Proposed Registration Decision PRD2026-04

Etofenprox, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray

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Overview

Proposed Registration Decision for Etofenprox, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Etofenprox Technical, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray, containing the technical grade active ingredient etofenprox, to control arthropod pests in and on various structures, including buildings, modes of transportation, kennels, and pet bedding, by broadcast, spot, crack and crevice, perimeter, void, and furniture treatments.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This Overview describes the key points of the evaluation, while the Science evaluation provides detailed technical information on the human health, environmental and value assessments of etofenprox, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray.

What does Health Canada consider when making a registration decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to individuals and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children). They also consider the unique characteristics of organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and pest management portion of Canada.ca.

1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on etofenprox, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray, Health Canada's PMRA will consider any written comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on etofenprox, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What is Etofenprox?

Etofenprox is an insecticide that kills insects by contact or ingestion. It is an active ingredient in products used to kill structural pests found inside and/or on the exterior surfaces of commercial, industrial and residential structures and transportation vehicles.

Health considerations

Can approved uses of etofenprox affect human health?

Products containing etofenprox are unlikely to affect your health when used according to proposed label directions.

Potential exposure to etofenprox may occur when coming into contact with treated surfaces, or when handling and applying the end-use products. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are selected to protect the most sensitive human population (for example, children and nursing parents). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose level at which no effects are observed. The health effects noted in animals occur at dose levels more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the acute toxicity of etofenprox was low via the oral, dermal, and inhalation routes of exposure. Etofenprox was minimally irritating to the eyes and skin and did not cause an allergic skin reaction.

[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.
[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

The acute toxicity of the end-use product RF2129 EC containing etofenprox and piperonyl butoxide was slight via the oral route of exposure. RF2129 EC was also mildly irritating to the eyes and skin; consequently, the signal word "CAUTION" and the hazard statements "POISON" and "EYE AND SKIN IRRITANT" are required on the label. It was of low acute toxicity dermally and through inhalation exposure, and did not cause an allergic skin reaction.

The acute toxicity of the end-use product RF2220 Premium Aerosol II-M Premise Spray containing etofenprox, (s)-methoprene, tetramethrin, piperonyl butoxide, and pyrethrins was low via the oral, dermal, and inhalation routes of exposure. It was slightly irritating to the skin, non-irritating to the eyes and did not cause an allergic skin reaction.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature, were assessed for the potential of etofenprox to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment were effects on the eyes, kidneys, and nervous system, as well as survival of the young. There was no evidence to suggest that etofenprox damaged genetic material. Etofenprox did, however, cause thyroid tumours in rats and kidney tumours in mice. There was an indication that the young were more sensitive than the adult animal. The risk assessment protects against the effects noted above and other potential effects by ensuring that the level of exposure to humans is well below the lowest dose level at which these effects occurred in animal tests.

Health risks to workers

Occupational risks are not of health concern when RF2129 EC is used according to the proposed label directions, which include protective measures.

RF2129 EC is a commercial class end-use product formulated as an emulsifiable concentrate. Workers handling RF2129 EC can come in direct contact with etofenprox residues through the dermal and inhalation routes during mixing, loading, application, clean-up and repair activities. Health risks to workers were of concern when handling the standard amount of diluted product per day and wearing a single layer of personal protective equipment (PPE). As such, additional PPE and restrictions on the amount handled per day are required to mitigate risk (Appendix I, Table 4). It is also recommended that the applicator wear appropriate eye, head and respiratory protection when applying above waist height and in confined spaces. Taking into consideration the label precautionary statements, exposure to workers during handling activities are not of health concern.

Health risks in residential and other non-occupational environments

Risks to people in residential and other non-occupational environments are not of health concern when RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray are used according to the proposed label directions and precautionary statements.

RF2220 Premium Aerosol II-M Premise Spray is a domestic class end-use product and is applied by adults in residential environments. As such, adults may be exposed to etofenprox through the dermal and inhalation routes during application. RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray can be applied in residential areas, therefore, adults and children may be exposed to etofenprox residues by the dermal route from both end-use products when entering treated

areas. Children may also be exposed to etofenprox residues as a result of hand- or object-to-mouth transfer from treated surfaces. No risks of concern were identified through any route of exposure for any age group.

