were 60 ppm (approximately 4 mg/kg bw per day). However, in the main study, there were no effects on reproduction, offspring or parents at the highest dose tested, 300 ppm (equal to 16 mg/kg bw per day). The Meeting concluded that the overall NOAELs from the two main reproductive toxicity studies for reproductive and offspring toxicity were 16 mg/kg bw per day.

There are four rat developmental toxicity studies on flutriafol. In the first guideline-compliant study, effects on the fetal skeleton mainly consistent with delayed ossification were seen at all dose levels; the LOAEL was 10 mg/kg bw per day. At the top dose level of 125 mg/kg bw per day, there

were reductions in body weight gain (20–50%), feed consumption (~15%) and litter size (30%), the latter associated with increased post-implantation loss (33%). In both subsequent range-finding studies, there were marked increases in skeletal anomalies (especially of the hyoid) and reduced ossification, as well as single incidences of cleft palate at the top dose levels of each study (150 and 100 mg/kg bw per day). Marked maternal toxicity, clinical signs, body weight deficits and fetal resorptions were seen at the top dose levels. In the second guideline-compliant study, there was a single incidence of cleft palate at the top dose level of 75 mg/kg bw per day, a dose that also produced significantly reduced maternal body weight gain (~30%), increases in post-implantation loss (3-fold), skeletal anomalies (including the hyoid bone and supernumerary ribs) and delayed ossification. The NOAELs in this study for both developmental and maternal toxicity were 10 mg/kg bw per day.

Cleft palate is a very rare finding in rats that has been seen at high dose levels with a number of triazole compounds. The presence of single incidences of cleft palate in three of the rat developmental toxicity studies, although not statistically significant in isolation, cannot be discounted when the database is considered as a whole. Litter sizes at the top dose levels were significantly lower as a result of post-implantation loss, which could reduce the number of malformed fetuses observed at caesarean section. The NOAEL for teratogenicity in the rat was 10 mg/kg bw per day, based on the findings of cleft palate at and above 75 mg/kg bw per day.

In a rabbit developmental toxicity study, there was evidence of clinical signs, reduced maternal body weight gain (30%), reduced litter size (40%) and delayed ossification at the highest dose level of 15 mg/kg bw per day. One fetus at the top dose level and one at the intermediate dose level had multiple malformations that could not be unequivocally linked to flutriafol administration. The NOAELs for maternal and developmental toxicity were 7.5 mg/kg bw per day.

The Meeting concluded that flutriafol is teratogenic in rats.

In an acute neurotoxicity study in rats, there was no evidence of neuropathy at 750 mg/kg bw, the highest dose tested. The NOAEL for acute neurotoxicity was 250 mg/kg bw, based on altered functional observational battery and motor activity findings on day 1 at 750 mg/kg bw. The NOAEL for general toxicity was less than 125 mg/kg bw, based on transient reductions in body weight gain in males at all doses.

In a repeated-dose neurotoxicity study, there were no signs of neuropathy or neurotoxicity at 3000 ppm (equal to 172 mg/kg bw per day), the highest dose tested. The NOAEL for general toxicity was 500 ppm (equal to 29 mg/kg bw per day), based on reductions in body weight gain at the start of the study at 1500 ppm (equal to 84 mg/kg bw per day) and above.

In a 28-day immunotoxicity study in female mice, there was no reduction in the immunoglobulin M response to challenge with sheep red blood cells or changes in spleen or thymus weights. The NOAEL for immunotoxicity was 1000 ppm (equal to 208 mg/kg bw per day), the highest dose tested. The NOAEL for general toxicity was 50 ppm (equal to 9.8 mg/kg bw per day), based on reduced erythrocyte mean cell volume and hepatotoxicity at 250 ppm (equal to 47 mg/kg bw per day).

Medical monitoring of production plant workers has not identified any cases of occupational illness related to flutriafol.

The Meeting concluded that the available database on flutriafol is adequate to characterize the potential risk to fetuses, infants and children.

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–0.01 mg/kg bw on the basis of the NOAEL of 1.0 mg/kg bw per day in the 2-year rat study, based on increases in fatty changes and increased weights of the liver in males at 10 mg/kg bw per day. A safety factor of 100 was applied. The ADI is supported by the NOAEL in the carcinogenicity study in mice of 1.2 mg/kg bw per day,

based on the increased incidence and severity of hepatic centrilobular fatty change in males at 6 mg/kg bw per day.

The Meeting established an acute reference dose (ARfD) of 0.05 mg/kg bw on the basis of the NOAEL of 5 mg/kg bw per day in the 90-day and 1-year toxicity studies in dogs based on reduced body weight gain (males) or body weight loss (females) after 1 week (the first time of measurement) and subsequently reduced body weight gain during the early part of the study, although feed consumption was unaffected by treatment. A safety factor of 100 was applied. This provides a margin of greater than 1000 between the ARfD and the LOAEL for cleft palate in rats (75 mg/kg bw per day).

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL	
Mouse	Two-year study of toxicity and carcinogenicity ^a	Toxicity	10 ppm, equal to 1.2 mg/kg bw per day	50 ppm, equal to 6 mg/kg bw per day	
		Carcinogenicity	200 ppm, equal to 25 mg/kg bw per day ^b	—	
Rat	Ninety-day study of toxicity ^a	Toxicity	200 ppm, equal to 13 mg/kg bw per day	2000 ppm, equal to 148 mg/kg bw per day	
		Toxicity	20 ppm, equal to 1.0 mg/kg bw per day	200 ppm, equal to 10 mg/kg bw per day	
	Two-year study of toxicity and carcinogenicity ^a	Carcinogenicity	2000 ppm, equal to 103 mg/kg bw per day ^b	—	
		Multigeneration studies of reproductive toxicity ^{a,c}	Reproductive toxicity	300 ppm, equal to 16 mg/kg bw per day	1000 ppm, equal to 56 mg/kg bw per day
			Parental toxicity	60 ppm, equal to 3.5 mg/kg bw per day	240 ppm, equal to 14 mg/kg bw per day
	Offspring toxicity	300 ppm, equal to 16 mg/kg bw per day	1000 ppm, equal to 56 mg/kg bw per day		
Developmental toxicity study ^d	Maternal toxicity	10 mg/kg bw per day	75 mg/kg bw per day		
	Embryo and fetal toxicity	10 mg/kg bw per day	75 mg/kg bw per day		
Rabbit	Developmental toxicity study ^d	Maternal toxicity	7.5 mg/kg bw per day	15 mg/kg bw per day	
		Embryo and fetal toxicity	7.5 mg/kg bw per day	15 mg/kg bw per day	
Dog	Ninety-day and 1-year studies of toxicity ^{c,e}	Toxicity	5 mg/kg bw per day	15 mg/kg bw per day	

^a Dietary administration.

^b Highest dose tested.

^c Two studies combined.

^d Gavage administration.

^e Capsule administration.

