

5.13 ETOXAZOLE (241)

TOXICOLOGY

Etoxazole is the International Organization for Standardization (ISO)-approved name for (*RS*)-5-*tert*-butyl-2-[2-(2,6-difluorophenyl)-4,5-dihydro-1,3-oxazol-4-yl]phenetole (International Union of Pure and Applied Chemistry [IUPAC]), with Chemical Abstracts Service (CAS) No. 153233-91-1. Etoxazole is a new acaricide that belongs to the diphenyloxazole class of miticides/ovicides, possibly acting by inhibiting chitin biosynthesis and causing adults to lay sterile eggs. Etoxazole has not been evaluated previously by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and was reviewed at the present Meeting at the request of the Codex Committee on Pesticide Residues (CCPR).

All the pivotal studies contained certificates of compliance with good laboratory practice (GLP).

Biochemical aspects

The absorption, distribution, metabolism and excretion of etoxazole were investigated in rats. ¹⁴C-labelled etoxazole was rapidly but only moderately absorbed from the gastrointestinal tract of rats following oral dosing. Maximum concentrations of radioactivity in plasma were observed within 2–4 h of dosing for the low dose group (5 mg/kg body weight [bw]) and within 4–6 h for the high dose group (500 mg/kg bw). At the low dose, the degree of absorption in males (50–54%) was less than that in females (63–70%), but there were no major sex-related differences in the pattern of excretion. Saturation of absorption occurred at a high dose (500 mg/kg bw per day), with less than 30% absorbed. Faecal excretion was the primary route of elimination, and excretion was essentially complete within 120 h after dosing. Very little etoxazole was retained in the tissues. By 168 h post-dose, concentrations of radioactivity remaining in liver, thyroid and fat of rats were 3.9–7.8 times higher in the repeated-dose experiment than in the same tissues from the single-dose group.

The parent compound was the major component in the faeces, at 17.8–29.1% in the low dose groups and 74.7–80.2% in the high dose groups. Based on the analyses of excreta, bile and liver, the biotransformation of etoxazole in rats primarily involves the hydroxylation of the 4,5-dihydrooxazole ring, followed by cleavage of the metabolite and hydroxylation of the *tert*-butyl side-chain.

Toxicological data

Etoxazole had low acute toxicity in rats, causing no mortality at the limit dose after oral (median lethal dose [LD₅₀] > 5000 mg/kg bw), dermal (LD₅₀ > 2000 mg/kg bw) or inhalation (median lethal concentration [LC₅₀] > 1.09 mg/L air, highest attainable concentration) exposure. Etoxazole was not irritating to the skin or eyes of rabbits and not sensitizing under the conditions of the Magnusson and Kligman maximization test in guinea-pigs.

Following repeated dietary dosing, the liver was the main target organ in mice, rats and dogs. Hepatotoxicity was manifest as increased liver weight, liver enlargement and centrilobular hepatocellular hypertrophy, as well as alterations in clinical chemistry (elevated serum levels of liver enzymes, cholesterol, triglycerides and protein). In several studies, effects on the liver were mild and considered to be non-adverse, reflecting an adaptive response of the liver rather than overt hepatotoxicity. The spectrum of liver effects and the doses eliciting hepatotoxicity did not change significantly with duration of dosing, although the severity of the histopathological lesions observed in the liver did increase slightly with longer-term dosing. For example, fatty change of the liver was observed in mice only after exposure to doses of 2285 ppm (equal to 241 mg/kg bw per day) and higher for 18 months and in rats in the second generation of a multigeneration reproduction study at 2000 ppm (equal to 157 mg/kg bw per day), and the degree of centrilobular hepatocellular

hypertrophy was graded as severe only in high-dose dogs after 12 months of dosing at 5000 ppm (equal to 116 mg/kg bw per day). Generally, the macroscopic observation of liver enlargement was more evident in females than in males, whereas the microscopic observation of hepatocellular hypertrophy was more prominent in males. Periportal necrosis of the liver was observed only in mice at 6400 ppm (equal to 878 mg/kg bw per day), the highest dose tested. An increased incidence of hyperplasia of the bile duct was observed at high doses in female rats only after dosing for 2 years. A special study revealed that drug metabolizing enzymes were not induced following exposure of rats to etoxazole for 4 or 13 weeks.

Dental and bone abnormalities were observed in rats after repeated dosing. The dental abnormalities included elongation of the upper incisors after subchronic dosing and elongation, whitening and abrasion of the upper and lower incisors as well as abnormal amelogenesis (formation of tooth enamel) of the upper incisor after longer-term dosing. It should be noted that the molecule contains fluorine. Although there are no specific studies on the release of fluoride from the molecule, these dental and bone effects would be consistent with the presence of free fluoride. The no-observed-adverse-effect level (NOAEL) for elongation of incisors in the 90-day study was 5000 ppm (equal to 300 mg/kg bw per day). In the 2-year study conducted at higher doses, the dental effects occurred at the lowest-observed-adverse-effect level (LOAEL) of 5000 ppm (equal to 187 mg/kg bw per day), and the NOAEL was 50 ppm (equal to 1.83 mg/kg bw per day). Thickening and hyperplasia of the parietal bone were observed in rats only after chronic dosing at the highest dose tested, 10 000 ppm (equal to 386 mg/kg bw per day). In the 2-year rat study conducted at lower doses, no dental or bone effects were observed at the highest dose tested (64 mg/kg bw per day). An overall NOAEL for dental and bone abnormalities and liver effects from the two long-term rat studies combined is 64 mg/kg bw per day.

The dog was the most sensitive species following short-term dosing. The NOAEL in the 90-day study was 200 ppm (equal to 5.33 mg/kg bw per day) based on liver effects (increased serum levels of triglycerides and alkaline phosphatase [AP], absolute and relative weights and incidence of centrilobular hepatocellular hypertrophy), as well as mucous stool (observed after repeated dosing), and decreased absolute and relative prostate weights and slight to moderate prostate acinar cell atrophy. The NOAEL in the 1-year dog study was also 200 ppm (equal to 4.62 mg/kg bw per day) based on liver effects (increased serum level of AP, incidence of liver enlargement and incidence of centrilobular hepatocellular hypertrophy) at the LOAEL of 1000 ppm (equal to 23.5 mg/kg bw per day). In contrast, the NOAEL in the 90-day mouse study was 1600 ppm (equal to 214 mg/kg bw per day), and the NOAEL in the 90-day rat study was 1000 ppm (equal to 61.8 mg/kg bw per day), in both cases based on liver effects.