Aggregate health risks from dietary and residential exposures

Etofenprox is not proposed for use on food/feed crops so an aggregate assessment was not conducted.

As etofenprox is not proposed for use on food crops, dietary exposure (food + drinking water) is not expected. Therefore, an aggregate assessment (dietary + residential exposure) was not conducted.

Health risks to bystanders

Bystander risks are not of health concern when RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray are used according to the proposed label directions.

Label directions prohibit people (other than the applicator) and pets from being present during application. As such, bystander exposure is expected to be minimal, so health risks are not of concern.

Environmental considerations

What happens when etofenprox is introduced into the Environment?

When used according to label directions, risks associated with etofenprox and associated end-use products are acceptable from the viewpoint of environmental protection.

Etofenprox is for use as broadcast, spot, crack and crevice, perimeter void, and furniture treatments in and on non-food/non-feed areas of buildings, structures and modes of transportation to control a wide variety of arthropod pests using a low-pressure sprayer, void injector, or as an aerosol spray where the product is applied directly to the target pests. As such, environmental releases are expected to be minimal, and a quantitative risk assessment was not conducted. Moreover, exposure to non-target organisms is unlikely and risks to the environment are not expected when the end-use products**,** RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray, are used according to label directions.

Value considerations

What is the value of RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray?

They are a low-pressure sprayer and void injector or aerosol spray to kill a variety of structural pests (for example, ants, cockroaches, ticks, wasps) inside and/or on the exterior surfaces of structures and vehicles.

These products kill labelled structural pests when applied as broadcast sprays, spot treatments, void injections, indoor perimeter treatments and/or crack and crevice treatments. RF2129 EC is a commercial class product and RF2220 Premium Aerosol II-M Premise Spray is a domestic class product. Some of these pests, such as cockroaches, impact the health and well-being of people.

Measures to minimize risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human health and the environmental. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Etofenprox Technical, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human Health

Health risks to workers were of concern when handling the standard amount of diluted product per day and wearing a single layer of personal protective equipment (PPE). As such, additional PPE and restrictions on the amount handled per day are required to mitigate risk (Appendix I, Table 4).

Environment

A label statement indicating toxicity to aquatic organisms is required.

Next steps

Before making a final registration decision on etofenprox, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray, Health Canada's PMRA will consider any written comments received from the public in response to this consultation document up to 30 days from the date of publication (by 11 April 2026) of this document. If more time is required to provide comments, a request for an extension of an additional 15 days can be made. Your request must be submitted in writing to the PMRA's Publications Section (pmra.publications-arla@hc-sc.gc.ca) within the 30-day consultation period.

Please forward all comments to PMRA Publications, through the Public Engagement Portal (Public Engagement Portal forms – Consultation Comment). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada's response to these comments.

Other information

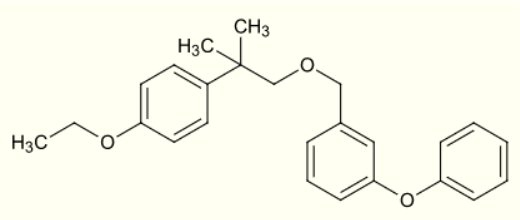
When the Health Canada makes its registration decision, it will publish a Registration Decision on etofenprox, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray (based on the Science evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

Science evaluation

Etofenprox

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Etofenprox
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	1-{[2-(4-ethoxyphenyl)-2-methylpropoxy]methyl}-3-phenoxybenzene
2. Chemical Abstracts Service (CAS)	1-[[2-(4-ethoxyphenyl)-2-methylpropoxy]methyl]-3-phenoxybenzene
CAS number	80844-07-1
Molecular formula	$C_{25}H_{28}O_3$
Molecular weight	376.5
Structural formula	
Purity of the active ingredient	99.7 %

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product — Etofenprox Technical

