Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2004-02

Lambda-cyhalothrin
Saber Insecticide Ear Tags

The end-use product, Saber Insecticide Ear Tags (containing 10% w/w lambda-cyhalothrin), for the control of horn and face flies on beef and non-lactating dairy cattle, is proposed for full registration under Section 13 of the Pest Control Products (PCP) Regulations.

This proposed regulatory decision document (PRDD) provides a summary of data reviewed and the rationale for the proposed full registration of this product. The Pest Management Regulatory Agency (PMRA) will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to the Publications Coordinator at the address below.

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Foreword

The submission for the conversion from temporary to full registration of the end-use product Saber Insecticide Ear Tags (containing the active ingredient lambda-cyhalothrin), an insecticide developed by Schering Plough Animal Health for use on beef and non-lactating dairy cattle for the control of horn and face flies, has been reviewed by the PMRA.

Health Canada's PMRA had previously issued a temporary registration (Regulatory Note REG2001-04) for this product with the requirement that Schering Plough Animal Health provide the following food residue chemistry data: a valid enforcement method capable of detecting residues of lambda-cyhalothrin and its associated epimer R157836 in animal tissues, freezer storage stability studies of the epimer R157836 in animal tissues, and additional livestock residue studies substantiating the low residues of lambda-cyhalothrin and its epimer R157836 in tissues of cattle exposed to ear tags. These have now been completed.

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCP Regulations and has found it sufficient pursuant to Section 18(*b*), to allow a determination of the safety, merit and value of the end-use product Saber Insecticide Ear Tags. The Agency has concluded that the use of the end-use product Saber Insecticide Ear Tags in accordance with the label directions has merit and value consistent with Section 18(*c*) of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18(*d*). Therefore, based on the considerations outlined above, the use of the end-use product Saber Insecticide Ears Tags is proposed for full registration, pursuant to Section 13 of the PCP Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

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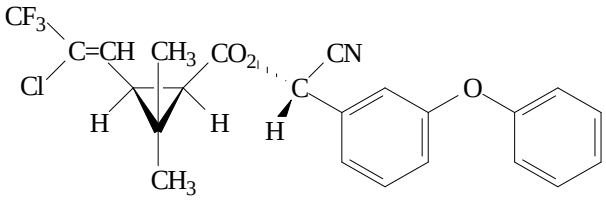
1.0 The active substance, its properties and uses

1.1 Identity of the active substance and impurities

Active substance:	Lambda-cyhalothrin
Function:	Insecticide
Chemical name:	
International Union of Pure and Applied Chemistry (IUPAC):	A reaction product containing equal quantities of (*S*)-α-cyano-3-phenoxybenzyl (*Z*)-(1*R*,3*R*)-3-(2-chloro-3,3,3-trifluoropropenyl) dimethylcyclopropanecarboxylate and (*R*)-α-cyano-3-phenoxybenzyl (*Z*)-(1*S*,3*S*)-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate
Chemical Abstract Services (CAS):	[1α(*S**),3α(*Z*)]-(±)-cyano(3-phenoxyphenyl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate
CAS No.:	91465-08-6
Molecular formula:	$C_{23}H_{19}ClF_3NO_3$
Molecular weight:	449.9
Structural formula:	 (*S*) (*Z*)-(1*R*)-*cis*
Minimum purity of active ingredient:	81.0%
PCP No.:	24567

1.2 Physical and chemical properties of active substances and end-use product

End-use product: Saber Insecticide Ear Tag

Property	Result
Colour	Blue-violet
Odour	Slight insecticide odour
Physical state	Solid
Formulation type	Insecticide in a plastic matrix
Minimum guarantee	Lambda-cyhalothrin: 10%
Formulants	The product does not contain any United States Environmental Protection Agency (USEPA) List 1 formulants or formulants known to be Toxic Substances Management Policy (TSMP) Track 1 substances as identified in Appendix II of Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*.
Container material and description	4 mL polyethylene pouch
Density	Not provided
pH	Product is a solid, insoluble in water.
Oxidizing or reducing action	Product does not contain any oxidizing or reducing agents.
Storage stability	Data showed that the product is stable at 50°C for three months and at ambient temperature for nine months when stored in commercial packaging.
Explodability	Product is not potentially explosive.

1.3 Details of uses

Saber Insecticide Ear Tag (10% weight/weight [w/w] lambda-cyhalothrin) will be used for season-long control of horn fly, *Haematobia irritans* (L.), and two-month control of face fly, *Musca autumnalis* DeGeer, on beef and non-lactating dairy cattle at a rate of one tag per animal.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

The methods for analysis of the active substance in the registered technical product of lambda-cyhalothrin have been submitted, reviewed and found acceptable for the analysis.

2.2 Method for formulation analysis

A gas chromatography (GC) method with flame ionization detection and internal standard quantitation was used to determine the level of active ingredient in this formulation. The method was fully validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for residue analysis

2.3.1 Multiresidue methods for residue analysis

The suitability and acceptability of existing multiresidue methods for the analysis of lambda-cyhalothrin and its epimer R157836 were not provided.

2.3.2 Methods for residue analysis of plants and plant products

Not applicable based on the nature of this submission.

2.3.3 Methods for residue analysis of food of animal origin

According to the livestock metabolism studies (lactating goat, lactating cow and laying hen) and the product chemistry of the TGAI, the residue of concern (ROC) is defined as lambda-cyhalothrin and its epimer R157836.

The analytical method INSECT-014-LAMBDACYHALOTHRIN, a gas chromatography with electron capture detection (GC/ECD) method using internal standardization, was developed to analyze residues of lambda-cyhalothrin and the epimer R157836 in bovine tissues. This method was used for data gathering in the livestock residue study and was proposed for enforcement. The method limit of quantitation (LOQ) was reported to be 0.05 ppm (0.018 ppm lambda-cyhalothrin and 0.031 ppm epimer R157836, given a 33:62 diastereoisomeric mixture of 95% purity) and the limit of detection (LOD) was reported to be 0.02 ppm (0.01 ppm lambda-cyhalothrin and 0.01 ppm epimer R157836) in muscle, fat, liver and kidney. Confirmation was run by gas chromatography with mass selective detection (GC/MSD) in either total ion or single ion mode, or by injecting the samples on an alternate column. Overall recoveries obtained during method validation for lambda-cyhalothrin and the epimer using bovine muscle, liver, kidney and kidney fat spiked at one-fold to eight-fold the LOQ were within guideline requirements of 70 to 120%.

The control chromatograms contained no peaks above the chromatographic background, and the spiked sample chromatograms contained only the analyte peaks of interest. The eluted peaks were well defined and symmetrical with no carry-over to the following chromatograms.

