Health Canada Santé Canada

Evaluation Report for Category A, Subcategory 1.3 Application

Application Number:	2008-0581
Application:	A.1.3, New Active Ingredient-Maximum Residue Limits (MRL)s only
Product:	Etoxazole Technical
Active ingredients (a.i.):	Etoxazole
PMRA Document Number:	1776498

Purpose of Application

Etoxazole is a technical grade active ingredient (TGAI) that is not currently registered in Canada. Valent USA Corporation wished to establish Maximum Residue Limits (MRLs) for etoxazole in grape, pome fruit, strawberry and tree nuts. Etoxazole Technical is the active ingredient in ZEAL WP Miticide, an etoxazole formulation, which is registered in the USA for use on the above mentioned crops. For specific details of uses, application rates and methods, precautions, restrictions, and personal protective equipment requirements, refer to the product label.

Chemistry Assessment

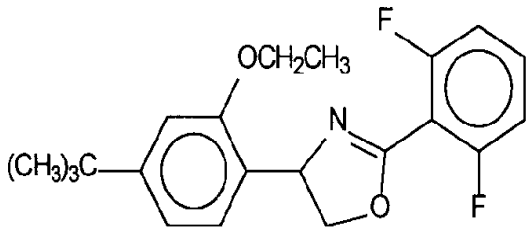
1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance:	Etoxazole
Function:	Insecticide
Chemical name:	
1. International Union of Pure and Applied Chemistry (IUPAC):	(*RS*)-5-*tert*-butyl-2-[2-(2,6-difluorophenyl)-4,5-dihydro-1,3-oxazol-4-yl]phenetole
2. Chemical Abstracts Service (CAS):	2-(2,6-difluorophenyl)-4-[4-(1,1-dimethylethyl)-2-ethoxyphenyl]-4,5-dihydrooxazole
CAS number:	153233-91-1
Molecular formula:	$C_{21}H_{23}F_2NO_2$
Molecular weight:	359.4

Canada

Structural formula:



Purity of the active ingredient: 97.2% (limits: 94.8-99.9%)

1.2 Physical and Chemical Properties of the Active Ingredient

Technical Product—Etoxazole Technical

Property	Result
Colour and physical state	White crystalline powder
Odour	No obvious odour
Melting range	101.5 to 102.5°C
Boiling point or range	The product is a solid
Specific gravity at 20°C	1.2389
Vapour pressure at 20°C	7.0×10^{-6} Pa
Henry's law constant at 20°C	3.574×10^{-2} Pa m^3/mole
Ultraviolet (UV)-visible spectrum	λmax(nm) Neutral 220 272 Acidic 222.5 272.5 Basic 272.5
Solubility in water	3.99×10^{-5} g/L in distilled water at 10°C 7.04×10^{-5} g/L in distilled water at 20°C 6.69×10^{-5} g/L in distilled water at 30°C
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) Acetone 309 1,2-Dichloroethane 402 Ethyl acetate 249 n-Heptane 18.7 Methanol 104 Xylene 252
n-Octanol-water partition coefficient (K_{ow})	log Kow = 5.52 at 20°C
Dissociation constant (pK_a)	Does not dissociate
Stability (temperature, metal)	The product was found to be stable under elevated temperature. The applicant stated that the TGAI was not tested for stability to metals since contact with metals in unlikely in normal product storage and use.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Etoxazole Technical have been validated and assessed to be acceptable for the determinations.

Health Assessments

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for etoxazole was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical pest control product.

Etoxazole was rapidly and moderately absorbed from the gastrointestinal tract of rats following oral dosing. The degree of absorption in males was approximately twice that in females, but there were no major sex-related differences in the pattern of excretion. Saturation of absorption occurred at high doses (500 mg/kg bw/day). Fecal excretion was the primary route of elimination, and excretion was essentially complete within 120 hours after dosing. The parent compound was the major component in the feces. Very little etoxazole was retained in the tissues, but repeated dosing of rats indicated some potential for accumulation.