Property	Result
Colour and physical state	White crystals
Odour	Odourless
Melting range	36.4–38.0°C
Boiling point or range	Decomposes at 200°C
Density	1.157 g/mL
Vapour pressure at 25°C	0.813 µPa

Property	Result
Ultraviolet (UV)-visible spectrum	Solution in methanol — λ_{max} (nm) — Log ε Neutral — 273.6 — 3.54 pH = 12 — 273.2 — 3.53 pH = 1 — 273.2 — 3.54 No absorption above 300 nm
Solubility in water at 25°C	< 0.1 ppm
Solubility in organic solvents at 20–25 °C	Solvent — Solubility (g/L) acetone — 877 dichloromethane — 924 ethanol — 98 ethyl acetate — 837 heptane — 621 hexane — 667 methanol — 49 toluene — 862 xylene — 856
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 6.9
Dissociation constant (pK_a)	Not applicable
Stability (temperature, metal)	Stable at 150°C; photodegradation DT_{50} is 2 days at 25°C.

End-Use Product— RF2129 EC

Property	Result
Colour	Clear, light amber
Odour	Chemical odour
Physical state	Liquid
Formulation type	Emulsifiable concentrate
Label concentration	Etofenprox ……... 16.2 % Piperonyl butoxide ... 64.8 %
Container material and description	Plastic jug
Density	1.034 g/mL at 20°C
pH	5.09
Oxidizing or reducing action	The product contains no oxidizing or reducing agents.
Storage stability	Stable when stored in plastic (Nyalene and HDPE) bottles for 12 months at warehouse/ambient temperature.
Corrosion characteristics	No adverse effects were noted to the plastic (Nyalene and HDPE) bottles over 12 months of storage at warehouse/ambient temperature.
Explodability	Not applicable

End-Use Product— RF2220 Premium Aerosol II-M Premise Spray

Property	Result
Colour	White
Odour	Weak/none, neutral paint-like
Physical state	Liquid
Formulation type	Pressurized product
Label concentration	Etofenprox …… 1 % S-methoprene …… 0.09 % Pyrethrins …….. 0.15 % Piperonyl butoxide …… 1.50 % Tetramethrin ……...0.25 %
Container material and description	Aerosol can
Density	0.9671 g/mL at 20°C
pH	6.50
Oxidizing or reducing action	The product contains no oxidizing or reducing agents.
Storage stability	Stable when stored in a steel can (commercial packaging) at warehouse conditions and 40°C for twelve months.
Corrosion characteristics	No changes to the steel can (commercial packaging) were observed when stored at warehouse conditions and at 40°C for twelve months.
Explodability	Product is explosive as its contents are under pressure and it contains a propellant.

1.3 Directions for use

RF2129 EC (low-pressure spray or void injection)

Apply a 0.25% etofenprox solution (15.6 mL product per L of water) per 93 m^2 as a broadcast spray (general surface), as a spot treatment (not more than 0.2 m^2 spots), injected into voids, along indoor perimeters (less than 0.1 m wide along edges of room), or as a crack and crevice treatment. Apply to areas where target pests hide, such as baseboards, corners, storage areas, closets, around water pipes, doors and windows, attics and eaves, behind and under refrigerators, cabinets, sinks, furnaces, and stoves, the underside of shelves, drawers and similar areas. Pay particular attention to cracks and crevices.

RF2220 Premium Aerosol II-M Premise Spray (spot spray or crack and crevice treatment)

For broadcast application, from a distance of 90 cm (3 feet), using a sweeping motion, apply a light, uniform spray to all surfaces. For application as a crack and crevice spray, spray at a rate of 6.5 seconds per linear metre (2 seconds per linear foot). For application as a spot spray, treat surface until slightly wet.