An independent laboratory validation of method INSECT-014-LAMBDACYHALOTHRIN was conducted by Enviro-Test Laboratories/Xenos Division using beef fat and beef muscle. Method validation performed by the independent laboratory demonstrated that when beef fat was spiked with lambda-cyhalothrin at 0.05 ppm and 0.2 ppm and with the epimer R157836 at 0.094 ppm and 0.376 ppm, the average recoveries were 101%, 116%, 109% and 116%, respectively. Overall mean recoveries were 108% ± 10 (relative standard deviation [RSD] = 9.3%) and 112% ± 6 (RSD = 5.3%) for lambda-cyhalothrin and the epimer R157836, respectively. Beef muscle spiked with lambda-cyhalothrin at 0.05 ppm, 0.2 ppm and 0.4 ppm gave average recoveries of 93%, 100%, and 114%. When spiked with the epimer R157836 at concentrations of 0.094 ppm, 0.376 ppm and 0.752 ppm, the average recoveries were 89%, 102% and 113%, respectively. Overall mean recoveries in beef muscle were 102% ± 10 (RSD = 10%) and 101% ± 12 (RSD = 12 %) for lambda-cyhalothrin and the epimer R157836, respectively. Although the method was not validated at the stated method LOQs (0.018 ppm lambda-cyhalothrin and 0.031 ppm for the epimer R157836), overall, the recoveries at all spiking levels were within the acceptable guideline requirement of 70 to 120%, thus demonstrating good reproducibility. Linear regression was used as this best fit the mode of calculation using a Varian GC/ECD instrument and the calibration curves constructed by plotting peak area vs standard concentration gave acceptable linearity, $r^2 = 0.9981$ and $r^2 = 0.9889$ for lambda-cyhalothrin and the epimer R157836, respectively. Control tissue of beef fat and muscle did not contain any interference at or near the retention times for either analyte. Therefore, method INSECT-014-LAMBDACYHALOTHRIN was proven to be acceptable for data gathering and enforcement purposes.

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

Lambda-cyhalothrin is a synthetic pyrethroid consisting of two of the four enantiomeric forms of cyhalothrin. The submission for technical grade lambda-cyhalothrin included toxicity studies with lambda-cyhalothrin and cyhalothrin. Core studies (chronic/oncogenicity studies, multigeneration reproduction study in rats, teratology studies in rats and rabbits) were conducted only with cyhalothrin and not with lambda-cyhalothrin. The acute, short-term and mutagenesis studies were carried out using both cyhalothrin and lambda-cyhalothrin. No acute toxicity studies were submitted for the end-use product, Saber Insecticide Ear Tags, and it was requested that the acute toxicity data from the TGAI be used for labelling purposes.

At the time of the original review, it was determined that there were sufficient data to demonstrate that the pharmacokinetics, metabolism and toxicity of cyhalothrin and lambda-cyhalothrin are similar. In short-term (90-day) studies in rats with both compounds, there was no difference in target organs or effect levels. Although clinical signs of toxicity were observed at lower dose levels in dogs that received lambda-cyhalothrin for 52 weeks, compared with dogs that received cyhalothrin for 26 weeks, the pattern of toxicity was similar for both compounds. Therefore, it was determined that the results obtained in the chronic toxicity/oncogenicity, teratology, and reproductive studies in the rat with cyhalothrin may be used to assess the toxicity of lambda-cyhalothrin.

A study conducted to compare the absorption, metabolism and excretion of lambda-cyhalothrin and cyhalothrin in the rat demonstrated that approximately 25 and 65% of a single oral dose of both chemicals was excreted in the urine and feces, respectively, within 72 hours. Levels of radioactivity in the tissues were similar, fat being the tissue with the highest concentration. Major metabolites were similar with both lambda-cyhalothrin and cyhalothrin, and included cyclopropylcarboxylic acid and its glucuronide conjugate, 3-phenoxybenzoic acid as well as 3,4'-hydroxyphenoxybenzoic acid and its sulphate conjugate.

Lambda-cyhalothrin is highly acutely toxic via the oral route of exposure in rats and mice. It is moderately acutely toxic to rats via both the dermal and inhalation routes of exposure. Lambda-cyhalothrin is mildly irritating to the eyes and not irritating to the skin of rabbits. The results of a sensitization study were equivocal, but Charge 100 EC, a formulation containing 100 g/L lambda-cyhalothrin, was a skin irritant and a sensitizer. In general, synthetic pyrethroids with similar chemical structures to lambda-cyhalothrin (i.e., cypermethrin, deltamethrin, etc.) are considered to be sensitizers. In a 21-day dermal study in rabbits with cyhalothrin only, skin irritation was the only effect observed at a limit dose of 1000 mg/kg bw/day.

In all the acute oral, dermal and inhalation studies, the overt signs of toxicity were characteristic of neurotoxic effects associated with the synthetic pyrethroids. However, no gross pathological lesions of the nervous tissues were observed.

In a subchronic (90-day) feeding study in rats with lambda-cyhalothrin, adaptive liver changes were observed at a dose of 12.5 mg/kg bw/day (no observable adverse effect level [NOAEL] of 2.5 mg/kg bw/day). In a one-year study in dogs, clinical signs that may indicate neurotoxicity (subdued behaviour, salivation, muscle tremors, severe ataxia and convulsions) were observed at the highest dose of 3.5 mg/kg bw/day (NOAEL = 0.5 mg/kg bw/day) without any corresponding neuropathology. This indicates that the dog is a more sensitive species than the rat to the toxic effects of lambda-cyhalothrin.

In long-term rodent studies, technical grade cyhalothrin was not oncogenic up to the highest dose tested in the rat or the mouse. The NOAEL in mice was 2 mg/kg bw/day, based on clinical signs in males (pilo-erection and aggressive behaviour) as well as increases in aspartate aminotransferase (AST)—both sexes and alanine aminotransferase (ALT)—females at the next highest dose. The NOAEL in rats was 2.5 mg/kg bw/day, based on a slight increase in mortality (males), decreases in body-weight gain (both sexes), alterations in clinical chemistry parameters, increased relative liver weight (both sexes) and increased absolute and relative adrenal weight (females). Lambda-cyhalothrin and cyhalothrin were both negative in a battery of genotoxicity studies (in vitro and in vivo).

In a three-generation reproduction study with cyhalothrin in rats, the NOAEL for both maternal and offspring toxicity was 0.6 mg/kg bw/day, based on decreased body weights in the dams and pups (during lactation) observed at the next highest dose (1.7 mg/kg bw/day). There was no indication of increased sensitivity of the young to exposure to lambda-cyhalothrin.