Etoxazole was of low toxicity following a single dose by the oral route. 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 pathology (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 adaptative response of the liver to an increased metabolic demand 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 high doses for 18 months (and in rats in the second generation of the multigeneration reproduction study), and the degree of centrilobular hepatocellular hypertrophy was graded as severe only in high-dose dogs after 12 months of dosing. Generally, the macroscopic observation of liver enlargement was more evident in females than in males, while the microscopic observation of hepatocellular hypertrophy was more prominent in males. Necrosis of the liver was observed only in mice at doses approaching the limit dose. An increased incidence of hyperplasia of the bile duct was observed at high doses in female rats only after dosing for two

years. A special study revealed that drug metabolizing enzymes were not induced following exposure to etoxazole for four or 13 weeks.

Changes in the weights of some organs (e.g. decreased kidney and spleen weight in mice; increased adrenal gland, thyroid gland, and kidney weight in rats) were observed at high doses in the absence of corroborating evidence of toxicity. In addition, slight changes in haematology parameters (e.g. increased platelets; altered clotting time; decreased red blood cell count, hemoglobin, hemotocrit, and mean cell volume) were observed in rats and dogs. Both the organ weight changes and alterations in haematology parameters were deemed not to be toxicologically relevant.

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. Thickening and hyperplasia of the parietal bone was observed in rats only after chronic dosing at the highest dose tested.

Effects on organs of the reproductive system were observed in dogs and rats after repeated dosing. Decreased prostate weights and atrophy of the glandular epithelium of the prostate were noted in male dogs. In the male rat, an equivocal increase in the incidence of atrophy of the seminiferous tubules was observed after chronic dosing. However, special studies conducted to examined testicular function in the rat revealed that exposure to etoxazole did not affect the proliferative activity of testicular interstitial cells after four 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 in the rat.

No effect on reproduction was noted in the multigeneration reproduction study in the rat. However, there was an increase in the mortality rate of the offspring during early lactation in both generations at the highest dose tested. An increase in pup deaths as well as litters with pup deaths was observed at the highest dose tested. 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 weight (increased liver weight in males, increased adrenal gland weight in females) in the first generation and slight hepatotoxicity in males (increased liver weight, slight centrilobular hepatocellular fatty change in two males) of the second generation.

No developmental toxicity was observed when pregnant rats were dosed at the limit dose (1000 mg/kg bw/day) over the period of major organogenesis. Slight reductions in body weight and food consumption were observed in maternal animals at this dose. In rabbits, skeletal variations (increased fetal and litter incidences of 27^{th} presacral vertebra and 27^{th} presacral vertebra with a 13^{th} rib) were noted in fetuses following prenatal exposure to etoxazole at the limit dose, which produced effects on the pregnant rabbit in the form of liver enlargement in two dams as well as body weight decrements.

The clinical observations of the repeat-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 one year in the two-year study in rats, yielded negative results for neurotoxicity.

Overall, etoxazole does not appear to be genotoxic. Negative results were obtained in a battery of in vitro and in vivo genotoxicity studies, with the exception of positive and equivocal responses for gene mutations in mouse lymphoma in the presence and absence of external metabolic activation, respectively. Two carcinogenicity studies each were conducted in the rat and the mouse due to inadequate dosing in the initial studies. In the second mouse carcinogenicity study, dosing was still not sufficient to produce adverse effects. However, based on a weight of evidence evaluation, the study was considered acceptable for the assessment of carcinogenicity in mice. Overall, there was no evidence of carcinogenicity in either the rat or the mouse when the results from all of these studies are considered.

Results of the acute and repeated-dose tests conducted on laboratory animals with etoxazole, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Tables 1, 2, and 3 of Appendix I.