Two carcinogenicity studies each were conducted in the rat and the mouse due to inadequate dosing in the initial studies. In the first mouse study, animals were dosed at 0, 15.1, 60.1 or 241 mg/kg bw per day (average concentrations in the diet were 0, 143, 564 and 2285 ppm), and no adverse effects were observed at any dose. In the second mouse carcinogenicity study, the animals were dosed at 0, 2250 or 4500 ppm (equal to 0, 242 and 482 mg/kg bw per day), and these doses were still not sufficient to produce adverse effects in females. In males, liver effects (increased incidence of fatty change) were observed at the highest dose. However, based on a weight of evidence evaluation, the study was considered acceptable for the assessment of carcinogenicity in mice. In the first rat study, animals were dosed at 0, 4, 16 or 64 mg/kg bw per day (approximately 0, 112, 449 and 1786 ppm). Testicular interstitial cell tumours were increased in all dose groups compared with controls (1/80, 10/80, 10/80 and 11/78, respectively); however, this was not considered to be treatment related, as it was not dose related, the incidence in the control group in this study was very low compared with historical control data for the laboratory and the strain, and an increase in the tumours was not observed in the second study at higher doses (5/50, 2/50, 4/50 and 1/50 at 0, 1.83, 187 and 386 mg/kg bw per day, respectively). Furthermore, special studies were conducted to examine testicular effects in the rat. These studies showed that etoxazole did not affect the proliferative activity of testicular interstitial cells after 4 or 13 weeks of dosing, nor did it have a significant impact on circulating levels of male reproductive hormones, the histology of the testis or

epididymides or spermatogenesis after 13 weeks of dosing. An increased incidence of pancreatic islet cell adenomas was observed in the females at 64 mg/kg bw per day; however, this was not considered to be treatment related in the absence of an increase in carcinomas in the same study or an increase in adenomas at higher doses in the second study. Therefore, no adverse effects were observed at any dose. In the second rat study, the animals were dosed at 0, 50, 5000 or 10 000 ppm (equal to 0, 1.83, 187 and 386 mg/kg bw per day), and no increase in tumours was observed. Overall, there was no evidence of carcinogenicity in either the rat or the mouse when the results from all of these studies are considered.

Etoxazole was adequately tested for genotoxicity in vitro and in vivo in a range of assays. Several negative results were obtained in a battery of in vitro and in vivo genotoxicity studies. A positive response was obtained at cytotoxic doses in a study with human lymphocytes. In the mouse lymphoma assay with metabolic activation, a weakly positive response occurred at a dose approaching cytotoxic doses, and an inconclusive result was found without metabolic activation.

The Meeting concluded that etoxazole was unlikely to be genotoxic.

On the basis of the absence of treatment-related carcinogenicity in rodents and the lack of genotoxicity, the Meeting concluded that etoxazole is unlikely to pose a carcinogenic risk to humans.

No effects on reproduction were noted in a multigeneration reproduction study in the rat. However, there was an increase in mortality of the offspring during early lactation in both generations at 2000 ppm (equal to 139 mg/kg bw per day), the highest dose tested. Increases in the number of pup deaths as well as the number of litters with pup deaths were observed. Furthermore, at this dose, the viability index on lactation day 4 was below historical control values. Effects in parental animals at the high dose were limited to non-adverse changes in organ weights (increased absolute and relative liver weights in males and increased relative weight in adrenal gland in females, with no corresponding histopathology noted in these tissues) in the first generation and slight hepatotoxicity in males (increased absolute and relative liver weights, slight centrilobular hepatocellular fatty change in two males) of the second generation. The NOAEL for parental and offspring toxicity was 400 ppm (equal to 28.2 mg/kg bw per day), and the NOAEL for reproductive toxicity was 2000 ppm (equal to 139 mg/kg bw per day), the highest dose tested.

No developmental toxicity was observed when pregnant rats were dosed up to 1000 mg/kg bw per day over the period of major organogenesis. Slight reductions in body weight and food consumption were observed in maternal animals at this dose. The NOAEL for maternal toxicity was 200 mg/kg bw per day, and the NOAEL for developmental toxicity was 1000 mg/kg bw per day, the highest dose tested. In rabbits, the fetal and litter incidence of skeletal variations was increased following prenatal exposure to etoxazole at 1000 mg/kg bw per day, in the presence of maternal toxicity (i.e., liver enlargement as well as body weight reduction). The NOAEL for maternal and developmental toxicity was 200 mg/kg bw per day.

The Meeting concluded that etoxazole induced developmental toxicity only in the presence of maternal toxicity and that it was not teratogenic.

The clinical observations of the repeated-dose studies did not reveal any evidence of neurotoxicity. In addition, a functional observational battery, which included an assessment of motor activity, grip strength and sensorimotor reaction to stimuli, conducted at 1 year in the 2-year study in rats, yielded negative results for neurotoxicity.

There were no reports of adverse health effects in manufacturing plant personnel or in operators and workers exposed to etoxazole formulations during their use. Also, there was no evidence to support any findings in relation to poisoning with etoxazole.

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

Toxicological evaluation

The Meeting established an acceptable daily intake (ADI) of 0–0.05 mg/kg bw on the basis of an overall NOAEL of 5.33 mg/kg bw per day in the 90-day and 1-year studies in dogs for liver effects (e.g., increases in serum levels of AP and triglycerides, absolute and relative liver weights and incidence of centrilobular hepatocyte hypertrophy). A safety factor of 100 was applied.

The Meeting concluded that it was not necessary to establish an acute reference dose (ARfD) for etoxazole in view of its low acute toxicity, the absence of relevant developmental toxicity in rats and rabbits that could have occurred as a consequence of an acute exposure, and the absence of any other toxicological effect that would be elicited by a single dose.

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	2250 ppm, equal to 242 mg/kg bw per day	4500 ppm, equal to 482 mg/kg bw per day
Rat	Two-year studies of toxicity and carcinogenicity ^{a,b}	Toxicity	1786 ppm, equal to 64 mg/kg bw per day	5000 ppm, equal to 187 mg/kg bw per day
		Carcinogenicity	10 000 ppm, equal to 386 mg/kg bw per day ^c	—
	Two-generation study of reproductive toxicity ^a	Parental toxicity	400 ppm, equal to 28.2 mg/kg bw per day	2000 ppm, equal to 139 mg/kg bw per day ^c
		Offspring toxicity	400 ppm, equal to 28.2 mg/kg bw per day	2000 ppm, equal to 139 mg/kg bw per day ^c
Developmental toxicity ^d	Reproductive toxicity	2000 ppm, equal to 139 mg/kg bw per day ^c	—	
	Maternal toxicity	200 mg/kg bw per day	1000 mg/kg bw per day	
Rabbit	Developmental toxicity ^d	Embryo and fetal toxicity	1000 mg/kg bw per day ^c	—
		Maternal toxicity	200 mg/kg bw per day	1000 mg/kg bw per day
Dog	Thirteen-week and 1-year studies of toxicity ^{a,b}	Embryo and fetal toxicity	200 mg/kg bw per day	1000 mg/kg bw per day
		Toxicity	200 ppm, equal to 5.33 mg/kg bw per day	1000 ppm, equal to 23.5 mg/kg bw per day

^a Dietary administration.