In teratology studies with cyhalothrin in rats and rabbits, no developmental effects were observed in either species. The maternal NOAEL in rats was 10 mg/kg bw/day, based on decreased body-weight gain and clinical signs of neurotoxicity observed in dams (lowest observed adverse effect level [LOAEL] = 15 mg/kg bw/day). The signs of neurotoxicity were observed in two animals between days 8-10 and days 12-18. The NOAEL for developmental effects was 15 mg/kg bw/day, the highest dose tested. No significant effects were observed in rabbits, with a NOAEL for maternal and developmental effects of 30 mg/kg bw/day. There was no indication of any increased sensitivity of the young to exposure to cyhalothrin.

In an acute neurotoxicity study conducted with lambda-cyhalothrin in rats, the NOAEL was 2.5 mg/kg bw, based on increased breathing rate observed in 5 males on day 2 and in 5 females on day 1 at the next highest dose (10 mg/kg bw). Clinical signs indicative of neurotoxicity (decreased activity, ataxia, reduced stability, salivation, piloerection, tiptoe gait, upward curvature of the spine, urinary incontinence and/or tremors) were observed in animals from both sexes at the highest dose (35 mg/kg) approximately 7 hours postadministration. Clinical signs of neurotoxicity, including decreased activity, ataxia, increased breathing rate, reduced stability and shaking, were also observed in some animals from either sex on days 2 and 3. All clinical signs were reversible by day 5 of the study. In addition, landing foot splay measurements were statistically significantly reduced on day 1 for males dosed with 35 mg/kg bw lambda-cyhalothrin. There were no corresponding alterations in brain weight, or gross and histologic neuropathology noted in any of the animals.

In a subchronic neurotoxicity study in rats, the NOAEL was 4.6/5.2 mg/kg bw/day (males/females, respectively) based on a decrease in body weight throughout the study period observed in males exposed to the next highest dose level (11.4/12.5 mg/kg bw/day for males/females, respectively). A decrease in food consumption was also observed at this dose level in both sexes for the first half of the study period. There were no treatment-related neuropathological effects observed at any dose level, in either sex.

No evidence for delayed neurotoxicity of cyhalothrin was observed in hens.

There is no evidence in the database to suggest lambda-cyhalothrin has any adverse effects on the endocrine or immune systems.

In both acute (rats and mice) and subchronic (dogs) toxicity studies, the primary endpoint of concern for lambda-cyhalothrin is clinical signs of neurotoxicity, characteristic of the neurotoxic effects associated with the synthetic pyrethroids. In addition, a teratology study in rats resulted in clinical signs of neurotoxicity (uncontrolled limb movements) observed in two dams. No corresponding neuropathology was observed, however, in the database.

Pyrethroid-induced paraesthesia (including symptoms of tingling, itching, numbness or a sensation of burning) is frequently seen after dermal exposure to pyrethroids in occupational settings. While large differences exist in individual susceptibility to paraesthesia, it can occur at doses lower than those causing central or system toxicity, and occurs as a result of a direct effect on intracutaneous nerve endings (Wilkes)[1]. In a dermal absorption study, lambda-cyhalothrin dermally applied to the backs of human volunteers resulted in symptoms of paraesthesia.

3.2 Determination of acceptable daily intake (ADI)

The acceptable daily intake is based on the NOAEL of 0.5 mg/kg bw/day from the 52-week dog study, with an uncertainty factor of 100×. The ADI is therefore 0.005 mg/kg bw/day. Effects observed at the LOAEL in this study included severe ataxia, convulsions, salivation, muscle tremors, auditory hyperaesthesia, subdued behaviour, vomiting, diarrhoea, decreased food consumption, decreased testes weight and slightly increased liver weights. The synthetic pyrethroid class of insecticides will be re-evaluated in the near future, at which time the ADI will be reassessed. A developmental neurotoxicity study will also be required in the future, based on the mode of action of the chemical.

[1] Wilkes, Martin F., (2000); "Pyrethroid-Induced Paresthesia - A Central or Local Toxic Effect?" *Clinical Toxicology*, 38(2).

3.3 Acute reference dose (ARfD)

The acute reference dose (ARfD) for lambda-cyhalothrin is 0.025 mg/kg bw, based on the NOAEL of 2.5 mg/kg bw from the acute neurotoxicity study in rats, and an uncertainty factor of 100× (10× for intraspecies variation and 10× for interspecies variation).

3.4 Toxicological endpoint selection—occupational and bystander risk assessment

The potential route of exposure to the active ingredient is limited to direct dermal contact. Exposure would occur once a year.

The registrant submitted a request to waive the acute toxicity data required for this end-use product on the basis that the Saber Insecticide Ear Tag consists of 1.29 g of lambda-cyhalothrin contained within an inert PVC matrix, and therefore, the only ingredient released is lambda-cyhalothrin. The toxicity data for the technical material (PCP No. 24567) have been used to support this registration.

Lambda-cyhalothrin is highly acutely toxic via the oral route of exposure in rats (lethal dose 50% [LD_{50}] of 79 and 56 mg/kg in males and females, respectively). It is moderately acutely toxic to rats via the dermal route of exposure (LD_{50} of 632 and 696 mg/kg in males and females, respectively). It is classified as a mild eye irritant in rabbits and is not irritating to rabbit skin. It is considered to be a potential skin sensitizer.

Although the technical material shows high acute oral toxicity, this route of exposure is not relevant for this agricultural-use pattern. For this reason, the acute dermal toxicity data are the most relevant data. These data were used in making labelling recommendations.

3.5 Impact on human and animal health arising from exposure to the active substance or to its impurities

3.5.1 Operator exposure assessment

A typical farmer would take 7 hours, once a year, to tag all animals in an average herd of 83 animals. The exposure is therefore considered to be acute in duration. The vapour pressure of the product is low (1.5×10^{-9} mm Hg); therefore, inhalation exposure would be negligible. The use of chemical resistant gloves should mitigate the potential dermal exposure. A quantitative risk assessment was not conducted.

3.5.2 Bystanders

Since the ear tags are slow release generators and are used only in agricultural application, bystander exposure will be negligible.

3.5.3 Workers

Postapplication exposure to the active ingredient is limited to the handling time during removal of the spent ear tags. The spent ear tags would typically contain very low concentrations of residual active ingredient. Potential exposure to the residual active ingredient should be minimized by wearing chemical resistant gloves when removing the used ear tags.

