Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2001-04

Lambda-Cyhalothrin
Saber Insecticide Ear Tags

The end-use product Saber Insecticide Ear Tag, containing lambda-cyhalothrin for the control of horn fly and face fly on cattle, has been granted Section 17 temporary registration.

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision concerning this product.

(publié aussi en français)

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration for Saber Insecticide Ear Tag, an insecticide developed by Schering-Plough Animal Health for use on beef and non-lactating dairy cattle, which contains the active ingredient lambda-cyhalothrin effective against horn fly and face fly.

Schering-Plough Animal Health will be carrying out additional residue studies as a condition of this temporary registration. Following the review of these new data, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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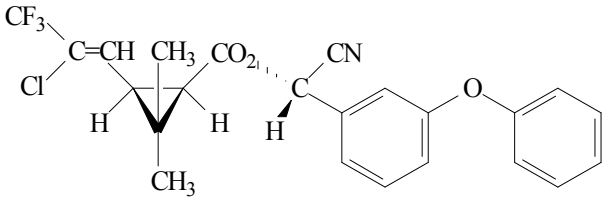
1.0 The active substance, its properties and uses

1.1 Identity of the active substance and impurities

Active substance:	Lambda-cyhalothrin
Function:	Insecticide
Chemical name:	
International Union of Pure and Applied Chemistry:	A reaction product containing equal quantities of (*S*)-"-cyano-3-phenoxybenzyl (*Z*)-(1*R*,3*R*)-3-(2-chloro-3,3,3-trifluoropropenyl) dimethylcyclopropanecarboxylate and (*R*)-"-cyano-3-phenoxybenzyl (*Z*)-(1*S*,3*S*)-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanecarboxylate
Chemical Abstract Services (CAS):	[1"(*S**),3"(*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	81.0%
Pest Control Product (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: 12.9% (proposed)
Formulants	The product does not contain any United States (U.S.) Environmental Protection Agency (EPA) 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 50EC 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 (12.9% w/w lambda-cyhalothrin) will be used for control of horn fly, *Haematobia irritans* (L.), and face fly, *Musca autumnalis* DeGeer, on beef and non-lactating dairy cattle.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

Not applicable, as technical active ingredient is already registered.

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 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 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 animal metabolism studies (lactating goat, lactating cow and laying hen) and the product chemistry of the technical grade active ingredient (TGAI), the residue of concern (ROC) is defined as lambda-cyhalothrin and its epimer. Three methods of analysis for the quantitation of lambda-cyhalothrin in animal matrices were submitted: the Plant Protection Division Residue Analytical Method No. 86 (PPRAM-86), used for the freezer storage stability study, an adapted version of the Braun and Stanek (1982) method and the actual published Braun and Stanek (1982) method, used for the supervised residue trials.

The PPRAM-86 analytical method determines residues of lambda-cyhalothrin in kidney, liver, muscle and fat using GC with electron capture detection (GC–ECD). An internal standard method was used as marker for retention time, response and calibration. The limits of quantitation (LOQ) were 0.01 ppm for tissues and 0.002 ppm for milk. Procedural method validation demonstrated that at spiking levels ranging from 0.005 to 5.0 ppm, the average recoveries in milk and tissues ranged from 84 to 92% with standard deviations of 16–22%, indicating acceptable repeatability. The chromatograms of the standard solutions were free from interference in the area of analytical interest and peak shapes were well defined and symmetrical. The detector response in matrix and solvent

was linear (correlation coefficient, $r > 0.99$) within the range of 0.05–5.0 ppm for lambda-cyhalothrin.

Schering Canada Inc. developed a GC–ECD analytical method (adapted from Braun and Stanek, 1982) to quantitate residues of lambda-cyhalothrin in kidney, liver, muscle, fat and hair of beef cattle and non-lactating dairy cattle. This method of analysis showed highly variable recoveries (42–172%) with high standard deviations (17–44%) and considerable background interferences in the representative chromatograms of control samples of kidney, liver, muscle and fat. There was no evidence that this method was capable of quantitating the components of the ROC. Based on these deficiencies, this method was deemed unsuitable for data gathering and enforcement.