^b Gavage administration.

^c Highest dose tested.

^d Two or more studies combined.

Estimate of acceptable daily intake for humans

0–0.05 mg/kg bw

Estimate of acute reference dose

Unnecessary

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

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

Critical end-points for setting guidance values for exposure to etoxazole*Absorption, distribution, excretion and metabolism in mammals*

Rate and extent of oral absorption	Rapid; approximately 60%
Distribution	Wide; highest concentrations in liver
Potential for accumulation	None
Rate and extent of excretion	Largely complete within 48 h; primarily via faeces (77–88%, bile 30–54%) and to a lesser extent via urine (8–17%)
Metabolism in animals	Extensive; mainly by hydroxylation of the 4,5-dihydrooxazole ring followed by cleavage of the molecule and hydroxylation of the <i>tert</i> -butyl side-chain
Toxicologically significant compounds in animals, plants and the environment	Parent compound

Acute toxicity

Rat, LD ₅₀ , oral	> 5000 mg/kg bw
Rat, LD ₅₀ , dermal	> 2000 mg/kg bw
Rat, LC ₅₀ , inhalation	> 1.09 mg/L (highest attainable concentration)
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Not irritating
Guinea-pig, dermal sensitization	Not sensitizing (Magnusson and Kligman test)

Short-term studies of toxicity

Target/critical effect	Increased absolute and relative liver weights, clinical chemistry changes, centrilobular hepatocyte hypertrophy, prostate atrophy
Lowest relevant oral NOAEL	5.33 mg/kg bw per day (13-week study in dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (28-day study in rats)
Lowest relevant inhalation NOAEC	No data

Long-term studies of toxicity and carcinogenicity

Target/critical effect	Increased absolute and relative liver weights, clinical chemistry changes, histopathological changes in liver, dental and bone abnormalities
Lowest relevant NOAEL	64 mg/kg bw per day (2-year study in rats)
Carcinogenicity	Not carcinogenic in rats or mice

Genotoxicity

Unlikely to be genotoxic

<i>Reproductive toxicity</i>			
Reproduction target/critical effect	No effect on fertility at highest dose tested; slight decrease in viability of pups and pup body weight at parentally toxic dose		
Lowest relevant reproductive NOAEL	28.2 mg/kg bw per day for offspring toxicity in two-generation reproduction study in rats		
Developmental target/critical effect	Increased incidence of skeletal variations at maternally toxic dose		
Lowest relevant developmental NOAEL	200 mg/kg bw per day in rabbits		
<i>Neurotoxicity/delayed neurotoxicity</i>			
	No evidence of neurotoxicity		
<i>Other toxicological studies</i>			
	Special studies on testicular function in rats revealed no effect on proliferative activity of interstitial cells, changes in circulating male hormones or histopathology		
<i>Medical data</i>			
	No data		
Summary			
	Value	Study	Safety factor
ADI	0–0.05 mg/kg bw	Dog, 90-day and 1-year study	100
ARfD	Unnecessary		

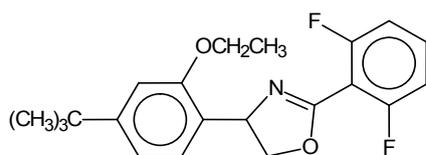
RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of etoxazole were considered for the first time by the present Meeting. The residue evaluation was scheduled for the 2010 JMPR by the Forty-first Session of the CCPR (ALINORM 09/32/24).

Etoxazole is an acaricide which belongs to the diphenyloxazoline group of chemicals, and controls mites by causing adults to lay sterile eggs and also inhibition of chitin biosynthesis. The Meeting received information on identity, animal and plant metabolism, environment fate in soil, rotational crops, analytical methods, storage stability, use patterns, supervised trials, farm animal feeding studies and fates of residues in processing.

The 2010 JMPR established an ADI for etoxazole of 0–0.05 mg/kg bw. For etoxazole the ARfD is unnecessary.

(*RS*)-5-*tert*-butyl-2-[2-(2,6-difluorophenyl)-4,5-dihydro-1,3-oxazol-4-yl]phenetole



Etoxazole is a 1:1 mixture of the enantiomers.

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

R-2	2-(2,6-difluorophenyl)-4-[2-ethoxy-4-(1-hydroxymethyl-1-methylethyl)phenyl]-4,5-dihydrooxazole
R-3	<i>N</i> -(2,6-difluorobenzoyl)-4- <i>tert</i> -butyl-2-ethoxybenzamide
R-4	<i>N</i> -(2,6-difluorobenzoyl)-2-amino-2-(4- <i>tert</i> -butyl-2-ethoxyphenyl) ethanol
R-7	2-amino-2-(4- <i>tert</i> -butyl-2-ethoxyphenyl)ethyl 2,6-difluorobenzoate hydrochloride
R-7-CO ₂ H	2-amino-2-[2-ethoxy-4-(1-carboxy-1-methylethyl)phenyl]ethyl 2,6-difluorobenzoate hydrochloride
R-8	2-amino-2-(4- <i>tert</i> -butyl-2-ethoxyphenyl)ethanol
R-10	<i>N</i> -(2,6-difluorobenzoyl)glycine
R-11	2,6-difluorobenzoic acid
R-12	4- <i>tert</i> -butyl-2-ethoxybenzoic acid
R-13	4-(4- <i>tert</i> -butyl-2-ethoxyphenyl)-2-(2,6-difluorophenyl)oxazole
R-15	4- <i>tert</i> -butyl-2-ethoxybenzamide
R-16	2-(2,6-difluorophenyl)-4-[2-ethoxy-4-(1-carboxy-1-methylethyl)phenyl]-4,5-dihydrooxazole
R-20	2-ethoxy-4-(1-hydroxymethyl-1-methylethyl)benzoic acid
R-24	2-amino-2-(2-ethoxy-4-[1'-hydroxymethyl-1'-methylethyl]phenyl)ethanol
DFB	2,6-difluorobenzamide
Metabolite 1	2-amino-2-(2-ethoxy-4-[1'-hydroxycarbonyl-1'-methyl-ethyl]phenyl)ethanol

Animal metabolism

The Meeting received animal metabolism studies with etoxazole in rats, lactating goats and laying hens. The metabolism and distribution of etoxazole in animals were investigated using the [U-¹⁴C-difluorophenyl] and [U-¹⁴C-*tert* butylphenyl]-labelled etoxazole.