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

0.05 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 flutriafol*Absorption, distribution, excretion and metabolism in mammals*

Rate and extent of oral absorption	Rapid and extensive absorption: > 90% based on urinary and biliary excretion
Dermal absorption, rat (125 g/l suspension concentrate formulation)	~1% concentrate; ~10% in use dilutions; 8 h exposure and 9-day monitoring
Distribution	Widely distributed; highest levels in red blood cells
Potential for accumulation	No evidence for accumulation
Rate and extent of excretion	Rapid, equally in urine and faeces; extensive biliary excretion (~80%) with enterohepatic circulation
Metabolism in animals	Extensive metabolism; only trace amount of unchanged parent detected
Toxicologically significant compounds (animals, plants and the environment)	Flutriafol

Acute toxicity

Rat, LD ₅₀ , oral	1140–1480 mg/kg bw
Rabbit, LD ₅₀ , dermal	> 2000 mg/kg bw
Rat, LC ₅₀ , inhalation	> 5.2 mg/L
Rabbit, dermal irritation	Non-irritant
Rabbit, ocular irritation	Mild irritant
Guinea-pig, dermal sensitization (Magnusson and Kligman)	No evidence
Mouse, dermal sensitization (local lymph node assay)	No evidence

Short-term studies of toxicity

Target/critical effect	Body weights (from start of dosing); red blood cells (anaemia) and liver (weight, clinical chemistry, fatty change)
Lowest relevant oral NOAEL	5 mg/kg bw per day (90-day and 1-year dog studies)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (systemic; rats)
Lowest relevant inhalation NOAEC	No data

Long-term studies of toxicity and carcinogenicity

Target/critical effect	Liver (increased weight and fatty change)
Lowest relevant NOAEL	1.0 mg/kg bw per day (rat); 1.2 mg/kg bw per day (mouse)
Carcinogenicity	Not carcinogenic

<i>Genotoxicity</i>			
	Some equivocal in vitro results; negative in vivo; considered unlikely to be genotoxic		
<i>Reproductive toxicity</i>			
Reproduction target/critical effect	Reduced litter size		
Lowest relevant reproductive NOAEL	16 mg/kg bw per day		
Developmental target/critical effect	Reduced litter size, delayed ossification (rat and rabbit); hyoid abnormalities (rat); cleft palate (rat)		
Lowest relevant developmental NOAEL	7.5 mg/kg bw per day (rabbit); 10 mg/kg bw per day (rat)		
<i>Neurotoxicity/delayed neurotoxicity</i>			
Acute study	Altered functional observation battery and motor activity; neurotoxicity NOAEL 250 mg/kg bw (rat)		
Ninety-day study	Not neurotoxic		
<i>Other toxicological studies</i>			
Immunotoxicity	Not immunotoxic (female mice)		
<i>Medical data</i>			
<i>No adverse effects reported in production plant operators</i>			
Summary			
	Value	Study	Safety factor
ADI	0–0.01 mg/kg bw	Two-year rat study (supported by 2-year mouse study)	100
ARfD	0.05 mg/kg bw	Ninety-day and 1-year studies in dogs	100

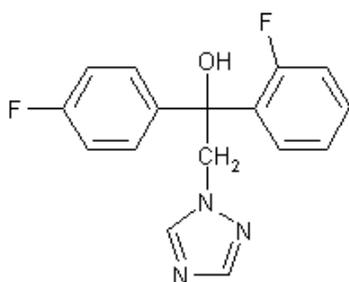
RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of flutriafol were considered for the first time by the present Meeting. The residue evaluation was scheduled for the 2011 JMPR by the Forty-second Session of the CCPR (ALINORM 10/33/24)

Flutriafol is a triazole fungicide used in many crops for control of a broad spectrum of leaf and cereal ear diseases, particularly embryo borne diseases, e.g., bunts and smuts. The Meeting received information on identity, animal and plant metabolism, environmental fate in soil, rotational crops, analytical methods, storage stability, use patterns, supervised trials, farm animal feeding studies and fates of residues in processing.

(*RS*)-2,4'-difluoro- α -(1*H*-1,2,4-triazol-1-ylmethyl)benzhydryl alcohol

Structural formula:



Flutriafol is a 1:1 mixture of the enantiomers.

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

M1B	4-hydroxyflutriafol
M1D	4-hydroxy-5-methoxyflutriafol
M2B	flutriafol-(trans)-dihydrodiol
M5	Mixture of two isomeric hydroxyflutriafol derivatives
R5a	Hexose conjugated flutriafol
C6	Defluorinated flutriafol
1,2,4-Triazole	1 <i>H</i> -1,2,4-triazole
Triazole alanine	1,2,4-triazoyl-3-alanine
Triazole acetic acid	1 <i>H</i> -1,2,4-triazol-1-ylacetic acid

Animal metabolism

The Meeting received results of animal metabolism studies with flutriafol in rats, lactating cows and laying hens. The metabolism and distribution of flutriafol in animals were investigated using [¹⁴C-carbinol] and [¹⁴C-triazole]-labelled flutriafol.

In rats, flutriafol was extensively absorbed following a single oral administration of 5 or 250 mg/kg dose. Bile was shown to be the major route of elimination of administered radioactivity excreted via this route over three days. Excretion of the dose was rapid at both dose levels and urinary excretion was the major route, accounting for 50–68% daily dose in the repeat dose animals and 61–68% for the single dose animals. The remaining radioactivity was excreted in the faeces (29–55%) with less than 6% dose remaining in the tissues 168 hours after the final repeat dose was administered and less than 0.8% 168 hours after the single dose. Only a minor amount of cleavage of the triazole moiety from the flutriafol molecule occurred. Furthermore, no metabolism was detected in the triazole group or in the 4-fluorophenyl ring of molecule. All identified metabolites were shown to be hydroxylated derivatives of the 2-fluorophenyl ring. Three of the major urinary metabolites were identified as a 3,4-(cis)- and the two M2B metabolites of flutriafol. The bulk of remaining urinary radioactivity was attributable to glucuronide conjugates, the two main aglycones were identified as M1B and M1D. Metabolism in rats was summarized and evaluated by the WHO panel of the JMPR in 2011.

A lactating cow were dosed with [¹⁴C-triazole]-flutriafol at 40 mg/animal/day, equivalent to approximately 2 ppm in the diet for 7 consecutive days. Gelatine capsules containing ¹⁴C-triazole flutriafol absorbed onto powdered maize were introduced directly into the stomach via a stomach tube. Most of the administered radioactivity was excreted in the urine and faeces (45 and 33% of the dose).

Radioactive residues in muscle and fat (subcutaneous, omental and perirenal) were insignificant (< 0.01 mg/kg equivalent to flutriafol). The liver, kidney and heart contained residues of 0.29, 0.061 and 0.011 mg/kg equivalent to flutriafol, respectively. A total of 0.1% of the radioactivity administered to the cow was collected in the milk over the 7 day dosing period. The radioactive residue in the milk gradually increased to 0.007 mg/L (flutriafol equivalent) by Day 4 of the study, and maintained this level until the end of the study.