In assessing the occupational, residential, and dietary risks from potential exposure to etoxazole products, the standard uncertainty factor (UF) of 100 has been applied to account for interspecies extrapolation and intraspecies variability. Additional factors may also be applied, where warranted, to protect the population from relevant endpoints of concern or any database uncertainty.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act (PCPA)* requires the application of an additional 10-fold factor to take into account potential prenatal and postnatal toxicity and completeness of the data with respect to the exposure of and toxicity to infants and children. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the exposure of and toxicity to infants and children, the database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to identified concerns relevant to the assessment of risk to infants and children, no evidence of increased susceptibility was seen following in utero exposure to rats or rabbits in the developmental toxicity studies. However, a serious endpoint (reduced viability) was observed in offspring in the rat multigeneration reproduction study in the absence of adverse effects on the parents. On the basis of this information, the 10-fold factor required under the *Pest Control Products Act* was retained.

3.2 Determination of Acute Reference Dose

An acute reference dose was not established as no endpoint of concern attributable to a single oral dose was identified. In the developmental toxicity study in rabbit, the developmental NOAEL of 200 mg/kg bw/day was based on an increased incidence of skeletal variations (27 presacral vertebrae and 27 presacral vertebrae with 13^{th} ribs) in the fetuses at the LOAEL of 1000 mg/kg bw/day (limit dose). Although these developmental effects may be attributed to a single dose, it was determined that quantification of the acute risk is not required since these effects were considered minor in magnitude and were observed at the limit dose (1000 mg/kg bw/day).

3.3 Determination of Acceptable Daily Intake

The recommended acceptable daily intake (ADI) for etoxazole is 0.028 mg/kg bw/day. The most appropriate study for selection of a toxicity endpoint for chronic dietary exposure was the multigeneration reproductive toxicity study in the rat, in which a NOAEL of 28 mg/kg bw/day was determined in offspring based on an increased incidence of pup deaths between lactation days 0 and 4 and a reduced viability index observed at the LOAEL of 139 mg/kg bw/day.

Although the one-year dog study yielded the lowest NOAEL of the database (4.6 mg/kg bw/day), it was not considered to be appropriate for the determination of the ADI since it would not be protective of the critical endpoint of concern, i.e., reduced offspring viability.

Uncertainty factors of 10-fold for interspecies extrapolation as well as a 10-fold for intraspecies variability were applied in the setting of the ADI. As indicated above in the PCPA Hazard Characterization section, the 10-fold PCPA factor was retained. This results in a composite assessment factor (CAF) of 1000.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{28 \text{ mg/kg bw/day}}{1000} = 0.028 \text{ mg/kg bw/day of etoxazole}$$

The selected ADI provides a margin of 164 to the lowest NOAEL in the database (4.6 mg/kg bw/day in the one-year dog study), a margin of greater than 4000 to the NOAEL (64 mg/kg bw/day) for dental abnormalities in the rat, and a margin of greater than 13000 to the NOAEL (200 mg/kg bw/day) for skeletal variations in the rabbit developmental toxicity study.

3.4. Dietary Exposure Assessment

The qualitative nature of etoxazole in livestock and plants is adequately understood based on the submitted animal metabolism studies for goat and hen, and plant metabolism studies submitted for cotton, orange, eggplant, and apple. The general metabolic pathway in hen and goat involves cleavage of the parent molecule (with further oxidation in hen) to form various metabolites. In plants, photo-oxidation with further opening of the oxazole ring gives rise to an assortment of

metabolites. Based on these studies, the residue definition for etoxazole in/on plant and livestock matrices is outlined in Appendix I, Table 4.

The analytical methods (PMRA No. 1551094; 1551093; 1551092), using either gas chromatography with nitrogen-phosphorous specific flame-ionization detector (GC-NPD) or gas chromatography with mass selective detector (GC-MSD), are adequate to quantitate residues of etoxazole in/on the imported crops. Based on acceptable method validation and independent laboratory validation, these methods are deemed adequate for data gathering and enforcement purposes.