1.4 Mode of action

Etofenprox is a pyrethroid-like ether insecticide and is classified as IRAC (Insecticide Resistance Action Committee) Mode of Action (MOA) group 3A. The pesticidal MOA of etofenprox is similar to that of pyrethroids, as it acts on sodium channels of the insect nervous system by disturbing the normal neurotransmission.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

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

2.2 Method for formulation analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for residue analysis

Not applicable

3.0 Impact on human and animal health

3.1 Toxicology summary

Etofenprox is a pyrethroid-like ether insecticide and is classified as IRAC Mode of Action (MOA) group 3A. The pesticidal MOA of etofenprox is similar to that of pyrethroids, as it acts on sodium channels of the insect nervous system by disturbing the normal neurotransmission. However, it differs in structure from pyrethroids in that it lacks a carbonyl group, and instead of an ester bond between the acid and alcohol moiety, it contains an ether bond. Additionally, etofenprox does not show stereoisomerism.

A detailed review of the toxicology database for etofenprox was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Additional studies included three special studies assessing developmental and reproductive toxicity with exposures during the pre-mating, gestational, or lactational periods; immunotoxicity studies conducted in the rat and the mouse; a mechanistic study investigating thyroid function and hepatic microsomal enzyme induction; and a comparative thyroid assay examining thyroid hormones in maternal animals, fetuses and offspring. The required studies were carried out in accordance with accepted international testing protocols in place at the time of conduct and Good Laboratory Practices. The human health risk assessment also considered any relevant information found in the published literature, which was limited to one study examining liver tumour-promoting effects in rats. The scientific quality of the data is acceptable and the database is considered adequate to characterize the potential health hazards associated with etofenprox.

The metabolism and toxicokinetics of etofenprox in the rat were investigated in two studies: one following the administration of a single oral dose of etofenprox radiolabelled at the α-^{14}C-benzyl moiety; and one following the administration of a single oral dose, as well as repeat dosing with a 1:1 mixture of etofenprox radiolabelled at the α-^{14}C-benzyl and 1-^{14}C-propyl moieties, or only with 1-^{14}C-propyl in the case of the bile duct-cannulated group. Peak plasma concentrations were reached within 3-5 hours after a single gavage dose. Absorption was incomplete, with estimates of 23% of the administered dose (AD) in low-dose intact rats (based on the radioactivity recovered after 48 hours in urine, cage wash, tissues, and carcass), and estimates of 20% and 39% of the AD in low-dose, and 14% and 13% of the AD in high-dose bile duct-cannulated male and female rats, respectively (based on radioactivity levels after 48 hours in urine, tissues, and bile). The study authors estimated that with additional considerations for the proportion of fecal radioactivity associated with metabolites in intact rats, absorption would be at least 65% of the AD at the low dose, and 58 and 48% of the AD at the high dose for males and females, respectively. This estimate was not considered to be appropriate, due to the difficulty in determining whether the presence of a metabolite in feces indicates that it was metabolized systemically after absorption or not. Furthermore, the estimate of fecal radioactivity stemming from absorbed etofenprox in intact rats contradicts the results from the bile duct-cannulated rats, which are more consistently relied upon to accurately determine oral absorption. Therefore, the estimate of approximately 30% oral absorption from low-dose bile duct-cannulated rats is considered to be the most appropriate for consideration in the hazard characterization, as the low dose of 30 mg/kg bw was more comparable than the high dose level of 180 mg/kg bw to points of departure for adverse effects observed in the database.

Elimination of orally-administered etofenprox occurred rapidly and was predominantly via the feces. Excretion patterns were similar between sexes. Tissues with the highest levels of radioactivity included fat, liver, kidney, adrenal gland, ovaries, and thyroid gland. The major components identified in feces were unchanged etofenprox and the metabolites desethyletofenprox and 4'-hydroxyetofenprox. Both of these metabolites were also major metabolites in bile. The metabolite α-CO (2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzoate) was determined to be a minor urinary metabolite.

A toxicokinetic study was conducted in rats to investigate transplacental and lactational transfer of etofenprox from dams to pups. Pregnant females were given a 1:1 mixture of etofenprox radiolabelled at moieties α-^{14}C-benzyl and 1-^{14}C-propyl for seven days during gestation, or 14 days from late gestation into lactation. From this study, it was determined that etofenprox crosses the placenta to the fetus during pregnancy, and unchanged etofenprox is secreted into maternal milk of rats.