A small amount of parent flutriafol and M1B were contained in the milk. No compound in this fraction accounted for more than 6% of TRR in the milk. Most of the radioactivity in the milk (75%) was associated with polar, water soluble metabolites which were converted to organosoluble fractions by extensive hydrolysis conditions. Parent flutriafol was identified (29% TRR) and no individual compound accounted for more than 10% of TRR in the liver. However, M1B was detected (23% TRR) and no individual compound accounted for more than 10% of TRR in the kidney. The radioactive residues were too low to identify the compound in muscle and fat.

Laying hens were orally dosed with [^{14}C -triazole]- or [^{14}C -carbinol]-flutriafol at doses equivalent to 13.9 or 11.6 ppm in the feed for 7 consecutive days. Most of the administered doses (89.7% for triazole label and 91.2% for the carbinol label) were recovered in the excreta at sacrifice. The radioactive residues in egg appeared to reach plateau concentrations by the end of the study, and ranged from 0.134 mg/kg (carbinol label) to 0.204 mg/kg (triazole label). The TRR values were the highest for liver (0.36–0.41 mg/kg), followed by muscle (0.01–0.06 mg/kg) and fat (0.02–0.04 mg/kg).

Parent flutriafol was the most abundant component of the residue (carbinol label: 0.088–0.119 mg/kg, 65.7–74.8% TRR, triazole label: 0.099–0.103 mg/kg, 48.3–50.5% TRR) in the eggs. 1,2,4-Triazole was also detected in the eggs (0.056–0.060 mg/kg, 27.5–29.3% TRR) and muscle (0.048 mg/kg, 75.0% TRR). Flutriafol was detected in liver at low concentrations (0.007–0.013 mg/kg, 1.9–3.2% TRR) and 1,2,4-Triazole was present in liver at 0.057 mg/kg (13.9% TRR). Flutriafol was found in fat (0.012–0.028 mg/kg, 75.0–80.0% TRR) but no flutriafol was detected in muscle.

In the lactating cow and laying hen studies, flutriafol was metabolized to several metabolites. All metabolites detected in the metabolism of the lactating cow were also found in the metabolism of rats. The major metabolic processes in laying hens were the binding of flutriafol to liver proteins, the formation of hydroxyl flutriafol derivatives (fluorophenyl moiety), and the formation of free 1,2,4-Triazole.

Plant metabolism

The Meeting received plant metabolism studies performed on apples, sugar beet, cereals (wheat and barley) and oilseed rape using [^{14}C -triazole]- or [^{14}C -carbinol]-flutriafol.

In an apple metabolism study, apple trees were treated once at a rate of 0.12 kg ai/ha. The application rate was equivalent to $1 \times$ the single application rate for apples. Samples of fruit and foliage were taken at a typical harvest time, 64 days after application. TRR values in apple fruits from the two radiolabelled forms of the test substance were similar with most of the radioactivity (72–78% TRR, equivalent to 0.030–0.051 mg/kg) extracted using acetonitrile or acetonitrile/water (1:1, v/v). Unextracted radioactivity comprised 18 to 23% TRR (0.009–0.012 mg/kg). Flutriafol comprised 50 to 56% TRR (0.023–0.032 mg/kg). The total unknowns comprised 22% TRR (0.013 mg/kg) in the triazole labelled sample and 9% TRR (0.003 mg/kg) in the carbinol labelled sample. The largest individual unknowns comprised only 5% and 3% TRR (0.003 and 0.001 mg/kg) respectively.

In attempt to confirm the presence of trace levels of triazole alanine and triazole acetic acid in apple fruit, the foliage from the [^{14}C -triazole]-flutriafol application was analysed since this contained higher radioactive residues. The results showed that flutriafol comprised 48% TRR (2.00 mg/kg). Triazole alanine was present at low level in the foliage extract (0.13 mg/kg) and comparison of chromatograms from fruit and foliage confirmed that triazole alanine was present in the fruit extracts

at trace levels. As with the fruit extracts, the presence of trace levels of Triazole acetic acid could not be confirmed. The radioactive residue was predominantly flutriafol. The triazole alanine metabolite is known to oxidise to triazole acetic acid in plants, however it did not appear that triazole acetic acid was present in apple extracts. The free 1,2,4-Triazole metabolite was not detected in the fruit or foliage samples.

In a sugar beet metabolism study, sugar beets grown in containers outdoors were sprayed at a rate of 0.125 kg ai/ha. Samples of foliage and beet (root) were taken within three hours after application and at 16 and 21 days after treatment (DAT). The TRRs in foliage samples taken just after application were 1.37 and 1.27 mg/kg for the [^{14}C -triazole] and [^{14}C -carbinol] radiolabels, respectively. No significant residue was observed in the root. In the 16 DAT sample, TRRs were 0.342 and 0.381 mg/kg in the foliage for [^{14}C -triazole] and [^{14}C -carbinol] radiolabels, respectively. The TRR of the root from the 16 DAT samples was \leq 0.005 mg/kg in both labelled forms. At harvest (21 DAT), the TRRs were 0.747 and 0.596 mg/kg in the foliage, and 0.009 and 0.005 mg/kg in the root for [^{14}C -triazole] and [^{14}C -carbinol] radiolabels, respectively. Flutriafol was the major residue in foliage samples, accounting for 69.2 and 70.8% TRR (0.412 and 0.519 mg/kg) at harvest, no other radioactive metabolite at harvest represented more than 5.4 and 5.0% TRR (0.033 and 0.038 mg/kg). There had been no cleavage of the flutriafol molecule that resulted in separation of the [^{14}C -carbinol] and [^{14}C -triazole] radiolabel positions. One metabolite of flutriafol in foliage extracts of sugar beet was identified as a hexose conjugate of flutriafol. This component represented a maximum of 0.026 mg/kg, 4.4% TRR at harvest (21 DAT).

In a cereal metabolism study, wheat and barley plants, grown both in a greenhouse and in the field, were treated at a rates of 0.081–0.105 kg ai/ha. In the greenhouse, both plants were treated with ^{14}C -flutriafol just prior ear emergence. In the field, ^{14}C -triazole-labelled flutriafol was applied to wheat just before ear emergence and to barley just after ear emergence. ^{14}C -carbinol-labelled flutriafol was applied just before ear emergence to barley and just after ear emergence to wheat.

At maturity in the greenhouse study no residues of flutriafol ($<$ 0.005 mg/kg) were detected in the grain. Following application of ^{14}C -triazole-labelled flutriafol, triazole alanine accounted for 40–48% of the TRR in the grain (0.08 and 0.04 mg/kg in barley and wheat respectively) and triazole acetic acid was also characterised as a significant metabolite (0.04 and $<$ 0.01 mg/kg in barley and wheat respectively). TRRs in barley and wheat grain following ^{14}C -carbinol-labelled flutriafol applications were considerably lower (0.02 and 0.01 mg/kg respectively) than those of ^{14}C -triazole-labelled flutriafol applications (0.41 and 0.18 mg/kg respectively). In barley straw, flutriafol was the major radioactive component, and accounted for 63% of the TRR (1.3 mg/kg).