The actual published Braun and Stanek (1982) method of analysis was used in the supervised residue trials to determine residues of lambda-cyhalothrin in kidney, liver, muscle and fat from animals treated with the Saber Insecticide Ear Tags. This GC–ECD multiresidue method permits the simultaneous determination of permethrin, cypermethrin and fenvalerate residues in animal tissues and the concurrent determination of organochlorine insecticides. The limit of detection was reported to be 0.005 ppm. Method validation indicated that recoveries, at spiking levels of 0.01, 0.1 and 1.0 ppm for each of the three pyrethrins in muscle, egg yolk and milk, averaged 82–97%. No internal or external standard method was used as a marker for retention time response and calibration.

No interlaboratory validation (ILV) was conducted for either of these three analytical methods; therefore, the reliability and reproducibility of these methods to quantitate the ROC (lambda-cyhalothrin and its epimer) in animal matrices were not demonstrated. Furthermore, in the absence of concurrent method validation of the Braun and Stanek data gathering method, the validity of the residue data was questionable, since it could not be determined whether the residues of lambda-cyhalothrin and its epimer were quantitated independently of the three pyrethrins (permethrin, cypermethrin and fenvalerate) and organochlorine insecticides.

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 lambda-cyhalothrin technical included toxicity studies with lambda-cyhalothrin and cyhalothrin. Core studies (chronic and oncogenicity studies, multigeneration reproduction study in rats, teratology studies in rats and rabbits) were conducted only with cyhalothrin rather than 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 are 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. In dogs, 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. It was determined, therefore, that the results obtained in the chronic toxicity and 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 were excreted in the urine and feces, respectively, within 72 h. 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, 3,4N-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 100EC, 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 all the acute oral, dermal and inhalation studies, the overt signs of toxicity were characteristic of neurotoxic effects associated with the synthetic pyrethroids. There were no gross pathological lesions, however, of the nervous tissues 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/d (no observable adverse effects level [NOAEL] of 2.5 mg/kg bw/d); whereas, 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/d (NOAEL = 0.5 mg/kg bw/d), 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 a 21-day dermal study in rabbits with cyhalothrin, skin irritation was the only effect observed at a limit dose of 1000 mg/kg.

In long-term rodent studies, cyhalothrin technical was not oncogenic up to the highest dose tested in the rat or the mouse. The NOAEL in mice was 2 mg/kg bw/d, based on clinical signs in males (piloerection and aggressive behaviour), and 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/d, 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/d, based on decreased body weights in the dams and pups (during lactation) observed at the next highest dose (1.7 mg/kg bw/d). 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/d, based on decreased body weight gain and clinical signs of neurotoxicity observed in dams (lowest observable adverse effect level [LOAEL] = 15 mg/kg bw/d). 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/d, the highest dose tested. No significant effects were observed in the rabbits, with a NOAEL for maternal and developmental effects of 30 mg/kg bw/d. There was no indication of any increased sensitivity of the young to exposure to cyhalothrin.

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, therefore, the primary end point 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. The toxicology database for lambda-cyhalothrin (including studies performed with cyhalothrin) does not contain acute or short-term neurotoxicity studies, or a developmental neurotoxicity study to further investigate this end point.

3.2 Determination of acceptable daily intake

The acceptable daily intake (ADI) for lambda-cyhalothrin established at the time of the original review is 0.005 mg/kg bw/d, based on the NOAEL of 0.5 mg/kg bw/d in the 52-week dog dietary study, and an uncertainty factor of 100 (10× for interspecies variation and 10× for intraspecies variation). To accommodate the current approach to risk assessment, using increased safety factors in the absence of acute, short-term and developmental neurotoxicity studies, an additional 3× uncertainty factor should be

employed to the existing ADI. The synthetic pyrethroid class of insecticides will undergo reevaluation in the near future, at which time the ADI will be considered.

3.3 Acute reference dose

An acute reference dose (ARfD) was not set at the time of the original review.

3.4 Toxicological end-point selection: occupational and bystander risk assessment

The potential route of exposure to the active 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 the 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, is not irritating to rabbit skin and is not a skin sensitizer in guinea pigs.

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 is the most relevant and was 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 h, 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

Post-application 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 should be minimized by wearing chemical resistant gloves when removing the used ear tags.