Etoxazole was metabolised in rats principally by hydroxylation of the 4,5-dihydrooxazole ring followed by cleavage of the molecule and hydroxylation of the tertiary-butyl side chain. There was a significant difference in the proportions of metabolites excreted in the urine of male and female rats. The major component in male rat urine was Metabolite 1 and in female urine was R-24. Metabolism in rats was summarized and evaluated by the WHO panel of the JMPR in 2010.

When lactating goats were orally dosed with [¹⁴C-*tert* butylphenyl]- and [¹⁴C-difluorophenyl]-etoxazole at 20 mg/animal/day, equivalent to approximately 10 ppm in the feed for 4 consecutive days, most of the administered radioactivity was recovered in the gastro-intestinal contents (80% and 29%). Radioactivity was excreted in urine (1.9% and 1.5%) and faeces (17% and 54%). Overall recoveries of the administered dose were 99% and 85%. The Meeting considered that the result of studies using [¹⁴C-*tert* butylphenyl]-etoxazole was unreliable, since most of radioactivity was recovered from the gastro-intestinal tracts. The result of studies using [¹⁴C-difluorophenyl]-etoxazole are summarized below.

Radioactive residues were highest in the bile (0.317 mg/kg) and livers (0.063 mg/kg). Total radioactive residues in all other tissues and milk were < 0.008 mg/kg. Parent etoxazole accounted for a total of 63–65% dose in the faeces and gastro-intestinal tracts. The major urinary metabolites corresponded to R-11 (0.5% dose) and R-10 (0.8% dose).

Laying hens were orally dosed with [¹⁴C-*tert*-butylphenyl]- or [¹⁴C-difluorophenyl]-etoxazole at doses equivalent to 12 or 11 ppm in the feed for 8 consecutive days. The majority (84.4–99.8%) of

the radioactive residues were extracted in egg yolk, egg white, abdominal and skin fat, thigh muscle, breast muscle and liver.

Parent etoxazole was the major ^{14}C residue in egg yolk, abdominal and skin fat, thigh muscle, and breast muscle. Its concentration in isolated egg yolk was approximately 0.1 mg/kg. It accounted for only about 3% of TRR in liver (0.057–0.078 mg/kg), but 90–92% of TRR in the composite fat (0.55–0.69 mg/kg). Most of ^{14}C residue in liver was metabolite R-16 (59–66% of TRR), a *tert*-butyl methyl group oxidation product of etoxazole. R-16 was also observed in minor quantities in all tissues except egg white. The analogous dihydrooxazole ring-opened product of R-16, designated as R-7-CO₂H, was observed only in liver. The liver contained unextracted ^{14}C residues in both radiolabel treatments (0.29 mg/kg or 12–15% of TRR). The majority (about 80%) was protein-bound and could be solubilised by treatment with protease.

Etoxazole was metabolized to several metabolites and the metabolic routes are similar in goats and hens. The major metabolic processes were oxidation of the *tert*-butyl moiety, and the hydrolysis of the hydrooxazole ring. Ruminant and poultry metabolism studies demonstrated that transfer of administered ^{14}C residues to milk, eggs, and tissues is low.

The metabolic pathway proposed for goats and hens is similar to that for rats. Some metabolites such as R-8 (0.7% TRR in poultry liver), R-10 (0.8% dose in goat urine), R-20 (11.5% TRR in goat liver) were observed in goat and hen metabolism studies, but not in rat studies.

Plant metabolism

The Meeting received plant metabolism studies performed on apples, oranges and egg plants using the *tert*-butylphenyl- and oxazole- U-[^{14}C] labelled etoxazole, and on cotton using the *tert*-butylphenyl- and difluorophenyl-U-[^{14}C] labelled etoxazole.

In an apple metabolism study, apple trees were treated once at a rate of 0.15 kg ai/ha. Samples of fruit and leaves were taken at Day 0, 14 or 15, 21 and 30 after application. The TRR in fruit declined from 0.46 to 0.13 mg/kg and 0.18 to 0.09 mg/kg from treatment with the *tert*-butylphenyl- and oxazole-labelled etoxazole, respectively. Similarly, the TRR in leaves declined from 14.9 to 2.5 mg/kg and 11.8 to 0.7 mg/kg. Parent etoxazole was the only component that exceeded 10% of the TRR in fruit (42% of TRR at harvest) and leaves (30% of TRR at harvest) at all sampling times. Metabolites accounting for 0.001–0.010 mg/kg (0.4–8.2% of TRR in fruit) were identified as R-3, R-7, R-13, R-11 (oxazole label), R-12 (*tert*-butylphenyl label), and R-15 (*tert*-butylphenyl label).

In an orange metabolism study, orange trees were treated at a rate of 0.4 kg ai/ha. Samples of fruit and leaves were taken immediately after application and at 21, 30, 60 and 90 days after application. The TRR in fruit declined from 0.25 to 0.11 mg/kg and 0.27 to 0.07 mg/kg from treatment with the *tert*-butylphenyl- and oxazole- labelled etoxazole, respectively. Similarly, the TRR in leaves declined from 9.3 to 0.81 mg/kg and 17.9 to 2.7 mg/kg from treatment. Parent etoxazole was the only component that exceeded 10% of the TRR in fruit (48% of TRR at harvest) and leaves (52% of TRR at harvest) at all sampling times. Etoxazole and metabolites R-3, R-7, R-13, R-14 and R-15 were identified by co-chromatography. The residue was a surface residue and translocation was minimal.

In an egg plant metabolism study, egg plants maintained under controlled conditions in a plant growth room were treated at a rate of 0.2 kg ai/ha. Samples of fruit were taken immediately after applications at 1 day, and 2 and 4 weeks. Samples of leaves were taken immediately after application at 1 day and 4 weeks. The TRR in fruit declined from 0.20 to 0.10 mg/kg from treatment with the *tert*-butylphenyl-labelled etoxazole, but for fruit-treated oxazole-labelled etoxazole the TRR did not decline (0.16 to 0.20 mg/kg). Parent etoxazole was the only component that exceeded 10% of the TRR in fruit (69–74% of TRR at harvest) and leaves (70–75% of TRR at harvest) at all sampling times. Metabolites accounting for 0.001–0.004 mg/kg (0.3–1.8% fruit radioactivity) were identified as R-2, R-3, R-7, R-13 (both radiolabels), R-11 (oxazole radiolabel), and R-12 (*tert*-butylphenyl radiolabel). Again, the residue was a surface residue and translocation was minimal.

In a cotton metabolism study, two foliar treatments were applied to cotton plants at a rate of 0.1 kg ai/ha at 42 and 21 days prior to harvest. Cottonseed (ginned from open cotton bolls) and gin trash was harvested for analysis. Cottonseed contained low amounts of radioactivity, with TRR values of 0.031 and 0.020 mg/kg for difluorophenyl and tert-butylphenyl cottonseed, respectively. Cotton gin trash samples contained TRR values of 6.9 and 5.3 mg/kg for the difluorophenyl- and tert-butylphenyl-labelled etoxazole. The major residues identified in gin trash were parent etoxazole (36–44% of TRR) and R-3 (16–18% of TRR).