At maturity in the field study, the TRR in the wheat grain, following the ^{14}C -triazole-labelled flutriafol application, was 0.05 mg/kg and no flutriafol was detected ($<$ 0.0002 mg/kg). Triazole alanine and triazole acetic acid accounted for 58 and 26% of this residue, respectively. The TRR in barley grain was 0.10 mg/kg. Flutriafol, triazole alanine and triazole acetic acid accounted for 24, 8 and 5% of this residue respectively. The TRRs in the grain in both plants following ^{14}C -carbinol-labelled flutriafol applications were less than 0.01 mg/kg.

Radioactive residues in the straw ranged from 0.12 to 0.72 mg/kg. Flutriafol was the major component (57% in wheat straw from ^{14}C -triazole-labelled flutriafol treatment). Radioactive residues in the straw were of a similar level for greenhouse and field-grown plants. Flutriafol was the dominant component of the radioactive residue. Triazole alanine and Triazole acetic acid were not detected in the straw. Some (16–40%) of the radioactive residue was not extractable.

In an oilseed rape metabolism study, oilseed rape plants grown in containers outdoors were sprayed at a rate of 0.125 kg ai/ha. The plants were treated at the early pod set growth stage, i.e., approximately 10% of the potential pods had formed. Plants were sampled just after treatment (0 DAT), at three intermediate stages (7, 14 and 21 DAT) and at harvest (42 DAT). The TRR and the nature of the radioactive residue were investigated in the whole plant taken just after application, in

the separated pods and remaining plant at the intermediate sampling (14 DAT) and in the separated seeds and remaining plant at harvest.

The TRR in the forage samples (whole plant) taken just after treatment (0 DAT) were 0.782 and 1.50 mg/kg for the [^{14}C -triazole] and [^{14}C -carbinol] radiolabels, respectively. At the pod development stage (14 DAT), TRRs were 0.751 and 0.779 mg/kg in the pods, and 1.17 and 1.60 mg/kg in the remaining plant. At harvest (42 DAT), TRRs were 1.32 and 0.729 mg/kg in the seeds, and 0.246 and 0.355 mg/kg in the remaining plant ([^{14}C -triazole] and [^{14}C -carbinol] radiolabels, respectively).

In the seeds at 42 DAT, flutriafol was the only radioactive component in the hexane extracts, accounting for 31.5 and 27.2% TRR (0.415 and 0.198 mg/kg) for the [^{14}C -triazole] and [^{14}C -carbinol] radiolabels, respectively. Flutriafol was the major radioactive component in the subsequent solvent/water extracts of the seeds, accounting for 29.8 and 27.4% TRR (0.392 and 0.200 mg/kg, [^{14}C -triazole] and [^{14}C -carbinol] radiolabels, respectively). Flutriafol was present in the enzyme extracts, in the weak base extracts and in the strong acid and strong base extracts. In total, flutriafol accounted for 6.3 and 7.3% TRR (0.082 and 0.054 mg/kg) in the acid and base extracts of seeds for the [^{14}C -triazole] and [^{14}C -carbinol] radiolabels, respectively.

Components R5a accounted for 3.8% TRR (0.028 mg/kg) in seeds of plants treated with [^{14}C -carbinol] flutriafol, and for 3.8% TRR (0.050 mg/kg) in seeds of plants treated with [^{14}C -triazole] flutriafol. Component C6, which was present in the strong acid and strong base extracts only, accounted for a total of 3.0 and 2.9% TRR (0.039 and 0.021 mg/kg, [^{14}C -triazole] and [^{14}C -carbinol] radiolabels, respectively). Unidentified radioactive components in these seed extracts did not individually represent more than 10% TRR.

In the forage samples taken at 0 DAT, and in the remaining plant samples at 14 DAT and 42 DAT, most of the residues were extractable by acetonitrile/water. In the pods and seeds, significant residues were released only by successive additional enzyme and acid/base treatments. Flutriafol was found both in the initial acetonitrile/water extracts and in the further enzyme/acid/base extracts, suggesting some binding to the plant matrix. A hexose conjugate of flutriafol was released by acetonitrile/water, while the other identified residue, a defluorinated flutriafol, was found only in the further extracts. All extractable residues contained both the carbinol carbon and triazole ring radiolabel centres indicating that no cleavage of the flutriafol molecule had occurred.

In the plant metabolism studies on apples, sugar beet, cereals (wheat and barley) and oilseed rape, flutriafol is the major component of the residues found in apples, sugar beet (forage), cereals (straw) and oilseed rape (seed and remaining plant). In wheat grain, the major components of the residues are triazole alanine and triazole acetic acid. In barley grain, flutriafol was the major component with low levels of 0.002 and 0.02 mg/kg. Radioactivity in sugar beet root was too low to characterize.

Environmental fate in soil

The Meeting received information on aerobic soil metabolism, soil photolysis and on rotational crops.

Aerobic soil metabolism and degradation has been studied in six different soils at a nominal average temperature of 20 °C for 252 days. Flutriafol is slowly degraded in laboratory incubated soils. Approximately 85% remained after 252 days in a loamy sand and a sandy clay loam.

The photodegradation of flutriafol was investigated on a sandy loam soil. After 7 days photochemical reactor irradiation, 60–67% of the total radioactivity applied to the soil plates was characterized as flutriafol. 1,2,4-Triazole and 2,4'-difluorobenzophenone accounted for 2–3% of the radioactive residues. After 30 days irradiation in natural sunlight, 75–82% of the applied radioactivity was characterized as flutriafol. The photodegradation products formed were similar to those seen after artificial irradiation and accounted for 7–10% of the applied radioactivity. Flutriafol appears to be relatively photochemically stable on a dry soil surface.

In a confined rotational crop study, wheat, peas, sugar beet and oilseed rape were planted at 30, 120 and 365 days after a soil application of [^{14}C -triazole] and [^{14}C -carbinol]-flutriafol at 0.125 kg ai/ha. The major components found were flutriafol, triazole alanine and triazole acetic acid. Small levels of M1B (1.5–2.5% TRR) were found in the wheat straw and sugar beet foliage.

Another confined rotational crop study was conducted using [^{14}C -triazole] and [^{14}C -carbinol] - flutriafol with lettuce, radish, and wheat planted at 30, 120 and 365 days after application to soil at 0.26 kg ai/ha. Residues in crops planted 120 DAT to soil had similar TRR values to those found in crops planted 30 DAT. Radish tops had higher residues than the corresponding radish roots samples, indicating that flutriafol and its metabolites were translocated within the xylem of the plant tissue. The TRR in the vegetative portions of wheat increased with maturity, in the order forage < hay < straw. Flutriafol was a significant component of the residue in all treated crop samples, ranging from barely detectable in wheat grain (0.003 to 0.009 mg/kg) to a high of 0.416 mg/kg in one straw sample. Triazole lactic acid and triazole alanine were detected in various commodities, present at more than 10% TRR for any individual commodity. Triazole alanine was detected as a major compound in wheat grains, and triazole acetic acid was also found at > 10% TRR.