4.0 Residues

4.1 Residue summary

The ruminant, poultry, rat and dog 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, as supported by its lipophilic nature (*n*-octanol–water partition coefficient [K_{ow}] = log P = 7). In liver and kidney, the lambda-cyhalothrin was extensively metabolized to CPA (1*RS*-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 4NOH-3-PBA (3-(4Nhydroxy)-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 pattern for lambda-cyhalothrin (insecticidal ear tag), these residues are unlikely to exceed the method LOQ. The metabolites should not be included, therefore, in the definition of the ROC. The epimer was identified as an impurity of the TGAI, accounting for approximately 10% of lambda-cyhalothrin residues. Accordingly, the ROC was defined as lambda-cyhalothrin and its epimer.

A GC–ECD method (adapted from Braun and Stanek, 1982) was developed by Schering Canada Inc. to quantitate residues of lambda-cyhalothrin in kidney, liver, muscle, fat and hair of beef cattle and non-lactating dairy cattle. The method of analysis demonstrated highly variable recoveries (42–172%) with high standard deviations (17–44%) and considerable background interferences in representative chromatograms of control samples of tissues. In addition, the peaks of the standards, spiked and treated samples were not well defined or symmetrical. There was no evidence that this method was capable of quantitating residues of the epimer. Based on these deficiencies, therefore, this method was deemed unsuitable for data gathering and enforcement.

Samples of animal hair and tissues from cattle treated with Saber Ear Tags were analysed using the actual published Braun and Stanek (1982) GC–ECD method. This method allows the simultaneous determination of the residues of three synthetic pyrethrins (permethrin, cypermethrin and fenvalerate) in vegetable and animal tissues with the concurrent determination of organochlorine insecticides. The only difference between the Schering Canada Inc. method and the Braun and Stanek method is the extraction solvent (dichloromethane vs hexane) used in the liquid–liquid partitioning phase. Method validation indicated that recoveries, at spiking levels of 0.01, 0.1 and 1.0 ppm of each of the three pyrethrins in muscle, egg yolk and milk, averaged 82–97%. No internal or external standard method was used as a marker for retention time response and calibration.

Neither of these analytical methods was validated by an independent laboratory; therefore, the reliability and reproducibility of these methods to quantitate the components of the ROC (lambda-cyhalothrin and its epimer) in animal matrices was not demonstrated. Furthermore, in the absence of concurrent method validation of the Braun and Stanek data gathering method, the validity of the residue results was questionable, since it could not be determined whether the residues of lambda-cyhalothrin and its epimer were quantitated independently of the other pyrethrins (permethrin, cypermethrin and fenvalerate) and organochlorine insecticides.

The freezer storage stability study demonstrated that residues of lambda-cyhalothrin were stable in liver, kidney, muscle and fat samples stored for up to 250 days at –20EC. Since tissue samples from the supervised residue trials were stored within the time periods studied, the residues of lambda-cyhalothrin will unlikely need to be adjusted to account for potential losses due to storage. The ROC was defined as the parent and its epimer; therefore, the stability of the epimer in stored samples of animal matrices should be addressed.

The Saber Insecticide Ear Tag supervised residue trial indicated that residues of lambda-cyhalothrin in kidney, liver, muscle and fat did not exceed 0.1 ppm, when animals were treated for periods ranging from 7 to 112 days and slaughtered immediately following treatment. In the absence of concurrent method validation or ILV of the data gathering method, however, the residue data was deemed unacceptable.

Previously submitted data demonstrated that the depletion rate of lambda-cyhalothrin from ear tags was 41% over a period of four months. Based on the assumption that all the depleted active ingredient is absorbed by the animal, one animal exposed to two ear tags (1000 mg a.i./ear tag) could absorb up to 800 mg of active ingredient over a four-month treatment interval. If 90% of the absorbed dose is excreted within 72 h (as per the rat metabolism study), however, residues of lambda-cyhalothrin and its epimer in animal tissues are unlikely to exceed 0.2 ppm. Hence, when Saber Insecticide Ear Tags are used as per the proposed label (guarantee 12.9% w/w, two tags per animal, four-month treatment period, 0-day preslaughter interval), total residues in kidney, liver, muscle and fat of beef cattle and non-lactating dairy cattle will likely be covered under the current

maximum residue limit (MRL) of 0.2 ppm, established on meat and meat by-products of cattle, goats, hogs, horses and sheep. As a result, Saber Insecticide Ear Tags, containing lambda-cyhalothrin, can be granted a temporary registration, provided Schering Canada Inc. submits concurrent and ILV of the data gathering method. In addition, the registrant will need to generate residue data to substantiate the low residue levels of lambda-cyhalothrin and its epimer anticipated in tissues of animals exposed to the Saber Ear Tags.