In the plant metabolism studies on apples, oranges, egg plants and cotton, the metabolic pathways were similar. Etoxazole was metabolized to several metabolites. In all plants investigated, the parent etoxazole was identified as the major component (30–75% of TRR). Metabolites were detected in concentrations < 10% of TRR in apples, oranges and egg plants. In cotton gin trash, the component (R-3) exceeded 10% of TRR. In all studies, the residue remained mainly in the surface, penetration into fruit was minimal and translocation was also minimal. The major metabolic processes were the hydrolysis and cleavage of the oxazole ring.

All plant metabolites identified except R-14 were found in rats, goats or hens. The structure of R-14 is similar to that of R-7 which was identified in rats and hens. These metabolites may be generated during the hydrolysis and cleavage of hydroxazole ring.

The stabilities of metabolites in plant metabolism studies during freezer storage were determined by re-extraction and comparison of radioresidue profiles to chromatographic profiles. The amounts of radioactivity extracted and the percentages of the major metabolites identified were similar after freezer storage intervals (5–13 months).

Environmental fate in soil

The Meeting received information on aerobic soil metabolism and rotational crop study.

Aerobic soil metabolism and degradation study was conducted using [¹⁴C-*tert*-butylphenyl] and [¹⁴C-difluorophenyl]-etoxazole in a sand loam soil under aerobic conditions at a nominal average temperature of 20 °C for 269 days. Etoxazole declined rapidly from 95.7–97.8% of total applied radioactivity (TAR) at 0 day to 11.2–12.6% of TAR at 30 days. Totals of 15.8–56.4% of TAR were evolved as CO₂ during 269 days. Several degradates were observed during the incubation period. The degradate R-13 rose to 10.9–11.7% of TAR at 60 days, declining to about 7% of TAR at 269 days. The degradate R-7 reached a maximum proportion of 11.5–21.6% of TAR after 7 days, declined to 5.5–5.9% of TAR at 60 days. The degradate R-8 reached a peak level of 44.8% TAR at 60 days and was still relatively great (28.6% TAR) at 269 days. The minor components R-3, R-4, R-12 and R-15 were never greater than 1.5, 4.4, 4.0 and 3.2% TAR respectively. ¹⁴C-etoxazole was degraded with a DT₅₀ of 9.9 to 10.6 days.

In confined rotational crop study, radish, lettuce and wheat were designated for planting at 30, 120 and 360 days after treatment (DAT) at an application rate of 0.11 kg ai/ha with [¹⁴C-*tert*-butylphenyl] and [¹⁴C-difluorophenyl]-etoxazole. The TRR in the 30 DAT rotational crop samples from the treated plots were below the significant residue level of 0.01 mg/kg. Uptake and accumulation of etoxazole-related radioactive residues is very low (< 0.005 mg/kg) in rotational crops of radish, lettuce and wheat planted at the earliest plant-back interval (30 DAT).

Etoxazole residues are not expected to occur in succeeding crops.

Environmental fate in water systems

In the hydrolysis study with [¹⁴C-*tert*-butylphenyl]-etoxazole conducted using sterile aqueous buffer solutions, the hydrolytic half-lives at 20 °C were found to be about 10 days at pH 5, 161 days at pH 7 and 165 days at pH 9. In pH 1.2 buffer at 37 °C and in pH 5 buffer at 20 °C, etoxazole was hydrolyzed to R-7, while in pH 7 and pH 9 buffer, it was hydrolyzed to R-4. No other radioactive products were detected in quantities greater than 6% of the recovered radioactivity. At 20 °C the

hydrolytic stability of etoxazole in aqueous buffer is of the order $\text{pH } 9 > \text{pH } 7 > \text{pH } 5$. In buffers of acidic pH, etoxazole is hydrolyzed to R-7 and in neutral or basic pH to R-4.

The photolysis study with [^{14}C -*tert*-butylphenyl] and [^{14}C -oxazole]-etoxazole was conducted using pH 9 buffer containing 10% acetonitrile. The photolytic half-life of etoxazole in pH 9 buffer was found to be 15.9–17.4 days summer sunlight equivalents at latitude 40 °N. The major degradates were identified as R-3, R-11, R-12 and R-15.

Methods of analysis

The Meeting received description and validation data for analytical methods for residues of parent etoxazole in raw agricultural commodities, processed commodities, feed commodities and animal commodities. In most of the methods for determination of etoxazole, homogenized samples were extracted with acetone (for plant materials) and ethyl acetate (for animal commodities), and the extract was cleaned up with liquid–liquid partition followed by column chromatography using SPE. Residues were determined by gas chromatography with FTD, NPD or MSD. The methods of analysis for a range of substrates were validated with LOQs of the 0.002–0.01 mg/kg range for etoxazole.

The multiresidue method DFG Method S19 (modified version) with GC-MS detection was validated for etoxazole in plant materials. LOQs were 0.01 mg/kg for etoxazole.

The Meeting received LC-MS/MS method of analysis for Metabolite 1 and R-20 in bovine liver and kidney. The method was validated with an LOQ of 0.02 mg/kg for both analytes.

Stability of residues in stored analytical samples

The Meeting received information on the freezer storage stability of etoxazole residues in plant commodities (apples, mandarin peel/pulp, strawberries, cantaloupes, grapes, almond hulls, hops, cotton seed/gin trash, cherries, plums fresh/dried, peaches, cucumbers, tomatoes, mint tops/oil and tea). The Meeting noted that the residue might be degrading during sample preparation. Spiking of chopped samples would not reveal this degradation. Nevertheless the Meeting decided to evaluate the results of residue trials, where the storage stability studies show adequate recoveries. Enforcement laboratories should be aware that special precautions may be necessary during sample preparations.

The Meeting received information on the freezer storage stability of etoxazole in milk cream, metabolite R-20 in liver, and Metabolite 1 in liver and kidney. The results of the studies showed that each compound is stable in each animal commodity tested for at least 2 months in frozen storage.

Definition of the residue

In the lactating goat metabolism study, TRRs in kidney (0.94 mg/kg) and liver (0.06–0.23 mg/kg) were higher than those in other tissues. Metabolite 1 is the major component of the residues in liver (12% TRR) and kidney (81% TRR). In the laying hen study, the major residue components are parent etoxazole (in all tissues) and R-16 (in muscle and liver). However, according to farm animal feeding studies, the parent, Metabolite 1 and R-20 are expected to be present at below the LOQ.