4.0 Residues

4.1 Residue summary

Nature of the residue in animals

The ruminant metabolism studies indicated that lambda-cyhalothrin was rapidly excreted, primarily as the unchanged parent compound. The parent compound was the predominant residue in muscle, fat, milk and egg yolks. In the liver and kidney, lambda-cyhalothrin was extensively metabolized to CPA (1RS-3-(ZE-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane carboxylic acid), HO-CPA (3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2- hydroxymethyl-2-methylcyclo-propanecarboxylic acid), 3-PBA (3-phenoxybenzoic acid) and 4'OH-3-PBA (3-(4'hydroxy)-phenoxybenzoic acid), suggesting that the parent undergoes hydrolysis of the ester linkage, followed by hydroxylation and conjugation of the cyclopropyl/benzyl moieties. While these metabolites represented the majority of the extractable residues in the tissues, based on the proposed Canadian-use patterns for lambda-cyhalothrin (oral exposure to treated feed and external exposure to ear tags), these residues are unlikely to be measurable. Therefore, these metabolites have not been included in the definition of the ROC.
The epimer R157836 was identified as an impurity of the TGAI, accounting for approximately 10% of lambda-cyhalothrin. Accordingly, the ROC was defined as lambda-cyhalothrin and its epimer R157836. The metabolism of lambda-cyhalothrin in animals is adequately understood.

Method of residue analysis of food of animal origin

The GC/ECD method INSECT-014-LAMBDACYHALOTHRIN was proposed for data gathering and enforcement purposes. The method LOQ was reported to be 0.05 ppm (0.018 ppm lambda-cyhalothrin and 0.031 ppm for the epimer R157836, based on a 33:62 diastereioisomeric mixture of 95% purity). This method was found to give acceptable recoveries of 74 to 102% and 75 to 107% for the analysis of lambda-cyhalothrin and the epimer R157836, respectively, in beef muscle, liver, kidney and kidney fat. The ILV demonstrated the reproducibility of the GC/ECD method INSECT-014-LAMBDACYHALOTHRIN to determine the residues of lambda-cyhalothrin and the epimer R157836 in livestock matrices.

Storage stability data—animals
Based on the freezer storage stability study of lambda-cyhalothrin in liver, kidney, muscle and fat samples and the rationale submitted to address the stability of the epimer R157836 in these animal tissues, residues of lambda-cyhalothrin and the epimer R157836 were determined to be stable in tissues stored for up to 250 days at -20°C. Since samples from the livestock residue trials (external applications) were stored for a maximum interval of 2 months, the residues of lambda-cyhalothrin and the epimer R157836 will not be adjusted to account for potential losses due to storage.

Livestock residue trials
The livestock residue trial indicated that residues of lambda-cyhalothrin in kidney, liver, muscle and fat did not exceed 0.05 ppm when animals were treated with two ear tags (each containing 10% w/w lambda-cyhalothrin) for 112 days and slaughtered immediately following removal of the tags (0-day preslaughter interval). Therefore, when beef and non-lactating dairy cattle are exposed to a single ear tag for up to four months and slaughtered immediately after removal of the ear tag (as per the proposed label), residues of lambda-cyhalothrin and the epimer R157836 in meat are not expected to exceed the current maximum residue limit (MRL) of 0.2 ppm. An MRL of 0.05 ppm is proposed for promulgation in Table II of Division 15 of the *Food and Drugs Act* and Regulations to cover the combined residues of lambda-cyhalothrin and the epimer R157836 in fat and meat by-products including liver and kidney.

Dietary risk assessment
The proposed use of Saber Insecticide Ear Tags (containing 10% w/w lambda-cyhalothrin) on beef and non-lactating dairy cattle in Canada does not pose an unacceptable chronic or acute dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors.

5.0 Fate and behaviour in the environment

Not applicable for ear tags.

6.0 Effects on non-target species

Not applicable for ear tags.

7.0 Efficacy

7.1 Effectiveness

Two field studies done in Canada to assess the control of horn fly and face fly on beef cattle by Saber Insecticide Ear Tags were submitted for review. To support these data, the applicant also submitted five studies from the United States, where ear tags containing lambda-cyhalothrin were used to control horn fly, and sometimes face fly, on cattle.

The submitted data support registration of Saber Insecticide Ear Tags for season-long control of horn fly. The submitted data also indicate Saber Insecticide Ear Tags provide adequate control of face flies for two months. The acceptable rate to control horn fly and face fly is one tag, containing 10% lambda-cyhalothrin, per animal.

7.2 Integrated pest management and the development of insecticide resistance

There is much evidence to indicate that horn flies develop resistance to insecticides administered through ear tags. Indeed, Canadian populations of horn flies were shown to be resistant to synthetic pyrethroid insecticides by 1991, six to seven years after the introduction of these compounds. Resistance has been exacerbated because most ear tagging programs use only synthetic pyrethroids and because horn flies spend almost all of their lives on cattle. Hence, the preconditions for the selection of horn fly resistance are in place. Given that resistance to pyrethroids is already present in horn fly, the label includes a resistance management statement, consistent with DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

8.0 Toxic substances management policy considerations

The product does not contain any USEPA List 1 formulants or formulants known to be TSMP Track 1 substances as identified in Appendix II of DIR99-03.

Although the *n*-Octanol–water partition coefficient (K_{ow}) of lambda-cyhalothrin is greater than 5.0, indicating a potential for bioaccumulation, the product will not enter the general environment under normal use conditions. The TGAI is contained in the plastic matrix of the ear tag, which is removed after use. The label includes instructions for proper disposal of the ear tag.

9.0 Proposed regulatory decision

9.1 Proposed regulatory decision

The PMRA has carried out an assessment of available information in accordance with Section 9 of the PCP Regulations and has found it sufficient, pursuant to Section 18(*b*), to allow a determination of the safety, merit and value of the end-use product, Saber Insecticide Ear Tags, manufactured by Schering Plough Animal Healths. The Agency has concluded that the use of the end-use product, Saber Insecticide Ear Tags, in accordance with the label directions has merit and value consistent with Section 18(*c*) of the PCP Regulations and does not entail an unacceptable risk of harm pursuant to Section 18(*d*). Therefore, based on the considerations outlined above, the use of the end-use product, Saber Insecticide Ear Tags for the control of face and horn flies on beef and non-lactating dairy cattle, is proposed for full registration, pursuant to Section 13 of the PCP Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

List of abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ALT	alanine aminotransferase
ARfD	acute reference dose
AST	aspartate aminotransferase
bw	body weight
CAS	Chemical Abstract Services
CODEX	Codex Alimentarius Commission
d	day(s)
DNA	deoxyribonucleic acid
ECD	electron capture detection
GC	gas chromatography
hr	hour
ILV	independent laboratory validation
IUPAC	International Union of Pure and Applied Chemistry
K_{ow}	*n*-octanol–water partition coefficient
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
MAS	maximum average score (at 24, 48 and 72 h)
MSD	mass selective detection
µg	microgram
MIS	maximum irritation score
MRL	maximum residue limit
N/A	not applicable
NOAEL	no observable adverse effect level
NZW	New Zealand white
PCP	pest control product
PMRA	Pest Management Regulatory Agency
ppm	parts per million
r	correlation coefficient
ROC	residue of concern
RSD	relative standard deviation
TGAI	technical grade active ingredient
TMP	trimethylpentane
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
v/v	volume/volume
w/w	weight/weight

Appendix I Summary of toxicity studies with lambda-cyhalothrin (with bridging of longer-term studies with cyhalothrin)

METABOLISM

Rate and extent of absorption and excretion: In rats, approximately 25 and 65% of a single oral dose of both cyhalothrin and lambda-cyhalothrin were excreted in the urine and feces, respectively, within 72 hours.