Residues in field rotational crops were studied at sites in the UK. A foliar spray was applied at four sites in the first year at 0.188 kg ai/ha and in each subsequent year at 0.25 kg ai/ha. After five consecutive years of application, with a total rate applied of 1.188 kg ai/ha, sugar beet, fodder beet, potato, carrot and spring barley, as rotational crops, were sown/planted on the test sites in the sixth growth season and grown to maturity. Sugar beet roots, fodder beet roots, potatoes and carrots from each of the sites contained non-detectable or low residues of flutriafol, i.e., < 0.01–0.02 mg/kg. Foliage samples of sugar beet and fodder beet also contained non-detectable or low residues, < 0.01–0.08 mg/kg. Grain from the spring barley contained a low residue of flutriafol, 0.05 mg/kg. Residues of flutriafol in the spring barley straw samples were 0.38 mg/kg.

The additional field rotational crop studies were carried out using the plots treated at the highest rate (4.0 kg ai/ha) at three trial sites in the UK. The field studies were designed to provide samples of potato, sunflower, maize, spring barley, spring wheat, oilseed rape, pea, cabbage, carrot and sugar beet grown in soil with artificially high levels of aged flutriafol residues, close to or in excess of the maximum predicted concentration in soil after 26 years continuous application of the maximum label rate (0.156 kg ai/ha) of field crops. The soil at the trial sites used had been treated in 1988 with a single application of flutriafol at a nominal rate of 4.0 kg ai/ha. The rotational crops were sown in 1991 and grown to maturity. Representative samples of the crops were taken at harvest and analysed for residues of flutriafol and its major metabolites triazole alanine and triazole acetic acid. No residues (< 0.05 mg/kg) of flutriafol were detected in the potato tuber, sunflower seeds, maize grains, rape seeds and pea seeds. Residues of flutriafol were found at low concentrations in the grain of spring barley (< 0.03–0.07 mg/kg), spring wheat (< 0.03–0.03 mg/kg), cabbage heads (< 0.05–0.12 mg/kg), carrot roots (< 0.05–0.13 mg/kg), sugar beet roots (< 0.01–0.03 mg/kg), maize straw (0.16–0.31 mg/kg) and sugar beet foliage (0.03–0.42 mg/kg). Residues in the spring barley straw (0.24–1.5 mg/kg), the spring wheat straw (0.29–2.5 mg/kg) and pea haulm (0.28–3.8 mg/kg) were found at higher levels of flutriafol. The samples of spring wheat grain (0.28–3.0 mg/kg), rape seeds (0.59–17 mg/kg) and pea seeds (0.15–7.7 mg/kg) contained high residues of triazole alanine.

Residues of flutriafol and triazole alanine may be found in rotational crops.

Analytical methods

The Meeting received description and validation data for analytical methods for residues of parent flutriafol and triazole metabolites (1,2,4-Triazole, triazole alanine and triazole acetic acid) in raw agricultural commodities, processed commodities, feed commodities and animal commodities. In most of the methods for determination of flutriafol, homogenized samples were extracted with acetonitrile/water (for plant materials) and acetonitrile (for animal commodities), and the extract was cleaned up with liquid–liquid partition followed by column chromatography using SPE (for plant

materials) or gel permeation chromatography (for animal materials). Residues were determined by gas chromatography with NPD or MSD, or HPLC with MS/MS. The methods of analysis for a range of substrates were validated with LOQs of the 0.01 mg/kg for flutriafol.

The multiresidue method DFG Method S19 (modified version) with GC employing TSD, NPD or MSD was validated for flutriafol in plant materials. LOQs were 0.01–0.05 mg/kg for flutriafol.

The Meeting received LC-MS/MS method of analysis for triazole metabolites in plant and animal materials. The method was specific for each metabolite. The method was validated with an LOQ of 0.01 mg/kg for all analytes.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the freezer storage stability of flutriafol residues in plants (apple, grape, cabbage, sugar beet root, pea seed, soya bean, barley grain, wheat and oilseed rape), processed commodities (apple juice, soya bean meal and refined oil) and animal commodities (milk, eggs, muscle and fat).

The Meeting also received information on the freezer storage stability of triazole metabolites in apple (fruit and juice), milk, eggs, muscle and fat.

Storage stability results indicate that flutriafol residues were stable for at least 4 months in animal commodities, for at least 5 months in soya bean seed, for at least 12 months in apple, barley grains and coffee beans, for at least 23 months in grapes, for at least 24 months in cabbage and oilseed rape, and for at least 25 months in wheat (grains and straw), pea seed, sugar beet root. The results also indicate that triazole metabolite residues were stable for at least 4 months in apple fruits and juice, and for at least 5 months in animal commodities.

The periods of storage stability studies cover the sample storage intervals of residue trials.

Definition of the residue

In the lactating cow metabolism study, TRRs in liver (0.29 mg/kg), kidney (0.06 mg/kg) and heart (0.01 mg/kg) were higher than those in milk and other tissues (< 0.01 mg/kg). Flutriafol is the major component of the residue in liver (29% TRR). However, M1B is the major component of the residue in kidney (23% TRR) but at low level. In the laying hen metabolism study, TRRs were the highest for liver (0.36–0.41 mg/kg), followed by muscle (0.01–0.06 mg/kg) and fat (0.02–0.04 mg/kg). Flutriafol is the major residue component in eggs and fat (48–80% TRR).

1,2,4-Triazole was found in muscle (75.0% TRR) and liver (13.9% TRR) of laying hens. However, according to farm animal feeding studies, concentrations of 1,2,4-Triazole, triazole alanine and triazole acetic acid were < 0.01 mg/kg.

The Meeting decided that parent flutriafol is a suitable analyte for enforcement purposes and dietary risk assessment in animal commodities.

The octanol/water coefficient ($\log P_{ow}$) of flutriafol is 2.3 at 20 °C. In the lactating cow metabolism and feeding studies, flutriafol residues were < 0.01 mg/kg in muscle and fat. However, in the laying hen metabolism and feeding studies, flutriafol residues in fat were at least 3 times higher than those in muscle. The Meeting considered flutriafol was fat soluble.

The plant metabolism studies of flutriafol were conducted with fruit (apple), root vegetables (sugar beet), cereals (wheat and barley) and oilseeds (rape). Each study was conducted with both triazole- and carbinol-radiolabelled flutriafol. Parent flutriafol was always the major component (24–71% TRR) in all matrices except wheat grains at harvest. Triazole alanine and triazole acetic acid accounted for 58 and 28% of TRR (0.05 mg/kg) in wheat grains. No other radioactive components in the extracts from plant matrices were individually present at more than 10% TRR.