The deficiencies in the analytical method and the freezer storage stability study resulted in invalid residue data and thus precluded the establishment of new MRLs for meat and meat by-products. The PMRA, however, has calculated a conservative estimate of residues that could be present in cattle meat. This calculated level is below the established MRL of 0.2 ppm that has an acceptable dietary risk.

Consequently, the proposed agricultural use of Saber Insecticide Ear Tags for the control of horn and face flies on beef cattle and non-lactating dairy cattle can only be supported on a temporary basis, provided the registrant addresses the deficiencies identified in the analytical methodology, freezer storage stability study and supervised residue trials.

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 Integrated efficacy summary

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 U.S. 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 (>90% reduction) of horn fly. The submitted data also indicate Saber Insecticide Ear Tags provide adequate control of face flies for two months only, but at a rate of one ear tag per animal rather than two ear tags per animal. The proposed rate of 12.9% lambda-cyhalothrin to control horn fly and face fly is higher that the 10% lambda-cyhalothrin shown to be effective. In the absence of a rationale to justify the need for a higher rate to control horn fly and face fly, there is no reason to support the 12.9 % rate, and therefore only the amount of insecticide in Saber Insecticide Ear Tags at 10% lambda-cyhalothrin is supported.

7.2 Integrated pest managment and the development of insecticide resistance

There is much evidence to indicate that horn fly develop resistance to insecticides administered through ear tags. Indeed, Canadian populations of horn fly were shown to be resistant to synthetic pyrethroid insecticides by 1991, six to seven years after the introduction of these compounds. This has been exacerbated because most ear tagging programs use only synthetic pyrethroids, and horn fly spend almost all of their lives on cattle. Hence, the preconditions for the selection of horn fly resistance are in place.

Because resistance to pyrethroids already is present in horn fly, it is unlikely that the proposed product would contribute in a meaningful way to a resistance management program. Indeed, there is every reason to expect that horn fly will develop resistance to lambda-cyhalothrin. To minimize this as a possibility, 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 EPA List 1 formulants or formulants known to be TSMP Track-1 substances as identified in Appendix II of DIR99-03.

Although the K_{ow} of lambda-cyhalothrin is $5.0, indicating a potential for bioaccumulation, under normal use conditions the product will not enter the general environment. The active is contained in the plastic matrix of the ear tag, which is removed after use. The label includes instructions for proper disposal.

9.0 Regulatory decision

Saber Insecticide Ear Tags at 10% lambda-cyhalothrin applied at a rate of one ear tag per animal, for the control of horn and face flies, has been granted a temporary registration for use on beef cattle and non-lactating dairy cattle, pursuant to Section 17 of the PCP Regulations, subject to the generation of the following studies: analytical methodology, freezer storage stability study and supervised residue trials.

List of abbreviations

a.i.	active ingredient
ADI	acceptable daily intake
ALT	alanine aminotransferase
ARfD	acute reference dose
AST	aspartate aminotransferase
bw	body weight
CODEX	Codex Alimentarius Commission
DNA	deoxyribonucleic acid
ECD	electron capture detection
EPA	Environmental Protection Agency
GC	gas chromatography
ILV	interlaboratory validation
K_{ow}	*n*-octanol–water partition coefficient
LD_{50}	lethal dose 50%
LOAEL	lowest observable adverse effect level
LOQ	limit of quantitation
MAS	maximum average score (at 24, 48 and 72 h)
Fg	micrograms
MIS	maximum irritation score
MRL	maximum residue limit
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
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
U.S.	United States
w/w	weight/weight

Appendix I Summary of the 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 h. **Distribution and 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, 3,4N-hydroxyphenoxybenzoic acid and its sulphate conjugate.			
STUDY	**SPECIES OR STRAIN AND DOSES**	**NOAEL and LOAEL (mg/kg bw/d)**	**TARGET ORGAN AND SIGNIFICANT EFFECTS AND 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 (**%**,**&**)	**Highly toxic**: most deaths in first 24 h. 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 (**%**) LD_{50} = 59 (**&**) 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.
Dermal (92.6% purity)	Rats, Alderley Park 5/sex/dose 300, 600, 750, 900, 1200 mg/kg	LD_{50} = 632 (**%**) LD_{50} = 696 (**&**)	**Moderately toxic**: Deaths occurred within 2–3 days. Clinical signs included decreased activity, tiptoe gait, splayed gait, loss of stability, dehydration, signs of urinary incontinence, piloerection, upward curvature of spine.
Inhalation	Rats, Wistar-derived 5/sex/dose 0.015, 0.041, 0.071 mg/L	lethal concentration 50% = 0.0648 mg/L (**%**, **&**)	**Moderately toxic**: Time of deaths not stated. Clinical signs included red nasal discharge, chromodacryorrhea, subdued or agitated behaviour, hunched posture, piloerection, abnormal respiratory noise, tiptoe gait, reduced righting reflex.
Eye irritation	Rabbits, New Zealand white (NZW) (6 **%**) 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