The metabolism and toxicokinetics of etofenprox in the dog were investigated following the administration of a single oral dose of a 1:1 mixture of etofenprox radiolabelled at the α-^{14}C-benzyl and 1-^{14}C-propyl moieties. In the dog, absorption and elimination were rapid, with excretion occurring primarily via the feces but with the bile identified as an important route of elimination. The highest tissue concentrations were found in the liver, kidneys and fat. As with the rat, the major components identified in feces were unchanged etofenprox and the metabolites desethyletofenprox (DE) and 4'-hydroxyetofenprox (4'-OH).

Both of these metabolites were also found in the urine, and the metabolite desethyl-4'-hydroxyethofenprox (DE-4'-OH) was also identified in bile and urine. Most of the radioactivity recovered in fat was associated with unchanged etofenprox, while in the liver, it was mainly associated with conjugates of the two major metabolites.

In acute toxicity studies, the technical grade active ingredient etofenprox was of low toxicity via the oral, dermal, and inhalation routes of exposure in rats. It was minimally irritating to the eyes and skin of rabbits, and was negative for skin sensitization in guinea pigs when tested using the maximization test.

The end-use product, RF2129 EC, containing etofenprox and piperonyl butoxide, was of slight acute toxicity via the oral route, and of low acute toxicity via the dermal and inhalation routes of exposure in rats. It was mildly irritating to the eyes and skin of rabbits, and was negative for skin sensitization in guinea pigs when tested using the Buehler method.

The end-use product, RF2220 Premium Aerosol II-M Premise Spray, containing etofenprox, (s)-methoprene, tetramethrin, piperonyl butoxide, and pyrethrins, was of low acute toxicity via the oral, dermal, and inhalation routes of exposure in rats. It was non-irritating to the eyes and slightly irritating to the skin of rabbits. It was negative for skin sensitization in guinea pigs when tested using the Buehler method.

Repeat-dose dietary toxicity studies with etofenprox were available in mice, rats, and dogs. Throughout the etofenprox database, effects were observed in numerous organs and tissues in rodents and dogs. Target organs after repeated oral exposure included the liver in rats, mice and dogs, as well as the thyroid in rats and the kidneys in mice. However, effects occurred at much higher doses in mice than in the rat or the dog. Liver effects observed among mice, rats, and dogs included increased organ weight and enlargement of centrilobular hepatocytes. In the rat and mouse, changes in liver enzymes were also observed. Enlarged liver was observed in rats, and lobular markings of the liver were observed in dogs. Effects observed in the kidneys in mice included increased organ weight, gross pathology findings, microscopic findings, and misshapen kidneys. The thyroid effects observed in rats included an increase in the number of microfollicles, changes in thyroid hormones, and increased organ weight. Changes in clinical chemistry and blood parameters; decreased body weight, food efficiency, and water consumption; as well as increased organ weight of adrenal glands were additionally observed in rats after repeated dietary exposure. Mice also had decreased body weight, and increased or decreased water consumption, as well as clinical signs of toxicity, some indicative of neurotoxicity, that occurred before death. Changes in clinical chemistry and blood parameters, as well as increased organ weights of the kidneys, pancreas, lungs, and adrenal glands were additionally observed in dogs. Additional effects noted after long-term dietary dosing in rats at the highest dose tested included increased lung weights, pale foci of the lungs, lung congestion, biliary hyperplasia, vascular mineralization of the testes, cystic follicles of the thyroid, and increased height of follicular epithelium.

With respect to species-related differences in sensitivity, the lowest points of departure among repeat-dose dietary toxicity studies were observed in the rat, followed by the dog, and then the mouse. There was no evidence of further target organs identifiable after chronic exposure in rats and mice that were not identified in short-term studies. Following short-term repeated dermal exposure of rats to etofenprox for 28 days, dermal lesions and erythema were observed, with

evidence of reversibility. Considering other endpoints of concern in the database, particularly those in the young, it was determined that a 90-day dermal toxicity study would not be required as it is unlikely to provide additional information critical to the human health assessment.