The 2007 JMPR noted that 1,2,4-Triazole, triazole acetic acid and triazole alanine may be derived from several sources. In a situation in which the metabolites arise from multiple triazole fungicides, they cannot be included in the residue definition. Since the metabolite cannot be linked to a specific triazole fungicide, they would have to be evaluated on their own.

Field trials conducted in the USA indicated that triazole alanine and triazole acetic acid were found in plant matrices. However, 1,2,4-Triazole was not detected in samples (except one trial) above LOQ. These findings agree with the information obtained from the metabolism studies. The relatively low level of the residues in food commodities and the low toxicity of triazole alanine and triazole acetic acid do not justify their inclusion for dietary risk assessment.

The Meeting decided that parent flutriafol is a suitable analyte for enforcement purposes and dietary risk assessment in plant commodities.

The Meeting recommended the following residue definition:

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

The Meeting considers the residue is fat soluble

Results of supervised trials on crops

The Meeting received supervised trial data for the foliar application of flutriafol on apples, grapes, bananas, sweet peppers, soya beans, wheat, peanuts and coffee. Residue trial data was made available from European countries, the countries of Latin America and the USA.

Labels were available from Argentina, Australia, Belarus, Brazil, Chile, Columbia, Croatia, Estonia, Italy, Kazakhstan, Lithuania, Malaysia, Mexico, Moldova, Romania, Russia, South Africa, Spain, Taiwan, the Ukraine and the USA describing the registered uses of flutriafol.

The OECD calculator was used as a tool to assist in the estimation of maximum residue levels from the selected residue data set obtained from the supervised residue trials. As a first step, the Meeting reviewed the trial conditions and other relevant factors related to each data set to arrive at a best estimate of the maximum residue level using expert judgement. Then the OECD calculator was employed. If the statistical calculation spreadsheet suggested a different value, a brief explanation of the deviation was supplied.

Pome fruits

Data were available from supervised trials on apples in European countries and the USA.

In Italy, flutriafol is registered for apples at two foliar applications of 0.030 kg ai/ha with a PHI of 21 days. However, the residue trials on apples conducted in Greece, Italy, France and Spain did not match the GAP of Italy.

The GAP on pome fruit of the USA is a maximum four foliar applications at a maximum rate of 0.12 kg ai/ha with a PHI of 14 days. Flutriafol residues in apples from trials in the USA matching GAP were (n = 16): 0.03, 0.04, 0.05 (3), 0.06 (3), 0.08 (2), 0.09, 0.10 (2), 0.12 (2) and 0.16 mg/kg.

Based on the trials for apples in the USA, the Meeting estimated a maximum residue level, an STMR value and an HR value for flutriafol in pome fruit of 0.3, 0.07 and 0.16 mg/kg respectively.

Grapes

Data were available from supervised trials on grapes from a number of European countries and the USA.

In the Ukraine, flutriafol is registered for use on grapes at two foliar applications of 0.025 kg ai/ha with a PHI of 45 days. In Romania, flutriafol is registered for use on grapes at six foliar applications of 0.038 kg ai/ha with a PHI of 30 days. However, the residue trials on grapes conducted in Greece, Italy, France and Spain did not match the GAP of the Ukraine or that of Romania.

The GAP on grapes of the USA allows a maximum six foliar applications at a maximum rate of 0.073–0.091 kg ai/ha with a PHI of 14 days. The Meeting concluded that the additional spray would have little influence on the final residue. The Meeting decided to use the principle of proportionality, as described in the JMPR Report 2010, to estimate a maximum residue level, an STMR value and an HR value for grapes.

Residues in grapes from the US trials at 0.128 kg ai/ha were (n = 13): 0.12, 0.21 (2), 0.25, 0.28, 0.30 (2), 0.31, 0.35, 0.37, 0.43, 0.61 and 0.86 mg/kg. Scaled residues in grapes were (scaling factor 0.71; 0.128→0.091 kg ai/ha): 0.09, 0.15 (2), 0.18, 0.20, 0.21 (2), 0.22, 0.25, 0.26, 0.31, 0.43 and 0.61 mg/kg.

Based on the scaled residues in grapes, the Meeting estimated a maximum residue level, an STMR value and an HR value of 0.8, 0.21 and 0.61 mg/kg, respectively.

Banana

Data were available from supervised trials on bananas from a number of South American countries.

In Columbia, flutriafol is registered for use as a foliar application to bananas at a rate of 0.1 kg ai/ha with a PHI of 0 days. The number of applications is not specified on the registered label of Columbia. The results from unbagged bananas in each trial were used to estimate a maximum residue level, an STMR and an HR value for banana. In all trials conducted, residue concentrations in bagged banana were never higher than those in unbagged banana. Residues in whole fruit of unbagged banana from trials matching GAP of Columbia were (n = 12): 0.01, 0.02 (2), 0.05, 0.07 (2), 0.09, 0.10 (2), 0.14 and 0.17 (2) mg/kg.

Based on the residues in whole fruit of unbagged banana, the Meeting estimated a maximum residue level for flutriafol in banana of 0.3 mg/kg.

Residues in unbagged banana pulp from trials matching the GAP of Columbia were (n = 12): 0.01, 0.02, 0.04 (2), 0.05 (4), 0.07, 0.08 (2) and 0.09 mg/kg.

Based on the residues in unbagged banana pulp, the Meeting estimated an STMR and an HR values for flutriafol in banana of 0.05 and 0.09 mg/kg respectively.

Sweet peppers

Data were available from supervised trials on sweet peppers in Spain.

In Spain, flutriafol is registered for use of three foliar applications on sweet peppers at a rate of 0.019 kg ai/hL with a PHI of 1 day. Because residues decline was slow, the Meeting decided to use the available 0 day PHI data. Residues in sweet peppers from trials in greenhouse approximately matching GAP of Spain were (n = 8): 0.15, 0.19, 0.24, 0.26, 0.29, 0.32 and 0.41 (2) mg/kg.

Based on the trials for sweet peppers in Spain, the Meeting estimated a maximum residue level, an STMR and HR values for flutriafol in sweet peppers of 1, 0.28 and 0.41 mg/kg, respectively.

The normal Meeting procedure is to round the value to the nearest units for maximum residue levels. Rounding up the value of 0.9 mg/kg obtained from the OECD calculator results in 1 mg/kg, which coincides with the recommendation of the current Meeting.

Soya bean

Data were available from supervised trials on soya bean in Brazil and the USA.

In Brazil, flutriafol is registered for use on soya bean at two foliar applications of 0.125 kg ai/ha with a PHI of 28 days. Residues in soya bean seeds from trials matching Brazilian GAP were (n = 3): < 0.05 (3) mg/kg. However, the numbers of trials on soya bean, matching Brazilian GAP, were considered insufficient to estimate a maximum residue level for the commodity.