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

The octanol/water coefficient ($\log P_{ow}$) of 5.5 for etoxazole suggests that etoxazole might be fat soluble. In the laying hen metabolism study, etoxazole found in the composite fat was 0.55–0.69 mg/kg and that in muscle was 0.01–0.08 mg/kg. In the dairy cow feeding study, the residue of etoxazole in fat was higher than that in other tissues. The ratio of etoxazole residues in muscle and fat observed in the laying hen metabolism study and the dairy cow feeding study indicates that etoxazole is fat soluble.

The plant metabolism studies of etoxazole were conducted with fruiting vegetables (egg plants), fruit crops (apples and oranges) and oilseed (cotton). Each study was conducted with both

tert-butylphenyl- and oxazole-radio-labelled etoxazole for apples, oranges and egg plants, and with both tert-butylphenyl- and difluorophenyl-radio-labelled etoxazole for cotton. Parent etoxazole was always the major component (30–75% TRR). Metabolite R-14 was found in oranges and cotton at low levels (< 3.2% TRR) but not in rat metabolism studies. In cotton seed, DFB and R-3 were also identified as the major residue components, but the concentration of each residue was less than 0.01 mg/kg.

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

The Meeting recommended the following residue definition for plants and animals (for compliance with the MRL and for estimation of dietary intake): *etoxazole*.

The residue is fat-soluble.

Residues of supervised trials on crops

The Meeting received supervised trial data for the foliar application of etoxazole on citrus fruits (mandarins and oranges), apples, pears, cherries, plums, nectarines, peaches, grapes, strawberries, cantaloupes, cucumbers, peppers, tomatoes, almonds, pecans, cotton seed, mints, hops and tea. Residue trial data was made available from Australia, member states of the European Union, Japan and the USA.

Labels (or translation of labels) were available from Australia, Brazil, France, Greece, Italy, Japan, Spain, the UK and the USA describing the registered uses of etoxazole, and GAP information was also provided from Australia and the Netherlands.

The Meeting decided that an ARfD for etoxazole is unnecessary. Therefore, it is not necessary to estimate HR values for etoxazole in the commodities.

As noted above, the Meeting decided to use the results of only these residue trials, for which the storage stability of etoxazole during the respective storage interval was demonstrated, to estimate a maximum residue level. The Meeting therefore recommended the maximum residue levels for citrus, grapes, cucumbers, tree nuts, mint, hops and tea.

Citrus fruits

Data were available from supervised trials on mandarins and oranges in Italy and Spain.

In Italy and Spain, etoxazole is registered for use on citrus at a foliar application of 5.5 g ai/hL (a maximum rate of 0.055 kg ai/ha) with a PHI of 14 days. Residues in whole fruit of mandarins from trials matching GAP of Italy and Spain were (n = 8): 0.01, 0.02 (2), 0.04 and 0.05 (4) mg/kg. Residues in whole fruit of oranges from trials matching GAP of Italy and Spain were (n = 6): 0.01 (2), 0.02 (3) and 0.05 mg/kg. The residue populations for trials conducted on mandarins and oranges were not similar (Mann-Whitney U test). The Meeting decided to use the data on the crop with the highest residues (mandarins) to estimate a maximum residue level for the group. Residues in mandarin pulp from trials of Italy and Spain were (n = 8): < 0.01 (7) and 0.01 mg/kg. Residues in orange pulp from trials of Italy and Spain were (n = 6): < 0.01 (6) mg/kg.

Based on the trials for mandarins in Italy and Spain, the Meeting estimated a maximum residue level and an STMR value for etoxazole in citrus of 0.1 and 0.01 mg/kg respectively.

The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was 0.09 mg/kg (Mean + 3SD). Rounding-up of the value to 0.1 mg/kg coincides with the recommendation of the current Meeting.

Pome fruits

Data were available from supervised trials on apples in member states of the EU and the USA.

According to the freezer storage stability study on apples conducted in 2001, etoxazole is declining even after 41 days storage interval. Insufficient data was available to demonstrate storage stability of pome fruits.

The Meeting could not estimate maximum residue levels for etoxazole in pome fruit.

Stone fruits

Cherries

Data were available from supervised trials on cherries in Spain and the USA.

Trials from the USA on cherries were reported for the foliar application of a WG formulation. However, the storage stability of etoxazole residues in the trials was unstable (60–68% remaining for 193 days storage interval). The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in cherries.

Residue trials were provided from Spain for use of etoxazole on cherries but no GAP was available.

The Meeting decided not to recommend a maximum residue level for etoxazole in cherries.

Plums

Trials were reported for plums from member states of the EU and the USA.

Trials from France on plums were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in plums.

Trials from the USA on plums were reported for the foliar application of a WG formulation. However, the storage stability of etoxazole residues in the trials was unstable (41–45% remaining for 207 days storage interval). The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in plums.

Nectarines

Trials on nectarines were reported from Australia (1 × 3.9 g ai/hL and PHI of 21 days). However, storage stability information was insufficient and the residue trials conducted in Australia did not match the GAP of Australia.

Peaches

Trials were reported for peaches from Australia, member states of the EU and the USA.

In Australia, etoxazole is registered for use on stone fruits at a foliar application of 3.9 g ai/hL with a PHI of 21 days. However, the residue trials on peaches conducted in Australia did not match the GAP of Australia.

Trials from France, Greece, Italy and Spain on peaches were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in peaches.

Trials from the USA on peaches were reported for the foliar application of a WG formulation. However, the storage stability of etoxazole residues in the trials was unstable (45–53% remaining for 278 days storage interval). The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in peaches.

*Berries and other small fruits**Grapes*

Data were available from supervised trials on grapes in France and the USA.

Trials from France on grapes were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in grapes.

Etoxazole is registered in the USA for use on grapes at a foliar application of a maximum rate of 0.15 kg ai/ha with a PHI of 14 days. Etoxazole residues in grapes from trials in the USA matching GAP were (n = 12): < 0.01, 0.01, 0.03, 0.04 (4), 0.05 (2), 0.06, 0.10 and 0.33 mg/kg. Adequate storage stability studies were available in the US trials.

Based on the US trials, the Meeting estimated a maximum residue level and an STMR value for etoxazole in grapes of 0.5 and 0.04 mg/kg respectively.

The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was 0.25 mg/kg (UCLMedian 95th), but this value was below the HR value and therefore disregarded.

Strawberry

Trials on strawberries were reported from the USA (GAP: one foliar application of a maximum rate of 0.15 kg ai/ha and PHI of 1 day). However, the storage stability of etoxazole residues in the trials was unstable (63% remaining for 32 days storage interval). The Meeting decided not to recommend a maximum residue level for etoxazole in strawberries

Fruiting vegetables—Cucurbits

Data were available from supervised trials on cantaloupe and cucumber in the USA.