Distribution / target organ(s): Distribution was comparable for both cyhalothrin and lambda-cyhalothrin with fat > kidney > liver > blood.

Toxicologically significant compound(s): Major metabolites were similar for cyhalothrin and lambda-cyhalothrin. After administration of cyhalothrin, analysis indicated there was no unchanged cyhalothrin in urine or bile, and the feces contained largely unchanged cyhalothrin. Urine and bile metabolites were formed by hydrolysis of the ester bond and included cyclopropylcarboxylic acid and its glucuronide conjugate, 3-phenoxybenzoic acid, 3,4'-hydroxyphenoxybenzoic acid and its sulphate conjugate.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
ACUTE STUDIES: Lambda-cyhalothrin			
Oral (92.6% purity)	Rats, Alderley Park 5/sex/dose 29.7, 50.8, 62.5, 75.3, 94.1 mg/kg	LD_{50} = 54 (male, female)	**Highly toxic** — Most deaths occurred in first 24 hrs. Clinical signs included decreased activity, splayed gait, upward curvature of the spine, urinary incontinence, piloerection, salivation.
Oral (96% purity)	Rats, Alderley Park 5/sex/dose 11.3, 23, 24, 47, 102, 136, 137, 216 mg/kg	LD_{50} = 100 (male) LD_{50} = 59 (female) combined = 75 mg/kg	**Highly toxic** — Deaths occurred between days 1 and 3. Clinical signs at doses above 11.3 mg/kg included ataxia, dehydration, piloerection, signs of urinary incontinence, ungroomed appearance, upward curvature of the spine.
Oral (96.5% purity)	Mice, Alderley Park 5/sex/dose 1, 5, 25, 100 mg/kg	LD_{50} = 19.9	**Highly toxic** — Deaths occurred between days 1 and 5. Clinical signs at 25 mg/kg included piloerection, upward curvature of spine, ataxia and salivation. No signs at 100 mg/kg since deaths occurred on day 1 at this dose.
Dermal (92.6% purity)	Rats, Alderley Park 5/sex/dose 300, 600, 750, 900, 1200 mg/kg	LD_{50} = 632 (male) LD_{50} = 696 (female)	**Moderately toxic** — Deaths occurred within 2 to 3 days. Clinical signs included decreased activity, tiptoe gait, splayed gait, loss of stability, dehydration, signs of urinary incontinence, piloerection and upward curvature of spine.
Inhalation	Rats, Wistar-derived 5/sex/dose 0.015, 0.041, 0.071 mg/L	LC_{50} = 0.0648 mg/L (male, female)	**Moderately toxic** — Time of deaths was not stated. Clinical signs included red nasal discharge, chromodacryorrhea, subdued or agitated behaviour, hunched posture, piloerection, abnormal respiratory noise, tiptoe gait, reduced righting reflex.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Eye irritation	Rabbits, New Zealand White (NZW) (6 males) 100 mg test material	maximum average score (MAS) = 3.8 maximum irritation score (MIS) = 11.3	**Mildly irritating** — All scores were not zero by day 3
Primary skin irritation	Rabbits, NZW(6 females) 500 mg test material	MAS = 0 MIS = 1 (1hr)	**Non-irritating**
Skin sensitization (maximiza-tion test)	Guinea pigs, Hartley albino (males; 20 test animals, 10 controls)	Potential skin sensitizer	**Potential skin sensitizer**
SHORT-TERM TOXICITY: **Lambda-cyhalothrin**			
90-day dietary	Rats, Alpk/AP Wistar 20/sex/dose 0, 10, 50, 250 ppm (0, 0.5, 2.5, 12.5 mg/kg bw/day)	NOAEL = 2.5 mg/kg bw/day LOAEL = 12.5 mg/kg bw/day	**2.5 mg/kg and above** —⇑ hepatic aminopyrine-N-demethylase activity and ⇑ relative liver weights (considered adaptive responses) **12.5 mg/kg** — ⇓ bw gain and food consumption.
52-week oral (in corn oil via gelatin capsules)	Dogs, Beagle 6/sex/dose 0, 0.1, 0.5, 3.5 mg/kg bw/day	NOAEL = 0.5 mg/kg bw/day LOAEL = 3.5 mg/kg bw/day	**0.5 mg/kg** — slight increases in incidence of subdued behaviour and fluid feces **3.5 mg/kg** — severe ataxia, convulsions, salivation, muscle tremors, auditory hyperaesthesia, subdued behaviour, vomiting, diarrhoea; ⇓ food consumption; ⇓ testes weight and slightly ⇑ liver weights
SHORT-TERM TOXICITY: Cyhalothrin			
90-day dietary	Rats, Alpk/AP Wistar derived 20/sex/dose 0, 10, 50, 250 ppm (0, 0.5, 2.5, 12.5 mg/kg bw/day)	NOAEL= 2.5 mg/kg bw/day LOAEL= 12.5 mg/kg bw/day	**2.5 mg/kg** — ↓ in plasma triglycerides, ↑ hepatic aminopyrine-N-demethylase, mild proliferation of smooth endoplasmic reticulum (considered non-adverse responses) **12.5 mg/kg** — ⇓ bw gain in males
21-day dermal	Rabbits, NZW 5/sex/dose 10, 100, 1000 mg/kg bw/day	NOAEL (systemic effects) = 1000 mg/kg bw/day	**1000 mg/kg** — increased incidence of erythema and edema compared to controls; no systemic toxicity