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Primary skin irritation	Rabbits, NZW (6 **&**) 500 mg test material	MAS = 0 MIS = 1 (1 h)	**Non-irritating**
Skin sensitization (Maximization test)	Guinea pigs, Hartley albino (**%**; 20 test animals, 10 controls)	Potential skin sensitizer	**Potential skin sensitizer**
SHORT-TERM TOXICITY: Lambda-cyhalothrin			
90-d dietary	Rats, Alpk/AP Wistar 20/sex/dose 0, 10, 50, 250 ppm (0, 0.5, 2.5, 12.5 mg/kg bw/d)	NOAEL = 2.5 mg/kg bw/d LOAEL = 12.5 mg/kg bw/d	**2.5 mg/kg and above**: 8hepatic aminopyrine-*N*-demethylase activity and 8relative liver weights (considered adaptive responses) **12.5 mg/kg**: 9bw 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/d	NOAEL = 0.5 mg/kg bw/d LOAEL = 3.5 mg/kg bw/d	**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, diarrhea; 9food consumption; 9testes weight and slightly 8liver weights
SHORT-TERM TOXICITY: Cyhalothrin			
90-d dietary	Rats, Alpk/AP Wistar derived 20/sex/dose 0, 10, 50, 250 ppm (0, 0.5, 2.5, 12.5 mg/kg bw/d)	NOAEL= 2.5 mg/kg bw/d LOAEL= 12.5 mg/kg bw/d	**2.5 mg/kg**: 9in plasma triglycerides, 8hepatic aminopyrine-*N*-demethylase, mild proliferation of smooth endoplasmic reticulum (considered non-adverse responses) **12.5 mg/kg**: 9bw gain in males
21-d dermal	Rabbits, NZW 5/sex/dose 10, 100, 1000 mg/kg bw/d	NOAEL (systemic effects) = 1000 mg/kg bw/d	**1000 mg/kg**: increased incidence of erythema and edema compared with controls; no systemic toxicity
26-week oral (in corn oil via gelatin capsule)	Dogs, Beagle 6/sex/dose 0, 1, 2.5, 10 mg/kg bw/d	NOAEL not determined	**1 mg/kg and above**: 8incidence of diarrhea (dose-dependent) **2.5 mg/kg and above**: 9serum albumin **10 mg/kg**: vomiting, unsteadiness, lack of coordination and excessive salivation