Frozen storage stability of etoxazole was demonstrated in more than five diverse matrices, ranging from 2-17 months, therefore providing confidence that residues will not decline to less than 70% of their original value under the actual storage intervals of the samples.

Crop field trials were conducted in NAFTA representative growing regions on grapes, apples, pears, almonds, pecans, strawberries, and cotton. Trials were conducted at 2-fold maximum label rates since they were completed before the U.S. established that a single application per season would be sufficient. U.S. data on the representative crops required for crop group 11 (pome fruits) and crop group 14 (tree nuts) were provided and summarized in Appendix I, Table 5.

Processing studies were conducted on cotton, apples, and grapes. Concentration was only observed in grape juice (1.2-fold) and raisins (4.7-fold). However, an MRL will only be required for raisins (1.5 ppm); residues in grape juice will be covered by the grape MRL. The processing factors for apple juice and cottonseed oil were 0.01-fold and 0.17-fold, respectively; therefore MRLs will not be required for the processed commodities of cotton and apple.

Based on the residue data provided, MRLs to cover residues of etoxazole in/on imported pome fruits (crop group 11), tree nuts, (crop group 14), grapes, strawberries, and cotton will be recommended as shown in Appendix I, Table 6.

The basic chronic dietary exposure assessment, using consumption estimates coupled with proposed MRLs, demonstrates that consumption of the above imported crops treated with etoxazole as per Good Agricultural Practices (GAP) will not pose a concern to human health for any segment of the population, including infants, children and seniors (Appendix I, Table 7).

Environmental and Value Assessment

Environmental and value assessments are not required for applications to establish import MRLs.

Conclusion

The toxicology database submitted for etoxazole is adequate to define the majority of toxic effects that may result from human exposure to etoxazole. In subchronic and chronic studies conducted with laboratory animals, the primary target was the liver. There was no evidence of carcinogenicity in rats or mice after longer-term dosing. There was no evidence of increased

susceptibility of the developmental toxicity studies, but effects in offspring were considered more serious than effects in parental animals in the reproductive toxicity study. Etoxazole was not considered to be genotoxic or neurotoxic.

Following the review of all available data, the MRLs have been proposed for residues of etoxazole in/on imported cottonseed, strawberries, grapes, apples, pears, pecans and almonds as according to the table below. Residues of etoxazole in/on the above mentioned imported crops will not pose an unacceptable risk to any segment of the population, including infants, children, adults and seniors.

Proposed MRL

Crop	Proposed MRL (ppm)
Cottonseed	0.05
Strawberries	0.50
Grapes	0.50
Apples	0.20
Pears	
Pecans	0.01
Almonds	

List of Abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
atm	atmosphere
bw	body weight
CAF	composite assessment factor
CAS	Chemical Abstracts Service
GAP	Good Agricultural Practices
g	gram(s)
ha	hectare(s)
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	octanol-water partition coefficient
L	litre(s)
LD	lethal dose
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
mg	milligram(s)
mL	millilitre
nm	nanometre
MRL	maximum residue limit
NAFTA	North American Free Trade Agreement
NOAEL	no observed adverse effect level
Pa	Pascal
PCPA	*Pest Control Product Act*
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
TGAI	technical grade active ingredient
USA	United States of America
UF	uncertainty factor
UV	ultraviolet

Appendix I Tables

TABLE 1 Acute Oral Toxicity of Etoxazole and its Metabolites

Study Type	Species	Result	Comment	Reference (PMRA #)
Acute Toxicity of Etoxazole				
Oral	Rat	LD_{50} > 5000 mg/kg bw	LOW TOXICITY	1550981
Oral	Mouse	LD_{50} > 5000 mg/kg bw	LOW TOXICITY	1550982
Acute Toxicity of Metabolites/Impurities				
Oral – R3	Rat	LD_{50} > 5000 mg/kg bw	LOW TOXICITY	1550983
Oral – R7	Rat	LD_{50} > 5000 mg/kg bw	LOW TOXICITY	1550984
Oral – R7	Rat	LD_{50} > 5000 mg/kg bw	LOW TOXICITY	1550985