Short-term repeated inhalation exposure (whole-body) of rats to etofenprox for 90 days resulted in thyroid effects (increased organ weight and microscopic changes), kidney effects (increased organ weight), liver effects (increased organ weight, enlargement and/or vacuolation of hepatocytes), as well as increased adrenal gland weight, adrenal cortical congestion, and increased water consumption.

With respect to the testing for genotoxic potential of etofenprox, negative results were obtained in a battery of in vitro and in vivo studies, which included a bacterial reverse mutation assay, an in vitro unscheduled DNA synthesis test, an in vitro mutation assay in Chinese hamster cells, an in vitro chromosomal aberration assay in human peripheral blood lymphocytes, an in vivo micronucleus assay in mice, and an in vitro micronucleus assay in human peripheral blood lymphocytes. Overall, it was concluded that there was no evidence of genotoxicity for etofenprox.

In an 18-month dietary oncogenicity study in mice, an increase in the combined incidence of renal cortical adenomas and carcinomas was observed in males at the highest dose level tested. The dose level at which the increase in these tumours was observed exceeded the maximum tolerated dose (MTD) based on the low survival rate of 19%; therefore, the tumours were not considered relevant to the human health assessment. After long-term exposure to etofenprox, mice developed pale livers and kidneys, and enlarged spleen and kidneys, and exhibited changes in hematology and clinical chemistry, in addition to the effects noted after short-term exposure. The severity of renal lesions contributed to the increased mortality observed at the highest dose tested.

In a 24-month dietary chronic toxicity and oncogenicity study in rats, an increased incidence of thyroid follicular cell adenomas was observed in both sexes at the highest dose level tested. The incidences of adenomas alone and combined adenomas and carcinomas for both sexes were statistically significantly increased by trend analysis. For pair-wise comparison, the incidences of adenomas alone, as well as adenomas and carcinomas combined for females receiving the highest dose tested were statistically significantly increased. There were no statistically significant differences for males in pair-wise comparisons. A mode of action (MOA) related to the induction of uridine diphosphoglucuronosyltransferase (UDP-GT), changes in thyroid hormone levels, and thyroid cell proliferation was proposed for tumour induction. A mechanistic study was provided by the applicant with a brief argument to support the proposed MOA. The mechanistic study investigating thyroid function and hepatic microsomal enzyme induction suggests that exposure to etofenprox caused lower circulating levels of thyroxine (T4), increased levels of thyroid-stimulating hormone (TSH), increased liver weight, increased activity of UDP-GT, and centrilobular hepatocellular hypertrophy. The study author noted that these results are consistent with etofenprox inducing the liver to produce more microsomal enzymes, which leads to a higher rate of metabolism of circulating triiodothyronine (T3) and T4, which then leads to a compensatory response in which production of TSH is increased. The chronic stimulation of the thyroid leads to thyroid cell proliferation and a greater risk of thyroid neoplasms.

This is a well-known MOA that was supported in this case by the results of this mechanistic study. Based on this, combined with the negative findings in the battery of genotoxicity studies and the fact that the tumour response is driven by benign adenomas, a threshold approach for thyroid follicular cell tumours was taken for risk assessment purposes.

A study was identified in the published scientific literature in which rats were injected with the tumour promoting initiator N-diethylnitrosamine (DEN) and then fed diets containing etofenprox for 8 weeks to investigate a possible MOA for liver tumour-promoting effects. Under the conditions of this study, the results suggested a MOA in which etofenprox enhances microsomal reactive oxygen species (ROS) which increases cellular proliferation and subsequently induces liver tumour-promoting effects. It is worth noting that no treatment-related tumours of the liver were observed in the long-term dietary studies in mice or rats in the etofenprox database.

The reproductive and developmental toxicity of etofenprox was tested in the rat in one guideline 2-generation dietary reproductive toxicity study and three special studies in which maternal rats were dosed by gavage during pre-mating, gestation, or lactation. In the rabbit, there were two acceptable developmental toxicity studies conducted by gavage, as well as a dose range-finding test, and an additional developmental toxicity study that ended in early termination.