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
26-week oral (in corn oil via gelatin capsule)	Dogs, Beagle 6/sex/dose 0, 1, 2.5, 10 mg/kg bw/day	NOAEL not determined	**1 mg/kg and above** — ⇑ incidence of diarrhoea (dose-dependent) **2.5 mg/kg and above** — ⇓serum albumin **10 mg/kg** — vomiting, unsteadiness, lack of coordination and excessive salivation
CHRONIC TOXICITY/ONCOGENICITY: Cyhalothrin			
2-yr dietary	Mice, Charles River 52/sex/dose 0, 20, 100, 500 ppm (0, 2, 10, 50 mg/kg bw/day) Four additional satellite groups of 12/sex/dose were sacrificed after 12 months	NOAEL = 2 mg/kg bw/day LOAEL = 10 mg/kg bw/day	**10 mg/kg** — piloerection and aggressive behaviour (males); ⇑ AST (males, females), ⇑ ALT (females). **50 mg/kg** — piloerection and aggressive behaviour (males), hunched posture (males, females), slightly ⇑ mortality (males), ⇓bw gain (males), ⇑ AST and ALT in plasma (males, females), ⇓ cholesterol (females), ⇓ total plasma protein and globulin (males) **Not oncogenic**
2-yr dietary	Rats, Alpk/AP, Wistar derived 62/sex/dose 0, 10, 50, 250 ppm (0, 0.5, 2.5, 12.5 mg/kg bw/day) Satellite groups of 10/sex/dose sacrificed at 12 months	NOAEL = 2.5 mg/kg bw/day LOAEL = 12.5 mg/kg bw/day	**2.5 mg/kg** — ⇓ bw gains (males), ⇓ total protein (females), ⇓ plasma cholesterol (males), ⇓ relative adrenal weight (all considered non-adverse) **12.5 mg/kg** — slight ⇑ mortality (males), ⇓ bw (males, females), ⇑ plasma AST (females), ⇑ total protein (females), ⇑ plasma cholesterol (males), ⇑ triglycerides (males, females), ⇓ urine volume (males, females), ⇑ relative liver weight (males, females), ⇑ absolute and relative adrenal weight (females) **Not oncogenic**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
REPRODUCTIVE / DEVELOPMENTAL TOXICITY: Cyhalothrin			
3-generation reproduction, dietary	Rat, Alpk/AP Wistar derived; 30♀/dose 0, 10, 30, 100 ppm (0, 0.6, 1.7, 5.5 mg/kg bw/day)	NOAEL (maternal) = 0.6 mg/kg bw/day LOAEL (maternal) = 1.7 mg/kg bw/day NOAEL (offspring) = 0.6 mg/kg bw/day LOAEL (offspring) =1.7 mg/kg bw/day	**1.7 mg/kg and above** — ⇓ bw gain in dams (10-15%) and pups (during lactation period) **5.5 mg/kg** — slight ⇓ in pup viability during lactation
Teratogen-icity, oral gavage	Rats, CD 24 females/dose 0, 5, 10, 15 mg/kg bw/day during days 6 to 15 of gestation.	NOAEL (maternal) = 10 mg/kg bw/day LOAEL (maternal) = 15 mg/kg bw/day NOAEL (developmental) = 15 mg/kg bw/day	**Maternal toxicity** **15 mg/kg** — ⇓ bw gain, uncoordinated limb movements **No evidence of teratogenicity**
Teratogen-icity, oral gavage	Rabbits, NZW 18-22 females/dose 0, 3, 10, 30 mg/kg bw/day during days 6 to 18 of gestation	NOAEL (maternal) = 30 mg/kg bw/day NOAEL (developmental) = 30 mg/kg bw/day	No significant effects on dams or fetuses were observed. **No evidence of teratogenicity**
NEUROTOXICITY: Lambda-cyhalothrin and cyhalothrin			
Acute neurotoxicity (lambda-cyhalothrin)	Rats, Alpk:AP_fSD 10/sex/dose 0, 2.5, 10, 35 mg/kg bw	NOAEL = 2.5 mg/kg bw LOAEL = 10 mg/kg bw	**10 mg/kg** — increased breathing rate in 5 males on day 2 and 5 females on day 1 **35 mg/kg** — Clinical signs indicative of neurotoxicity (decreased activity, ataxia, reduced stability, salivation, piloerection, tiptoe gait, upward curvature of the spine, urinary incontinence, and/or tremors) were observed in both sexes approximately 7 hours postdose. Signs were observed in some animals from either sex on days 2 and 3. All signs were reversible by day 5. Reduced landing foot splay measurements on day 1 for males.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Subchronic neurotoxicity (lambda-cyhalothrin)	Rats, Alpk:AP_fSD 12/sex/dose 25, 60, 150 ppm in diet (2.0, 4.6, 11.4 mg/kg bw/day in males, and 2.2, 5.2, 12.5 mg/kg bw/day in females)	NOAEL = 4.6/5.2 mg/kg bw/day (male/female) LOAEL = 11.4/12.5 mg/kg bw/day (male/female)	**11.4/12.5 mg/kg bw/day —** Decreased bw in males throughout the study period. Decreased food consumption in males and females for first half of the study.
Delayed neurotoxicity (cyhalothrin)	Hens, 10/dose Dosed singly at 0, 2 500, 5 000, 10 000 mg/kg bw then observed for 21 days 10 positive controls received tri-ortho cresyl phosphate at 500 mg/kg bw	N/A	**5000 mg/kg and above** — treatment-related decreases in bw No signs of neurotoxicity or histopathological changes in the spinal cord observed in any cyhalothrin-treated animals. Positive control animals developed ataxia and exhibited histopathological changes in the spinal cord.
Dermal absorption (cyhalothrin)	Human subjects (5) Single dermal dose of 20 mg/800 cm^2 applied to backs	N/A	All subjects reported symptoms of paraesthesia, including mild to moderate tingling sensation and mild itchiness and in some cases a warm feeling over the back. Mild irritation was noted in one subject over the whole back.

GENOTOXICITY: **Lambda-cyhalothrin**

STUDY	SPECIES/STRAIN OR CELL TYPE AND CONCENTRATIONS/DOSES EMPLOYED	RESULTS
Reverse mutation in bacteria	*Salmonella typhimurium*, TA1535, TA1537, TA1538, TA98, TA100. 1.6, 8.0, 40, 200, 1000, 5000 µg/plate ± S9 enzyme	Negative
In vitro chromosomal aberration	Human blood lymphocytes 100, 500, 1000 µg/mL ± S9 enzyme	Negative
In vitro unscheduled DNA synthesis	HeLa cells 1, 10, 100, 1000 µg/mL ± S9 enzyme	Negative
In vivo erythrocyte micronucleus assay	Mice (males, females, C57BL/6J), bone marrow 0, 22, 35 mg/kg bw/day	Negative