TABLE 2 Toxicity Profile of Technical Etoxazole

Study Type	Species	Results[1] (mg/kg/day in M/F)	Reference (PMRA #)
28-day dietary	Rat	A NOAEL and LOAEL were not established as this was a dose range-finding study and was considered supplemental. No adverse effects were noted at 30/32 mg/kg bw/day in M/F. The following effects were noted at the next highest dose level of 151/161 mg/kg bw/day in M/F: increased triglycerides (F); increased cholesterol (F); increased BUN (M); liver enlargement; increased liver weight; centrilobular hepatocellular hypertrophy; increased adrenal gland weight (M).	1550994
28-day dietary Special study to assess testicular function	Rat	Overall, there did not appear to be a treatment-related effect on testicular function as measured in this study (serum levels of estradiol, prolactin, luteinizing hormone, and testosterone; microscopic examination of the testis and epididymides; cell index of germ cells; proliferative activity of testicular interstitial cells) up to a dose of 64 mg/kg bw/day.	1551005
90-day dietary	Rat	**NOAEL (M):** 61.8 mg/kg bw/day **LOAEL (M):** 184 mg/kg bw/day, based on decreased hematocrit and haemoglobin, increased cholesterol, increase liver weight, liver enlargement, and centrilobular hepatocellular hypertrophy **NOAEL (F):** 205 mg/kg bw/day (HDT) **LOAEL (F):** not established as no adverse effects were noted up to the highest dose tested	1550998

Study Type	Species	Results[1] (mg/kg/day in M/F)	Reference (PMRA #)
90-day dietary	Rat	**NOAEL:** not established as adverse effects were noted at the lowest dose tested **LOAEL:** 300/337 mg/kg bw/day in M/F, based on decreased hematocrit and mean cell volume (M); decreased prothrombin time (F); increased cholesterol; increased total protein (M) and globulin; increased platelets (F); increased liver weight; and centrilobular hepatocellular hypertrophy	1550993
90-day dietary Special study to assess the proliferative activity of testicular interstitial cells	Rat	No treatment-related effect on the proliferative activity of interstitial cells up to a dose of 184 mg/kg bw/day.	1551000
90-day dietary Special study to assess the induction of liver enzymes	Rat	No induction of liver enzymes (cytochrome P450, ethoxycoumarin-O-dealkylase, pentoxyresorufin-O-dealkylase) up to a dose of 201/134 mg/kg bw/day in M/F.	1550995
28-day dietary	Mouse	A NOAEL and LOAEL were not established as this was a dose range-finding study and was considered supplemental. No adverse effects were noted at 239/294 mg/kg bw/day in M/F. The following effects were noted at the next highest dose level of 1465/1476 mg/kg bw/day in M/F: decreased body weight and food conversion efficiency (M); increased ALK (M), AST and ALT; increased triglycerides (F); increased liver weight; liver dark in colour, decreased kidney weight (M).	1550996
90-day dietary	Mouse	**NOAEL:** 214/251 mg/kg bw/day in M/F **LOAEL:** 878/995 mg/kg bw/day in M/F, based on increased triglycerides (F); increased ALK, ALT (F), and AST (F); increased liver weight; centrilobular hepatocellular hypertrophy; periportal hepatocellular necrosis; decreased kidney weight (M).\	1550992