Trials from the USA on soya bean were reported for the foliar application of a SC formulation (GAP: three foliar applications of a maximum rate of 0.128 kg ai/ha, 0.256 kg ai/ha per season, PHI of 21 day). Flutriafol residues in soya bean seeds from trials in the USA matching GAP were (n = 20): < 0.01, 0.01, 0.02 (3), 0.03, 0.04 (3), 0.05, 0.06 (2), 0.07, 0.08 (3), 0.11, 0.17, 0.19 and 0.30 mg/kg.

Based on the trials on soya beans in the USA, the Meeting estimated a maximum residue level and an STMR value for flutriafol in soya bean seeds of 0.4 and 0.055 mg/kg, respectively.

Wheat

Data were available from supervised trials on wheat in European countries and the USA.

In Lithuania, flutriafol is registered for use on wheat at two foliar applications of 0.125 kg ai/ha with a PHI of 30 days. Residue in wheat grains from trial in Northern France and UK matching GAP of Lithuania was < 0.01 mg/kg. However, the trials for wheat matching the GAP of Lithuania were insufficient to estimate a maximum residue level for the commodity.

In Spain, flutriafol is registered for use on wheat at the foliar application of 0.125 kg ai/ha between the end of stem elongation and flowering. The frequency of application is not specified in the registration label. Residues in wheat grains from trials in South France and Spain matching the GAP of Spain were (n = 8): < 0.01 (2), 0.01 (2), 0.02 (2), 0.04 and 0.1 mg/kg.

Trials from the USA on wheat were reported for the foliar application of a SC formulation (GAP: two foliar applications of a maximum rate of 0.128 kg ai/ha, PHI of 30 day). However, flutriafol residue trials on wheat in the USA did not match the GAP of the USA.

Based on the trials for wheat in Southern France and Spain, the Meeting estimated a maximum residue level, an STMR value for flutriafol in wheat grains of 0.15 and 0.015 mg/kg respectively.

Peanuts

Data were available from supervised trials on peanuts from the USA.

Trials from the USA on peanuts were reported for the foliar application of a SC formulation (GAP: four foliar applications of a maximum rate of 0.128 kg ai/ha, PHI of 7 day). Flutriafol residues in peanut nutmeat from trials in the USA matching GAP were (n = 13): < 0.01 (2), 0.01 (2), 0.02 (4), 0.03 (2), 0.04 (2) and 0.08 mg/kg.

Based on the trials for peanuts from the USA, the Meeting estimated a maximum residue level and an STMR value for flutriafol in peanut nutmeats of 0.15 and 0.02 mg/kg respectively.

The OECD calculator estimated a maximum residue level of 0.1 mg/kg. However, the Meeting recommended 0.15 mg/kg because the result of the OECD calculator was too close to the highest residue value.

Coffee beans

Data were available from supervised trials on coffee in Brazil, Columbia, Guatemala and Vietnam.

Trials from Brazil on coffee were reported for the foliar application of a SC formulation. (GAP: initial soil application of a rate of 0.69 kg ai/ha followed by two foliar applications of a rate of 0.25 kg ai/ha, PHI of 30 day). Flutriafol residues in coffee beans from trials in Brazil, Columbia and Guatemala matching GAP of Brazil were (n = 8): 0.01, 0.04, < 0.05 (4), 0.05 and 0.10 mg/kg.

Based on the trials for coffee in Brazil, Columbia and Guatemala, the Meeting estimated a maximum residue level and an STMR value for flutriafol in coffee beans of 0.15 and 0.05 mg/kg respectively.

Animal feedstuffs

Wheat forage and straw

Data were available from supervised trials on wheat in European countries and the USA.

In Lithuania, flutriafol is registered for use on wheat at two foliar applications of 0.125 kg ai/ha with a PHI of 30 days. Residues in wheat whole plant from trial in Northern France and UK matching GAP of Lithuania were (n = 3): 0.16 (2) and 0.17 mg/kg. Residues in wheat straw from trials in Northern France and UK matching GAP of Lithuania were 0.44 mg/kg. However, the trials for wheat matching the GAP of Lithuania were insufficient to estimate a maximum residue level for the commodity.

In Spain, flutriafol is registered for use on wheat at the foliar application of 0.125 kg ai/ha between the end of stem elongation and flowering. The frequency of application and the timing of harvest for forage are not specified in the registration label. Residues in wheat straw from trials in Southern France and Spain matching GAP of Spain were (n = 8): 0.15, 0.35, 0.55, 1.4, 1.5, 1.9, 3.6 and 4.1 mg/kg (fresh weight basis).

Based on the residues in wheat straw from trials in Southern France and Spain, the Meeting estimated a maximum residue level, a median residue value and a highest residue value for flutriafol in wheat straw and fodder, dry of 8, 1.45 and 4.1 mg/kg respectively.

Trials from the USA on wheat were reported for the foliar application of a SC formulation (GAP: two foliar applications of a maximum rate of 0.128 kg ai/ha, PHI of 0 day for wheat forage). Residues in wheat forage from trials in the USA matching GAP were (n = 20): 4.0, 4.1, 4.2, 5.1, 5.2, 5.5, 5.6, 5.7, 7.3, 7.6, 8.4, 8.6, 9.2, 9.3, 11 (2), 13 (2), 16 and 19 mg/kg (fresh weight basis).

Based on the residues in wheat forage from trials in the USA, the Meeting estimated a median residue value and a highest residue value for flutriafol in wheat forage of 8.0 and 19 mg/kg respectively.

Peanut fodder

Data were available from supervised residue trials on peanut in the USA

Trials from the USA on peanut were reported for the foliar application of a SC formulation (GAP: four foliar applications of a maximum rate of 0.128 kg ai/ha, PHI of 7 day). Flutriafol residues in peanut hay from trials in the USA matching GAP were (n = 13): 0.74, 1.5, 1.7, 2.0, 2.1, 2.5, 2.6, 3.1, 4.3, 7.3, 7.7, 8.8 and 8.9 mg/kg (fresh weight basis).

Based on the trials for peanut in the USA, the Meeting estimated a maximum residue level, a median residue value and a highest residue value for flutriafol in peanut fodder of 20, 2.6 and 8.9 mg/kg respectively.

Rotational crops

The Meeting noted that residues may occur in rotational crops. However, available field rotational crop studies were not adequate to propose maximum residue levels to cover rotational crops.

Fate of residues during processing

The fate of flutriafol residues has been examined in apple, grapes, soya bean seeds, wheat grains and peanut nutmeats processing studies. Based on the results of processing studies conducted in the USA, processing factors were calculated for apples, grapes, sweet peppers, soya bean, wheat and peanut. Estimated processing factors and the derived STMR-Ps are summarized in the Table below.