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
GENOTOXICITY: Cyhalothrin			
Reverse mutation in bacteria	*Salmonella typhimurium*, TA1535, TA1537, TA1538, TA98, TA100 4, 20, 100, 500, 2500 µg/plate ± S9 enzyme		Negative
In vivo chromosomal aberration	Male rats, bone marrow sampled at 6 and 24 hrs after treatment 1 or 5 consecutive oral dose of 0, 1.5, 7.5 mg/kg bw		Negative
In vivo dominant lethal assay	Male mouse (CD-1) 5 consecutive daily oral (gavage) doses of 0, 1, 5 or 10 mg/kg bw		Negative
ARfD: The ARfD is 0.025 mg/kg bw, based on the NOAEL of 2.5 mg/kg bw from the acute neurotoxicity study in rats and an uncertainty factor of 100× (10× for intraspecies variation and 10× for interspecies variation).			
ADI: The ADI is 0.005 mg/kg bw/day, based on the NOAEL of 0.5 mg/kg bw/day from the 52-week dietary dog study and an uncertainty factor of 100× (10× for interspecies extrapolation and 10× for intraspecies extrapolation). Further, the synthetic pyrethroid class of insecticides be re-evaluated in the near future, at which time the ADI will be reassessed.			

Appendix II Residues

Table 1 Integrated food residue chemistry summary

DIRECTIONS FOR USE OF LAMBDA-CYHALOTHRIN ON BEEF AND NON-LACTATING DAIRY CATTLE					
Trade name	Application timing, type and equipment	Application rate (g a.i./tag)	Max. number of applications per season	Preslaughter interval (days)	Use directions and limitations
Saber Insecticide Ear Tag	Use when flies are present. Controls horn fly for the season and face fly for up to two months.	0.95	1 tag/animal	0	Use on beef and non-lactating cattle only. Remove at the end of fly season or before slaughter.
PHYSICOCHEMICAL PROPERTIES					
Water solubility at 20°C (mg/L)	0.005				
Solvent solubility at 20°C (g/L)	Solvent Methanol Acetone Dichloromethane Toluene Ethyl acetate Hexane	Solubility > 500 > 500 > 500 > 500 > 500 > 500			
n-Octanol–water partition coefficient (Log K_{ow}) at 20°C	Log K_{ow} = 7				
Dissociation constant	pKa > 9, hydrolysis prevents measurement				
Vapour pressure	Vapour Pressure 2×10^{-4} mPa 2×10^{-1} mPa	Temperature (°C) 20 (estimated) 60 (interpolated)			
Relative density at 25°C (g/mL)	1.33				
Melting point (°C)	49.2				

ANALYTICAL METHODOLOGY	
Parameters	**Animal matrices**
Method ID	**INSECT-014-LAMBDACYHALOTHRIN**
Type	Data gathering and enforcement
Analytes	Lambda-cyhalothrin and the epimer R157836
Instrumentation	Gas chromatograph with electron capture detection (GC/ECD)
LOQ	0.018 ppm (lambda-cyhalothrin) and 0.031 ppm (R157836)
Standard	An analytical standard (95% purity) prepared in trimethylpentane (TMP) and containing lambda-cyhalothrin and the epimer R157836 in a 33:62 composition was used for method validation. An internal standard (R171544) was used as a retention time marker surrogate and eluted separately from the analytes of interest.
ILV	Independent laboratory validation [ILV], report XEN02-20, was conducted to verify the reliability and reproducibility of method INSECT-014-LAMBDACYHALOTHRIN for the determination of residues of lambda-cyhalothrin and the epimer R157836 in bovine tissues. The recoveries obtained are indicative that method INSECT-014-LAMBDACYHALOTHRIN is reproducible.
Extraction/clean-up	acetonitrile:water (85:15, v:v) and freezing overnight to extract out lipids/Revised Mills Column Clean-up Procedure
Multiresidue method	There is no information on file indicating that lambda-cyhalothrin and the epimer R157836 have been subjected to a recognized multiresidue method (CFIA or USFDA PAM Vol. I).

NATURE OF THE RESIDUE IN LAYING HEN			
Species	Dose level	Length of dosing (d)	Sacrifice
Hen	10.8 ppm ^{14}C-cyclopropyl-lambda-cyhalothrin	14	24 hours after last dose
	10.0 ppm ^{14}C-benzyl-cypermethrin (Note: the alcohol moiety of cypermethrin is identical to that of lambda-cyhalothrin)	14	4 hours after last dose

^{14}C-cyclopropyl-lambda-cyhalothrin was rapidly eliminated. At termination, 98-100% of the administered dose was excreta-related. Lambda-cyhalothrin residues in egg yolk peaked on day 7, at a maximum of 0.32 ppm. Residues in egg white never exceeded 0.01 ppm. ^{14}C-residues were highest in liver (0.60 ppm), followed by fat (0.46 ppm) and muscle (0.01 ppm).

^{14}C-benzyl labelled cypermethrin was rapidly eliminated. Four hours following the final dose, 91-99.5% of the administered dose was excreta-related. Residues of cypermethrin in egg yolk peaked on day 9, at a maximum of 0.19 ppm. Residues in egg white never exceeded 0.01 ppm. ^{14}C-residues were highest in liver (0.41 ppm), followed by fat (0.11 ppm) and muscle (0.025 ppm).

Radiolabel position	^{14}C-cyclopropyl-lambda-cyhalothrin		^{14}C-benzyl labelled cypermethrin	
Metabolites identified	**Major metabolites (> 10% TRRs)**	**Minor metabolites (< 10% TRRs)**	**Major metabolites (> 10% TRRs)**	**Minor metabolites (< 10% TRRs)**
Egg whites	not further analysed	not further analysed	not further analysed	not further analysed
Egg yolks	lambda-cyhalothrin (61% of the TRRs)	unidentified metabolite (7% of the TRRs), polar compounds (1% of the TRRs), hexane soluble radioactivity (9% of the TRRs)	cypermethrin (33% of the TRRs), hexane soluble radioactivity (66% of the TRRs)	3-PBA (2% of the TRRs)
Muscle	not further analysed	not further analysed	not further analysed	not further analysed
Fat	lambda-cyhalothrin (80% of the TRRs)	unidentified metabolite (9% of the TRRs), polar compounds (3% of the TRRs), water soluble radioactivity remaining after acid hydrolysis (1% of TRR)	cypermethrin (56-59% of the TRRs)	
Liver	CPA (51% of the TRRs), HO-CPA (10% of the TRRs)	unidentified metabolites (11% of the TRRs; each less than 10% of the TRRs), polar compounds (8% of the TRRs)	cypermethrin (16% of the TRRs)	3-PBA (up to 5% of the TRRs) 4'OH-3-PBA (less than 4% of the TRRs)

NATURE OF THE RESIDUE IN LACTATING GOAT			
Species	Dose level	Length of dosing (d)	Sacrifice
Lactating goat	10.8 ppm	7	16 hours after last dose

^{14}C-cyclopropyl-lambda-cyhalothrin was rapidly eliminated. At termination, approximately 71% of the administered dose was excreta-related (42% in urine and 29% in faeces). Residues in milk increased the first few days following dosing, reaching a peak level on the fifth day (0.27 ppm), and decreasing thereafter. ^{14}C-residues were highest in fat (0.44 ppm), followed by liver (0.34 ppm), kidney (0.20 ppm) and muscle (0.028 ppm).