Study Type	Species	Results[1] (mg/kg/day in M/F)	Reference (PMRA #)
28-day dietary	Dog	A NOAEL and LOAEL were not established as this was a dose range-finding study and was considered supplemental. Adverse effects noted at 31/36 mg/kg bw/day in M/F, the lowest dose tested, included: increased ALK, increased liver weight, centrilobular hepatocellular hypertrophy.	1551001
90-day dietary	Dog	**NOAEL:** 5.3/5.4 mg/kg bw/day in M/F **LOAEL:** 53.7/55.9 mg/kg bw/day in M/F, based on mucous stool (M); increased triglycerides (M); increased ALK; increased liver weight; centrilobular hepatocellular swelling; decreased prostate weight; and prostate acinar cell atrophy	1551003
1-year dietary	Dog	**NOAEL:** 4.6/4.8 mg/kg bw/day in M/F **LOAEL:** 23.5/23.8 mg/kg bw/day in M/F, based on increased ALK; liver enlargement (F); increased liver weight; and centrilobular hepatocellular swelling	1551002
Carcinogenicity (18-month dietary)	Mouse	**NOAEL:** 241/243 mg/kg bw/day in M/F **LOAEL:** not established as no adverse effects were observed	1551009 1551010 1551011 1551012
Carcinogenicity (18-month dietary)	Mouse	**NOAEL (M):** 243 mg/kg bw/day **LOAEL (M):** 484 mg/kg bw/day, based on increased liver weight and centrilobular hepatocellular fatty change **NOAEL (F):** 482 mg/kg bw/day, the highest dose tested **LOAEL (F):** not established as no adverse effects were observed	1551016 1551017
Chronic/ Carcinogenicity (2-year dietary)	Rat	**NOAEL:** 64.4/64.5 mg/kg bw/day in M/F **LOAEL:** not established as no adverse effects were noted	1551018 1551019 1001021 1551022 1551024 1551025

Study Type	Species	Results[1] (mg/kg/day in M/F)	Reference (PMRA #)
Chronic/ Carcinogenicity (2-year dietary)	Rat	**NOAEL:** 1.8/2.1 mg/kg bw/day in M/F **LOAEL:** 187/216 mg/kg bw/day in M/F, based on emaciation (F); dental abnormalities; decreased body weight and body weight gain; decreased hematocrit (F), haemoglobin (F), and mean cell volume (M); increased platelets (F); increased activated partial thromboplastin time (M), increased cholesterol (M); increased total protein and albumin; increased thyroid weight (M); increased liver weight; and abnormal amelogenesis of the upper incisor	1551006 1551008
Two-generation reproduction	Rat	**Parental toxicity:** NOAEL (M): 35.6 mg/kg bw/day LOAEL (M): 157 mg/kg bw/day, based on increased liver weight and centrilobular hepatocellular fatty change NOAEL (F): 159 mg/kg bw/day LOAEL (F): not established as no adverse effects were noted **Offspring toxicity:** NOAEL: 28.2/33.4 mg/kg bw/day in M/F LOAEL: 139/159 mg/kg bw/day in M/F, based on increased pup mortality LD 0-4 **Reproductive toxicity:** NOAEL: 139/159 mg/kg bw/day in M/F LOAEL: not established as no adverse effects on reproduction were noted	1551030
Developmental toxicity	Rat	**Maternal:** NOAEL: 200 mg/kg bw/day LOAEL: 1000 mg/kg bw/day, based on decreased food consumption and body weight gain during treatment **Developmental:** NOAEL: 1000 mg/kg bw/day LOAEL: not established as no adverse effects were noted	1551032