Processing factors, STMR-P and HR-P for food and feed

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors	PF (Mean or best estimate)	RAC STMR (mg/kg)	STMR-P (mg/kg)	RAC HR (mg/kg)	HR-P (mg/kg)
Apple	Juice	0.50, 0.45	0.48	0.07	0.034	0.16	
	Wet pomace	1.9, 1.9	1.9		0.13		
	Dry pomace	10, 8.5	9.3		0.65		1.5
Grape	Juice	0.63	0.63	0.21	0.13	0.61	
	Raisin	2.8	2.8		0.59		1.7
Sweet pepper	Preserved	0.57, 0.67, 0.74 (2), 0.79, 1.1, 1.3, 1.4	0.77	0.28	0.22	0.41	0.32
Soya bean	Meal	1.3	1.3	0.055	0.072		
	Refined oil	1.3	1.3		0.072		
	Hulls	0.97	0.97		0.053		
	Aspirated grain fraction	1.7	1.7		0.094		
Wheat	Bran	2.1	2.1	0.015	0.032		
	Flour	0.33	0.33		0.005		
	Germ	2.8	2.8		0.042		
	Aspirated grain fraction	13	13		0.20		
Peanut	Meal	0.79	0.79	0.02	0.016		
	Refined oil	1.4	1.4		0.028		
Coffee	Roasted coffee beans	0.95	0.95	0.05	0.048		

^a Each value represents a separate study. The factor is the ratio of the residue in processed commodity divided by the residue in the RAC.

The Meeting estimated a maximum residue level of 2 mg/kg ($0.8 \times 2.8 = 2.2$ mg/kg) for raisins, 0.3 mg/kg ($0.15 \times 2.1 = 0.315$ mg/kg) for wheat bran by the processing factor.

On the basis of the STMR and HR for sweet peppers and default dehydration factor of 10, the Meeting estimated at an STMR value and an HR value for dried chili peppers of 2.7 and 4.1 mg/kg respectively. Based on the maximum residue level of sweet peppers, the Meeting recommended a maximum residue level of 10 mg/kg for chili peppers (dry).

Residue in animal commodities***Farm animal dietary burden***

The Meeting estimated the dietary burden of flutriafol 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 maximum residue levels, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed in a dry weight basis.

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).

Livestock dietary burden, flutriafol, ppm of dry matter diet								
	US-Canada		EU		Australia		Japan	
	Max	Mean	Max	Mean	Max	Mean	Max	Mean
Beef cattle	0.50	0.19	15	6.5	76 ^a	32 ^b	0.064	0.064
Dairy cattle	17	6.9	15	6.5	50	20 ^c	0.055	0.055
Poultry-broiler	0.041	0.041	0.050	0.050	0.039	0.039	0.029	0.029
Poultry-layer	0.041	0.041	7.6 ^d	3.2 ^e	0.038	0.038	0.024	0.024

^a Highest maximum beef or dairy cattle dietary burden suitable for maximum residue level estimates for mammalian meat and milk

^b Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat

^c Highest mean dairy cattle dietary burden suitable for STMR estimates for milk

^d Highest maximum poultry dietary burden suitable for maximum residue level estimates for poultry meat and eggs

^e Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs

Farm animal feeding studies

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

Lactating dairy cows

Holstein dairy cows were dosed with flutriafol for 29 days at the equivalent of 0.5, 1.5 and 5.0 ppm in the diet. Residues of flutriafol were below the LOQ (0.01 mg/kg) in whole milk at the 5.0 ppm feeding level. Kidney, muscle and fat contained no residue (< 0.01 mg/kg) of flutriafol at 0.5 and 5.0 ppm feeding levels. Liver contained flutriafol residues of < 0.01–0.04 mg/kg at the 0.5 ppm feeding level, 0.09–0.10 mg/kg at the 1.5 ppm level and 0.23–0.39 mg/kg at the 5.0 ppm level respectively.

Laying hens

Laying hens were dosed with flutriafol for 29 days at the equivalent of 0.5, 1.5 and 5.0 ppm in the diet. Residues of flutriafol were below the LOQ (0.01 mg/kg) in eggs at the 0.5 ppm feeding level. At the 5.0 ppm level, flutriafol residues in eggs were 0.02–0.04 mg/kg from day 3 to day 28. Muscle contained no residue (< 0.01 mg/kg) of flutriafol at 0.5 and 5.0 ppm feeding levels. Liver contained no residues (< 0.01 mg/kg) of flutriafol at 0.5 feeding level and 0.03–0.10 mg/kg at the 5.0 ppm level. Fat contained no residues (< 0.01 mg/kg) of flutriafol at 0.5 feeding level and 0.05–0.07 mg/kg at the 5.0 ppm level.

Animal commodities maximum residue levels

For MRL estimation, the residue in animal commodities is flutriafol.

The maximum dietary burden for beef and dairy cattle is 76 ppm and is much higher than the highest dose level in the feeding study of 5.0 ppm. In a feeding study, in which flutriafol equivalent to 5.0 ppm in the diet was dosed to lactating cows for 29 consecutive days, no flutriafol residues were detected in kidney, muscle, fat and milk (< 0.01 mg/kg). The Meeting considered it is not applicable to extrapolate the residues in kidney, liver, muscle, fat and milk at a dietary burden of 76 ppm from the results of the feeding study.

The Meeting could not estimate a maximum residue level of mammalian meat, mammalian edible offal and milk.

The maximum dietary burden for broiler and layer poultry is 7.6 and is higher than the highest dose level in the feeding study of 5.0 ppm. In a feeding study, in which flutriafol equivalent to 5.0 ppm in the diet was dosed to laying hens for 29 consecutive days, no flutriafol residues were detected in muscle (< 0.01 mg/kg). The Meeting considered it is not applicable to extrapolate the residues in muscle at a dietary burden of 7.6 ppm from the results of the feeding study.

The Meeting could not estimate a maximum residue level of poultry meat, poultry edible offal and eggs.

FURTHER WORK OR INFORMATION

Desirable

- Field rotational crop studies suitable for estimation of maximum residue levels for rotational crops.
- Animal feeding studies covering the estimated maximum dietary burden of farm animals.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Dietary Intakes (IEDIs) of flutriafol were calculated for the 13 GEMS/Food cluster diets using STMRs/STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.01 mg/kg bw and the calculated IEDIs were 0–7% of the maximum ADI (0.01 mg/kg bw). The Meeting concluded that the long-term intakes of residues of flutriafol, resulting from the uses considered by current JMPR, are unlikely to present a public health concern.

Short-term intake

The International Estimated Short-Term Intakes (IESTI) of flutriafol were calculated for food commodities and their processed commodities using HRs/HR-Ps or STMRs/STMR-Ps estimated by the current Meeting (Annex 4). The ARfD is 0.05 mg/kg bw and the calculated IESTIs were a maximum of 50% of the ARfD. The Meeting concluded that the short-term intake of residues of flutriafol, when used in ways that have been considered by the JMPR, is unlikely to present a public health concern.