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
CHRONIC TOXICITY AND ONCOGENICITY: Cyhalothrin			
2-year dietary	Mice, Charles River 52/sex/dose 0, 20, 100, 500 ppm (0, 2, 10, 50 mg/kg bw/d) Four additional satellite groups of 12/sex/dose were sacrificed after 12 months	NOAEL = 2 mg/kg bw/d LOAEL = 10 mg/kg bw/d	**10 mg/kg**: piloerection and aggressive behaviour (**%**); 8AST (**%**, **&**), 8ALT (**&**) **50 mg/kg**: piloerection and aggressive behaviour (**%**), hunched posture (**%**,**&**), slightly 8mortality (**%**), 9bw gain (**%**), 8AST and ALT in plasma (**%**,**&**), 9cholesterol (**&**), 9total plasma protein and globulin (**%**) **Not oncogenic**
2-year dietary	Rats, Alpk/AP, Wistar derived 62/sex/dose 0, 10, 50, 250 ppm (0, 0.5, 2.5, 12.5 mg/kg bw/d) Satellite groups of 10/sex/dose sacrificed at 12 months	NOAEL = 2.5 mg/kg bw/d LOAEL = 12.5 mg/kg bw/d	**2.5 mg/kg**: 9bw gains (**%**), 9total protein (**&**), 9plasma cholesterol (**%**), 9relative adrenal weight (all considered non-adverse) **12.5 mg/kg**: slight 8mortality (**%**), 9body weight (**%**,**&**), 8plasma AST (**&**), 8total protein (**&**), 8plasma cholesterol (**%**), 8triglycerides (**%**,**&**), 9urine volume (**%**,**&**), 8relative liver weight (**%**,**&**), 8absolute and relative adrenal weight (**&**) **Not oncogenic**
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: Cyhalothrin			
3-generation reproduction, dietary	Rat, Alpk/AP Wistar derived 30 **&**/sex/dose 0, 10, 30, 100 ppm (0, 0.6, 1.7, 5.5 mg/kg bw/d)	NOAEL (maternal) = 0.6 mg/kg bw/d LOAEL (maternal) = 1.7 mg/kg bw/d NOAEL (offspring) = 0.6 mg/kg bw/d LOAEL (offspring) = 1.7 mg/kg bw/d	**1.7 mg/kg and above**: 9bw gain in dams (10–15%) and pups (during lactation period) **5.5 mg/kg**: slight 9in pup viability during lactation
Teratogenicity, oral gavage	Rats, CD 24 **&**/dose 0, 5, 10, 15 mg/kg bw/d during days 6–15 of gestation	NOAEL (maternal) = 10 mg/kg bw/d LOAEL (maternal) = 15 mg/kg bw/d NOAEL (developmental) = 15 mg/kg bw/d	Maternal toxicity: **15 mg/kg**: 9bw gain, uncoordinated limb movements **No evidence of teratogenicity**

STUDY	SPECIES OR STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN AND SIGNIFICANT EFFECTS AND COMMENTS
Teratogenicity, oral gavage	Rabbits, NZW 18–22 **&**/dose 0, 3, 10, 30 mg/kg bw/d during days 6–18 of gestation	NOAEL (maternal) = 30 mg/kg bw/d NOAEL (developmental) = 30 mg/kg bw/d	No significant effects on dams or fetuses were observed. **No evidence of teratogenicity**
NEUROTOXICITY: Cyhalothrin			
Delayed neurotoxicity	Hens, 10/dose Dosed singly at 0, 2500, 5000, 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.

STUDY	SPECIES OR STRAIN OR CELL TYPE AND CONCENTRATIONS OR DOSES EMPLOYED	RESULTS
GENOTOXICITY: Lambda-cyhalothrin		
Reverse mutation in bacteria	*Salmonella typhimurium*, TA1535, TA1537, TA1538, TA98, TA100 1.6, 8.0, 40, 200, 1000, 5000 **F**g/plate ± S9 enzyme	Negative
In vitro chromosomal aberration	Human blood lymphocytes 100, 500, 1000 **F**g/mL ± S9 enzyme	Negative
In vitro unscheduled DNA synthesis	HeLa cells 1, 10, 100, 1000 **F**g/mL ± S9 enzyme	Negative
In vivo erythrocyte micronucleus assay	Mice (**%**,**&** C57BL/6J), bone marrow 0, 22, 35 mg/kg bw/d	Negative
GENOTOXICITY: CYHALOTHRIN		
Reverse mutation in bacteria	*S. typhimurium*, TA1535, TA1537, TA1538, TA98, TA100 4, 20, 100, 500, 2500 **F**g/plate ± S9 enzyme	Negative
In vivo chromosomal aberration	Male rats, bone marrow sampled at 6 and 24 h 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: Not determined at time of original review
ADI: The ADI established at the time of the original review is 0.005 mg/kg bw/d, based on the NOAEL of 0.5 mg/kg bw/d from the 52-week dietary dog study and an uncertainty factor of 100. To accommodate the current approach to risk assessment, using increased safety factors in the absence of acute, short-term and developmental neurotoxicity studies, an additional 3× uncertainty factor should be employed to the existing ADI. The synthetic pyrethroid class of insecticides will undergo reevaluation in the near future at which time the ADI will be considered.