Study Type	Species	Results[1] (mg/kg/day in M/F)	Reference (PMRA #)
Developmental toxicity	Rabbit	**Maternal:** NOAEL: 200 mg/kg bw/day LOAEL: 1000 mg/kg bw/day, based on decreased body weight gain, body weight loss, and liver enlargement **Developmental:** NOAEL: 200 mg/kg bw/day LOAEL: 1000 mg/kg bw/day, based on increased incidences of skeletal variations (27th presacral vertebra and 27th presacral vertebra with 13th rib)	1551036
Reverse gene mutation assay - TGAI	*S. thypimurium, E. Coli*	Negative	1551037 1551038
Reverse gene mutation assay - R3	*S. thypimurium, E. Coli*	Negative	1551040
Reverse gene mutation assay - R7	*S. thypimurium, E. Coli*	Negative	1551039
Reverse gene mutation assay - 2,5-YI	*S. thypimurium, E. Coli*	Negative	1551041
Gene mutations in mammalian cells in vitro	Mouse lymphoma cells	Positive in the presence of metabolic activation Equivocal in the absence of metabolic activation	1551042
In vitro/In vivo unscheduled DNA synthesis	Rat hepatocytes	Negative/Positive	1551043
In vitro mammalian chromosomal aberration	Chinese hamster lung cells	Negative/Positive	1551045
In vivo mammalian cytogenetics	Mouse	Negative/Positive	1551044
Metabolism		**Absorption** Absorption was rapid but moderate at low doses (48-68%) and limited at higher doses (15-19%), indicating saturation of absorption. Systemic absorption was greater in males (2-3x) than in females. **Distribution** Radioactivity remaining in tissues and the residual carcass by 168 hours post-dose accounted for 0.06-0.76% of the dose. Maximum concentrations of radioactivity in tissues were observed at 3-6 hours post-dose. Excluding the GIT, concentrations of radioactivity over time were generally highest in the liver, lymph nodes, thyroid, and fat and were	1551046 1551048

Study Type	Species	Results[1] (mg/kg/day in M/F)	Reference (PMRA #)
		lowest in the brain. Concentrations of radioactivity in tissues of males were generally 1.5-2x higher than in females. Repeated dosing of rats indicated some potential for accumulation. **Excretion** Fecal excretion was the primary route. Excretion was essentially complete by 120 hours post-dose. In the low-dose group, 77-88% of the dose was recovered in the feces and 8-17% recovered in the urine. In the high-dose group, 91-94% of the dose was recovered in the feces and 2-3% was recovered in the urine. **Metabolism** Etoxazole was eliminated primarily in the feces as parent compound (18-29% of the dose in feces for the low dose and 75-80% for the high dose).Two other minor metabolites were identified in the feces (R13 and R7). Two metabolites were identified in the urine of the rats dosed with the butylphenyl-label (R24 and Met 1); one metabolite was identified in the urine of rats dosed with the oxazole-label (R11). At the low dose, levels of Met 1 were higher in the urine of males than females, whereas levels of R24 were higher in the urine of females than males. Two additional metabolites were identified in the bile (R2 and Met 4). Parent and metabolite R2 were detected in plasma at Tmax (levels of the parent were higher in females, while levels of R2 were higher in males). Parent and five metabolites (R2, R6, R16, R24 and Met 1) were identified in the liver (Met 1 and R24 were detected only in the liver of rats dose with the butylphenyl-label). The biotransformation of etoxazole in rats primarily involves the hydroxylation of the 4,5-dihydrooxazole ring, followed by cleavage of the parent molecule, and hydroxylation of the tertiary-butyl side chain.	

1 Effects observed in males as well as females unless otherwise reported

TABLE 3 Toxicology Endpoints for Use in Health Risk Assessment for Etoxazole

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	CAF[1]
Chronic Dietary	NOAEL = 28	Multigeneration reproduction	Decreased offspring viability LD 0-4.	1000
	ADI = 0.028 mg/kg bw/day			

1 CAF = Composite Assessment Factor

TABLE 4 Summary of Residue Definition for Etoxazole

Matrix		Dietary Exposure Assessment	Enforcement	Reference (PMRA #)
Plants	Apple, Orange, Eggplant, Cottonseed	Etoxazole	Etoxazole	1551065, 1551067 1551069, 1551070
Livestock - Ruminant	Muscle, Fat, Milk	Etoxazole	Etoxazole	1551061
	Liver, Kidney	Etoxazole, Metabolite 1	Etoxazole	
Livestock - Poultry	Muscle, Fat, Eggs	Etoxazole	Etoxazole	1551062
	Liver, Egg Whites	Etoxazole, Metabolite R-16	Etoxazole	