Metabolites identified	Major metabolites (> 10% TRRs)	Minor metabolites (< 10% TRRs)
Radiolabel position	**^{14}C-cyclopropyl-lambda-cyhalothrin**	
Milk	lambda-cyhalothrin (99% of the TRRs)	
Muscle	lambda-cyhalothrin (94% of the TRRs)	
Fat	lambda-cyhalothrin (89% of the TRRs)	4 unidentified metabolites (10% of the TRRs)
Liver	CPA (mainly free, but some conjugated; 22% of the TRRs), HO-CPA (free and conjugated; up to 15% of the TRRs), water soluble radioactivity remaining after acid hydrolysis (25% of the TRRs)	lambda-cyhalothrin (6% of the TRRs), 5 characterized compounds (2% of the TRRs), unidentified organosoluble polar compounds (total of 12% of the TRRs)
Kidney	CPA (up to 58% of the TRRs; largely conjugated), water soluble radioactivity remaining after acid hydrolysis (11% of the TRRs)	lambda-cyhalothrin (2% of the TRRs), HO-CPA (free and conjugated; up to 7% of the TRRs), unidentified organosoluble polar compounds (up to 6% of the TRRs)

NATURE OF THE RESIDUE IN LACTATING COW (ORAL)			
Species	Dose level	Length of dosing (d)	Sacrifice
Lactating cow	10.8 ppm ^{14}C-benzyl-cypermethrin (Note: the alcohol moiety of cypermethrin is identical to that of lambda-cyhalothrin)	7	16 hours after last dose

^{14}C-benzyl-cypermethrin was rapidly eliminated. At termination, approximately 90% of the administered dose was excreta-related (46% in urine and 44% in faeces). Residues in milk increased the first few days following dosing, reaching a peak level on the seventh day (0.03 ppm), and decreasing thereafter. ^{14}C-residues were highest in liver (0.21 ppm), followed by kidney (0.11 ppm), fat (0.08 ppm) and muscle (0.01 ppm).

Metabolites identified	Major metabolites (> 10% TRRs)	Minor metabolites (< 10% TRRs)
Radiolabel position	**^{14}C-benzyl-cypermethrin**	
Milk	cypermethrin (90% of the TRRs)	
Muscle	not further analysed	not further analysed
Fat	cypermethrin (up to 80% of the TRRs)	2 unidentified metabolites (up to 10% of the TRRs)

Liver	3-PBA (56% of the TRRs), 4'OH-3-PBA (16% of the TRRs)	cypermethrin (0.5% of the TRRs), 3 unidentified metabolites (10% of the TRRs), polar compounds (5% of the TRRs), water soluble radioactivity (5% of the TRRs)
Kidney	3-PBA (59% of the TRRs), polar compounds (16% of the TRRs)	cypermethrin (0.7% of the TRRs), 4'OH-3-PBA (4% of the TRRs), unidentified metabolites (4% of the TRRs), polar compounds (16% of the TRRs), water soluble radioactivity (9% of the TRRs)

NATURE OF THE RESIDUE IN LACTATING COW (DERMAL)			
Species	Dose level	Length of dosing (d)	Sacrifice
Lactating Jersey cattle	0.36 mg ai/kg bw or 0.41 mg ai/kg bw	3	24 hours after final application

Excreta was not collected. Milk samples were collected twice daily until slaughter. Residues in milk increased during the study, reaching a maximum on the morning prior to slaughter. The radioactivity was largely, but not entirely, located in the butter prepared from the milk.

Metabolites identified	**Major metabolites (> 10% TRRs)**	**Minor metabolites (< 10% TRRs)**
Radiolabel position	**^{14}C-acid labelled lambda-cyhalothrin**	
Milk	lambda-cyhalothrin (92-100% of the TRRs)	
Muscle	lambda-cyhalothrin (% TRR not reported)	
Fat	lambda-cyhalothrin (85-92% of the TRRs)	up to 3 unidentified metabolites (each consisting less than 10% of the TRRs)
Liver	CPA (free and conjugated; 19% of the TRRs), HO-CPA (free and conjugated; 12% of the TRRs)	lambda-cyhalothrin (10% of the TRRs), unidentified metabolites (none accounting for more than 10% of the TRRs)
Kidney	lambda-cyhalothrin (37% of the TRRs), CPA (free and conjugated; 23% of the TRRs)	HO-CPA (5% of the TRRs), unassigned residues consisting of several metabolites (none comprising more than 8.5% of the TRRs)

LIVESTOCK RESIDUE TRIALS (EXTERNAL APPLICATION)						
Lambda-cyhalothrin residues (ppm) in bovine tissue samples following exposure to two Saber Insecticide Ear Tags (containing 10% w/w lambda-cyhalothrin); 0-day preslaughter interval						
	Days post-treatment					
Tissue	7	14	28	56	112	Control
Hair	18	20	7.9	8.7	1.5	< 0.05
Omental fat	0.07	0.05	0.067	0.054	< 0.05	< 0.05
Perirenal fat	0.059	0.05	0.066	0.068	< 0.05	< 0.05
Liver	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Kidney	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Muscle	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Table 2 Food residue chemistry overview of metabolism studies and risk assessment

ANIMAL STUDIES		
ANIMALS	**Poultry**	**Ruminant**
ROC FOR ENFORCEMENT	N/A	lambda-cyhalothrin and the epimer R157836
ROC FOR RISK ASSESSMENT	N/A	lambda-cyhalothrin and the epimer R157836
METABOLIC PROFILE IN ANIMALS	N/A	The metabolism consisted of cleavage of the ester linkage followed by hydroxylation and conjugation.
FAT SOLUBLE RESIDUE	N/A	lambda-cyhalothrin and the epimer R157836
DIETARY RISK FROM FOOD AND WATER		
The proposed use of the Saber Insecticide Ear Tags (containing 10% w/w lambda-cyhalothrin) on beef and non-lactating dairy cattle in Canada does not pose an unacceptable chronic or acute dietary (both food and water) risk to any segment of the population, including infants, children, adults and seniors.		