Appendix II Food residue chemistry summary

Parameter	Pertinent information
Chemical	Lambda-cyhalothrin
Formulation	Saber Insecticide Ear Tag (guarantee: 12.9% w/w)
Animals	Beef cattle and non-lactating dairy cattle
Type of application	Ear tags
No. of ear tags per animal	1 for the control of horn flies 2 for the control of face flies
Duration of treatment	3–4 months
Preslaughter interval	0 days
Nature of the residue in animals **Lactating cattle and goat and laying hen** **ROC**	The majority of the administered dose was excreta-related. Lambda-cyhalothrin was the predominant residue in muscle, fat, milk and egg yolks, as demonstrated by its lipophilic nature (K_{ow} = log P = 7). In liver and kidney tissues, the metabolites resulting from the cleavage of the ester linkage were identified as major residues. Based on the proposed Canadian use pattern for lambda-cyhalothrin (insecticidal ear tag), however, these residues are unlikely to exceed the method LOQ and therefore were not included in the definition of the ROC. The epimer was identified as an impurity of the TGAI, accounting for 10% of lambda-cyhalothrin. Parent and its epimer
Nature of the residue in plants **Crop radiolabelling positions proposed metabolic pathway** **ROC**	Not applicable, based on the nature of the submission

Parameter	Pertinent information
Residue analytical method: plant	Not applicable, based on the nature of the submission
Data gathering method	
LOQ	
Confirmation method	
Enforcement method	
ILV	
Residue analytical method: animal	ROC defined as parent and its epimer
Data gathering method	The published GC–ECD multiresidue method of Braun and Stanek (1982), used to simultaneously determine residues of permethrin, cypermethrin and fenvalerate in vegetable and animal tissues with concurrent determination of organochlorine insecticides, was assumed capable of quantitating residues of lambda-cyhalothrin in liver, kidney, muscle and fat.
LOQ	The LOQ was established at 0.005 ppm; however, there was no evidence that it relates to lambda-cyhalothrin.
Confirmation method	Confirmation of the three pyrethroids was obtained using GC and mass spectrometric detection. Data gathering method not suitable for enforcement
Enforcement method	Not performed. In the absence of concurrent method validation or ILV, the specificity of the Braun and Stanek method to quantitate the components of the ROC (lambda-cyhalothrin and its epimer) is questionable.
ILV	
Multiresidue method	Not provided
Storage stability data	Residues of lambda-cyhalothrin in kidney, liver, muscle and fat were stable at –20EC for up to 250 days. Stability of epimer in animal matrices was not addressed.

Parameter	Pertinent information
Meat, milk, poultry or eggs (external application)	Residues of lambda-cyhalothrin in kidney, liver, muscle and fat did not exceed 0.1 ppm when animals were treated with 2 ear tags for 7–112 days and slaughtered immediately following removal of the ear tags. The published Braun and Stanek method (1982) was used to determine residues of lambda-cyhalothrin; however, there was no evidence that the components of the ROC were quantitated. Residue data was unreliable, therefore, based on the lack of concurrent method validation or ILV. Based on the rate of depletion of lambda-cyhalothrin from ear tags (41% over a period of 4 months) and on the assumption that all the depleted active ingredient is absorbed by the animal, one animal exposed to 2 ear tags (10% w/w lambda-cyhalothrin equivalent to 1000 mg a.i./ear tag) could absorb up to 800 mg of active ingredient over a 4-month treatment interval. If 90% of the absorbed dose is excreted within 72 h (as per the rat metabolism study), however, residues of lambda-cyhalothrin and its epimer in animal tissues are unlikely to exceed 0.2 ppm. When used according to the proposed label, therefore, total residues will likely be covered under the current MRL of 0.2 ppm, established on meat and meat by-products of cattle, goats, hogs, horses and sheep. As a result, Saber Insecticide Ear Tags, containing lambda-cyhalothrin, can be granted a temporary registration, provided the registrant submits concurrent and ILV of the data gathering method and additional supervised residue trials substantiating the low residues of lambda-cyhalothrin and its epimer expected in tissues of cattle exposed to the ear tags.
Proposed MRLs	No new MRLs are being proposed, due to invalid residue data.
Proposed import tolerances	No import tolerances were proposed.
U.S. tolerances	Tolerances (established on the combined residues of lambda-cyhalothrin and its epimer) of 0.2 ppm in meat and meat by-products and 3.0 ppm in fat of cattle, goats, horses, hogs and sheep are a result of exposure to treated feed.
Codex MRLs	No Codex MRLs have been established for residues of lambda-cyhalothrin and its epimer.
Dietary risk assessment	New MRLs could not be established due to significant deficiencies in the analytical method resulting in invalid residue data. The PMRA, however, calculated a conservative estimate of residues that could be present in cattle meat. This calculated level is below the established MRL of 0.2 ppm, which has an acceptable dietary intake.