TABLE 5 Summary of Etoxazole Residue Data from Crop Field Trials

Commodity[1]	Formulation	Total Rate (g a.i./ha)	PHI [2] (days)	Residue Levels					
				n	Min.	Max.	HAFT [3]	Mean	Std. Dev.
Pome Fruit (Crop Group 11) US label rate: 101-151 g a.i./ha/season; PHI = 14									
Pear	72% WDG	299-308	28	6	0.032	0.108	0.102	0.058	0.034
Pear	72% WDG	301	14	2	0.135	0.143	--	--	--
Apple	72% WDG	293-304	27-29	16	0.017	0.070	0.068	0.041	0.016
Apple	72% WDG	302	14	2	0.019	0.048	--	--	--
Comment: The majority of the pome fruit trials were conducted according to the originally registered US use pattern (28-day PHI). A label amendment was submitted by the applicant to shorten the PHI from 28 days to 14 days after the crop field trials were completed. Because this reduction in PHI is accompanied by the reduction in number of applications per season from 2 to 1, it is not expected that residues present in/on pome fruit harvested 14 days after application would exceed the recommended MRL of 0.20 ppm. Therefore, although the majority of the residue data reflect 28-day PHI, the residues following treatment at 101-151 g a.i./ha/season with a 14-day PHI will be covered by the proposed MRL.									
Tree Nut (Crop Group 14) US label rate: 101-151 g a.i./ha/season; PHI = 28									
Pecan	72% WDG	297-306	28	10	<0.01	<0.01	--	--	--
Almond	72% WDG	302-307	28	10	<0.01	0.01	0.01	--	--
Grape US label rate: 101-151 g a.i./ha/season; PHI = 14									
Grape	72% WDG	296-310	13-14	24	<0.005	0.330	0.270	0.058	0.071
Strawberry US label rate: 101-151 g a.i./ha/season; PHI = 1									
Strawberry	72% WDG	299-305	1	12	0.028	0.318	0.304	0.115	0.105
Cotton US label rate: 33-50 g a.i./ha/season									
Cottonseed	80% WP	99-103	27-28	14	<0.01	0.017	0.014	<0.01	0.004

1 residue data from processed food and feed (cotton, apples, grapes) and crop field trials (grapes, apples, strawberries, pears, almonds, and pecans): PMRA No. 1551103, 1551104, 1551105, 1551106, 1551107, 1551109 and 1551111

2 Pre-harvest Interval

3 Highest Average Field Trial

TABLE 6 Etoxazole MRL Calculations

Crop	Formulation	Rate (g a.i./ha)	PHI	n	MRL Calc. (ppm)	U.S. Tolerance (ppm)	Proposed MRL (ppm)
Cottonseed	80% WP	99-103	27-28	14	0.02	0.05	0.05
Strawberries	72% WDG	299-305	0-1	12	0.45	0.50	0.50
Grapes	72% WDG	296-310	13-14	24	0.30	0.50	0.50
Apples	72% WDG	293-304	28-29	16	0.15	Pome Fruits (CG 11) 0.20	Pome Fruits (CG 11) 0.20
Pears	72% WDG	301-308	28	6	0.20		
Pecans	72% WDG	297-306	28	10	NA	Tree Nuts (CG 14) 0.01 (LOQ)	Tree Nuts (CG 14) 0.01 (LOQ)
Almonds	72% WDG	301-307	28	10	NA		

TABLE 7 Summary of Chronic Dietary Exposure and Risk for Etoxazole

Population Subgroup	% ADI (Basic)
Total Population	2.6
All Infants (<1 year old)	4.5
Children 1-2 years old	11.8
Children 3-5 years old	8.1
Children 6-12 years old	3.6
Youth 13-19 years old	1.5
Adults 20-49 years old	1.7
Adults 50+ years old	2.0
Females 13-49 years old	1.6

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