Melons

Trials on cantaloupes were reported from the USA (two foliar applications of a maximum rate of 0.15 kg ai/ha and PHI of 7 days). However, the storage stability of etoxazole residues in the trials was unstable (55% remaining for 50 days storage interval). The Meeting decided not to recommend a maximum residue level for etoxazole in melons

Cucumber

The GAP on cucumbers of the USA is a maximum two foliar applications at a maximum rate of 0.15 kg ai/ha with a PHI of 7 days. Etoxazole residues in cucumbers from trials in the USA matching GAP were (n = 9): < 0.01 (7) and 0.01 (2) mg/kg. Adequate storage stability studies were available in the US trials.

Based on the US trials for cucumbers, the Meeting estimated a maximum residue level and an STMR value for etoxazole in cucumbers of 0.02 and 0.01 mg/kg respectively.

The NAFTA calculator could not be used, as residues from seven of the nine trials, matching GAP, were below the LOQs.

*Fruiting vegetables, other than Cucurbits**Peppers*

Trials from Australia on peppers were reported for the foliar application of a SC formulation. However, the residue trials conducted did not match the GAP on peppers in Australia. The Meeting could not estimate a maximum residue level for peppers.

Tomatoes

Data were available from supervised trials on tomatoes in Australia, member states of the EU and the USA.

Trials from France, Greece, Italy, Netherlands and Spain on tomatoes were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in tomatoes.

Trials from the USA on tomatoes were reported for the foliar application of a WG formulation (GAP: two foliar applications of a maximum rate of 0.14 kg ai/ha and PHI of 1 day). Etoxazole residues in tomatoes from trials in the USA matching GAP were (n = 3): 0.01 and 0.05 (2) mg/kg. Adequate storage stability studies were available in the US trials. However, the trials for tomatoes matching the US GAP were insufficient to estimate a maximum residue level for the commodity.

Trials from Australia on tomatoes were reported for the foliar application of a SC formulation. However, the residue trials conducted did not match the GAP on tomatoes in Australia.

The Meeting could not estimate a maximum residue level for etoxazole in tomatoes.

Tree nuts

Data were available from supervised trials on almonds and pecans in the USA.

Etoxazole is registered in the USA for use on tree nuts at a foliar application of a maximum rate of 0.15 kg ai/ha with a PHI of 28 days. Etoxazole residues in almond nutmeat from trials in the USA matching GAP were (n = 5): < 0.01 (5) mg/kg. Etoxazole residues in pecans from trials in the USA matching GAP were (n = 5): < 0.01 (5) mg/kg. Adequate storage stability studies were available in the US trials.

The use pattern in the USA is for tree nuts and the Meeting decided that trials in almonds and pecans could be used to support a group maximum residue level for tree nuts. The Meeting decided to combine the data for the purpose of estimating a maximum residue level for the group.

Based on the US trials for almond nutmeat and pecans, the Meeting estimated a maximum residue level of 0.01 (*) mg/kg, and an STMR value of 0 mg/kg for etoxazole in tree nuts.

The NAFTA statistical calculator was not used as all residues were below the LOQ.

Cotton seed

Data were available from supervised trials on cotton seeds in Australia, member states of the EU and the USA.

Trials from Greece and Spain on cotton seeds were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in cotton seeds.

Trials from the USA on cotton seeds were reported for the foliar application of a SC formulation or a WP formulation. Adequate storage stability studies were available in the US trials. However, the residue trials conducted in the USA did not match the GAP on cotton seeds in the USA.

Trials from Australia on cotton seeds were reported for the foliar application of a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate a maximum residue level for etoxazole in cotton seeds.

Mints

Data from the USA on mints were reported for the foliar application of a WG formulation.

Etoxazole is registered in the USA for use on mint at a maximum rate of 0.20 kg ai/ha and PHI 7 days with a maximum seasonal application of 0.40 kg ai/ha. Etoxazole residues in mints from trials in the USA matching GAP were (n = 5): 3.1, 3.2, 4.9, 5.6 and 7.6 mg/kg. Adequate storage stability studies were available in the US trials.

Based on the US trials, the Meeting estimated a maximum residue level and an STMR value for etoxazole in mints of 15 and 4.9 mg/kg respectively.

The normal Meeting procedure is to round values to the nearest units of 5 for maximum residue levels between 10 and 30 mg/kg. The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was 12 mg/kg (95/99 Rule). Rounding of the value to 15 mg/kg coincides with the recommendation of the current Meeting.

Hops

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

Trials from Germany on hops were reported for the foliar application of a SC formulation. However, there was no approved GAP/label provided for hops.

Etoxazole is registered in the USA for use on hops at a foliar application of a maximum rate of 0.20 kg ai/ha with a PHI of 7 days. Etoxazole residues in dried cones of hops from trials in the USA matching GAP were (n = 3): 2.5, 4.2 and 4.3 mg/kg. Adequate storage stability studies were available in the US trials.

Based on the US trials, the Meeting estimated a maximum residue level and an STMR value for etoxazole in hops of 15 and 4.2 mg/kg respectively.

The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was 8.0 mg/kg (95/99 Rule), however, due to the small number of trials (n = 3) this value was considered unreliable.

Tea

Data from Japan on tea were reported for the foliar application of a SC formulation and a WP formulation.

Etoxazole is registered in Japan for use on tea at a foliar application of 10 g ai/hL (a maximum rate of 0.4 kg ai/ha) with a PHI of 14 days. Etoxazole residues in green tea from trials in Japan matching GAP were (n = 8): 2.4, 3.1, 4.1, 4.7, 4.8, 6.4, 7.3 and 8.0 mg/kg. Adequate storage stability studies were available in Japanese trials.

Based on Japanese trials, the Meeting estimated a maximum residue level and an STMR value for etoxazole in tea of 15 and 4.75 mg/kg respectively.

The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was 13 mg/kg (95/99 Rule). With rounding the value coincides with the recommendation of the current Meeting. The normal Meeting procedure is to round the value to the nearest units of 5 for maximum residue levels between 10 and 30 mg/kg.

Animal feedstuffs

Almond hulls

Trials on almond hulls were reported from the USA (GAP: a foliar application of a maximum rate of 0.15 kg ai/ha with a PHI of 28 days). Etoxazole residues in almond hulls from trials in the USA matching GAP were (n = 5): 0.14, 0.17, 0.23, 0.39 and 1.8 mg/kg. Adequate storage stability studies were available in the US trials.

The Meeting estimated a maximum residue level and an STMR value for etoxazole in almond hulls of 3 and 0.23 mg/kg respectively.

The maximum residue level estimate, derived from use of the NAFTA statistical calculator, was of 2.5 mg/kg (UCLMedian 95th), which when rounded-up is in agreement with the Meeting's estimation.

Cotton gin trash

Data were available from supervised residue trials on cotton gin trash in Australia and the USA

Trials from the USA on cotton gin trash were reported for the foliar application of a SC formulation or a WP formulation. However, storage stability information was insufficient and the residue trials conducted in the USA did not match the GAP on cotton gin trash in the USA.

Trials from Australia on cotton gin trash were reported for the foliar application of a SC formulation or a SC formulation. However, the storage stability of etoxazole residues in the trials was not clear. The Meeting could not use the results of the trials to estimate an STMR value for etoxazole in cotton gin trash.

Fate of residues during processing

The fate of etoxazole residues has been examined in oranges, apples, grapes, cotton seeds and mints processing studies. Processing studies were conducted for apples and grapes in France. However, RAC samples were below the LOQ (0.010 mg/kg), and no residues were found in any processed commodities. Based on the results of processing studies conducted in the USA, processing factors were calculated for apples and grapes. Estimated processing factors and the derived STMR-Ps are summarized in the Table below.

Processing factors and STMR-P for food and feed

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors ^a	PF (Mean or best estimate)	RAC STMR (mg/kg)	STMR-P (mg/kg)
Orange	Wet pomace	1.5	1.5	0.01 (for citrus)	0.015
	Dry pomace	1.5	1.5		0.015
	Juice	< 0.5	0.5		0.005
Grape	Juice	1.7	1.7	0.04	0.068
	Raisin	1.1	1.1		0.044
Mint	Oil	3.0, 0.19	1.6	4.9	7.8

^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 an STMR-P of 0.015 mg/kg ($0.01 \times 1.5 = 0.015$ mg/kg) for citrus dried pulp, 0.005 mg/kg ($0.01 \times 0.5 = 0.005$ mg/kg) for citrus juice, 0.068 mg/kg ($0.04 \times 1.7 = 0.068$ mg/kg) for grape juice, 0.044 mg/kg ($0.04 \times 1.1 = 0.044$ mg/kg) for dried grapes and 7.8 mg/kg ($4.9 \times 1.6 = 7.8$ mg/kg) for mint oil

Residue in animal commodities

Farm animal dietary burden

The Meeting estimated the dietary burden of etoxazole 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. 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/CAN, EU, Australia and Japan in the Table (Appendix IX of the FAO manual).

Livestock dietary burden, etoxazole, ppm of dry matter diet								
	US/CAN		EU		Australia		Japan	
	Max	mean	max	mean	Max	mean	max	Mean
Beef cattle	0.03	0.03	0.00	0.00	0.03 ^a	0.03 ^b	0.00	0.00
Dairy cattle	0.03	0.03	0.00	0.00	0.03 ^a	0.03 ^{bc}	0.00	0.00
Poultry-broiler	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Poultry-layer	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

^a Highest maximum beef or dairy cattle dietary burden suitable for MRL 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

Farm animal feeding studies

The Meeting received a lactating dairy cow feeding study, which provided information on likely residues resulting in animal commodities and milk from etoxazole residues in the animals' diets.

Lactating dairy cows

Holstein dairy cows were dosed with etoxazole for 28 days at the equivalent of 1, 3 and 10 ppm in the diet. Residues of etoxazole were below the LOQ (0.01 mg/kg) in whole milk at the 1 and 3 ppm feeding levels. At the 10 ppm level, etoxazole residues in milk were the LOQ level from day 3 to day 27. Cream (day 27) from the 3 ppm level contained at the LOQ (0.02 mg/kg) level of etoxazole residues. Kidney and muscle contained no residue (< 0.005 mg/kg) of etoxazole at 1 and 3 ppm feeding levels, and the LOQ level from only one cow at the 10 ppm level. Liver contained etoxazole residues of the LOQ at the 3 ppm level, and 0.01–0.02 mg/kg at the 10 ppm level. Fat contained etoxazole residues of 0.01–0.02 mg/kg at the 1 ppm, 0.02–0.03 mg/kg at the 3 ppm and 0.06–0.11 mg/kg at the 10 ppm level respectively.

At the 10 ppm feeding level at day 27, etoxazole residue levels in milk were approximately 10% of the levels in cream.

Animal commodities maximum residue levels

For the estimation of maximum residue levels, the residue in the animal commodities is etoxazole.

The maximum dietary burden for beef and dairy cattle is 0.03 ppm, allowing residue levels to be obtained from the 1 ppm feeding level. In a feeding study, in which etoxazole equivalent to 1 ppm in the diet was dosed to lactating cows for 28 consecutive days, no etoxazole residues were detected in liver, kidney and muscle (< 0.01 mg/kg) and milk (< 0.01 mg/kg). Etoxazole residues in fat were < 0.01, 0.014 and 0.015 mg/kg at the 1 ppm level. Therefore no residues (< LOQ) are to be expected at the maximum estimated dietary burden of 0.03 ppm feed for beef cattle and dairy cattle.

The Meeting estimated a maximum residue level of 0.01 (*) mg/kg in mammalian meat and mammalian edible offal, and 0.01 (*) mg/kg in milk.

The mean estimated dietary burden for dairy cattle is 0.03 ppm. No etoxazole residues (< 0.01 mg/kg) were found in any samples of milk at the 1 ppm feeding level. Therefore the Meeting estimated an STMR of 0 mg/kg in milk.

The mean estimated dietary burden for cattle is 0.03 ppm. In muscle, kidney and liver, no etoxazole residues (< 0.01 mg/kg) were detectable at the 1 ppm feeding level. In fat, etoxazole residues above the LOQ (0.01 mg/kg) were found at the 1 ppm level, but no residues ($0.015 \times 0.03 = 0.0005$ mg/kg; LOD: 0.005 mg/kg) are expected to be detected in fat at the mean estimated dietary burden of 0.03 ppm. The Meeting estimated STMRs of 0 mg/kg in meat and offal and 0.0005 mg/kg of fat.

On the fat basis, the Meeting estimated a maximum residue level of 0.01 (*) mg/kg for meat (fat) from mammals (other than marine mammals) and an STMR value of 0.0005 mg/kg.

The maximum and mean dietary burden for broiler and layer poultry are 0.00 ppm. Therefore, no residues are to be expected at the estimated dietary burden for poultry.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Dietary Intakes (IEDIs) of etoxazole were calculated for the 13 GEMS/Food cluster diets using STMRs/STMR-Ps estimated by the current Meeting (Annex 3). The ADI is 0–0.05 mg/kg bw and the calculated IEDIs were 0–1% of the maximum ADI (0.05 mg/kg bw). The Meeting concluded that the long-term intakes of residues of etoxazole, resulting from the uses considered by current JMPR, are unlikely to present a public health concern.

Short-term intake

The 2010 JMPR decided that an ARfD was unnecessary. The Meeting therefore concluded that the short-term intake of residues of etoxazole is unlikely to present a public health concern.