In the 2-generation reproductive toxicity study in the rat, offspring effects included the serious endpoint of pup mortality, which occurred in the presence of parental toxicity. Pups also had increased liver weights, decreased body weights, body tremors, distended abdomens, abnormal gait, and pathological kidney findings (enlarged, swollen, pale, cystic, misshapen, irregular cortical scarring). This study was conducted according to older test guidelines and although it did not include in-depth assessments of estrous cyclicity, sperm parameters, or sexual maturation, concern for these limitations was tempered by the fact that the toxicology reference values selected for risk assessment afford intrinsic protection to the dose levels employed in the 2-generation reproductive toxicity study.

In two of the special studies in rats assessing developmental and reproductive toxicity with pre-mating and gestational exposure, increased resorptions and post-implantation loss occurred at the same dose that caused maternal toxicity. In the study with pre-mating exposure, increased pre-implantation loss was also observed. Reduced male sex ratio of fetuses, and an increased incidence of the malformations microphthalmia and/or anophthalmia also occurred in the presence of maternal toxicity in the special study with gestational exposure. In the special study with lactational exposure, increased pup mortality and total litter losses occurred at the highest dose tested in the presence of maternal toxicity. Pups also showed clinical signs such as tremors, subcutaneous hemorrhage around the nose, and general incoordination shortly before death. Other offspring effects included reduced pup body weight, increased kidney weight, gross kidney lesions (enlarged, pale, scarred cortices), and microscopic kidney effects.

In rabbits, there was evidence of a treatment-related malformation, bifurcated gallbladder, in the presence of maternal toxicity, in one of the acceptable developmental toxicity studies. Spontaneous abortions and increased resorptions were also observed in the rabbit at maternally toxic dose levels. A variation identified as unossified talus bone was observed in both of the acceptable rabbit developmental toxicity studies. In one study this observation was noted in the presence of maternal toxicity, while in the other it occurred in the absence of maternal effects.

The neurotoxic potential of etofenprox was investigated in rats following acute gavage dosing and 90 days of dietary administration, as well as in a developmental neurotoxicity study with dietary administration from gestation day 6 to lactation day 21.

In the acute oral neurotoxicity study in rats, there was evidence of potential neurotoxicity based on axonal degeneration at the highest dose tested. The acute neurotoxicity study lacked positive control data and axonal degeneration was not assessed in the intermediate dose groups, leading to uncertainty with respect to the true NOAEL in the study. However, concern for these limitations was tempered by the fact that points of departure selected for risk assessment were well below the dose level showing effects in the acute neurotoxicity study. No evidence of neurotoxicity was identified in the 90-day dietary neurotoxicity study in rats. Effects in the adult animals tested in this study were consistent with those noted in rats throughout the database. The minimal evidence of neurotoxicity in adult animals differentiates etofenprox from other pyrethroid insecticides that typically exhibit rapid neurotoxic effects in the form of clinical signs that may include tremors, salivation, increased sensitivity to stimuli, or writhing movements. In the etofenprox toxicity studies conducted with adult animals, such signs were only noted in mice above the limit dose of toxicity testing.

In the developmental neurotoxicity study in rats, treatment-related effects were noted in maternal animals and offspring at the highest dose tested. Maternal animals exhibited increased rearing activity. In offspring, an increased incidence of ocular abnormalities (large/prominent/dark eyes and opacity noted during clinical examinations; lenticular degeneration with retinal folds and minimal accumulation of macrophages in the iris or the uvea noted upon pathological examination) was observed. There was evidence of neurotoxicity in offspring, including increased amplitude and decreased habituation in the auditory startle response as well as a decrease in total motor activity and changes in brain morphometry including increased corpus callosum thickness and changes in hippocampus thickness (increased in males and decreased in females). Brain morphometry measurements were only recorded for offspring from the control and high-dose groups. Other offspring effects at the highest dose tested included increased mortality, reduced body weight gains, and renal pelvic dilation. Additionally, equivocal increases of bleeding, reddened, swollen, and/or bruised areas on the tail and paws were observed starting at the mid-dose level.

In the evaluations of other pyrethroid insecticides, a database uncertainty factor has been applied when a comparative oral gavage neurotoxicity study considering time-to-peak effect in pups, weanlings and adult animals was not available. This uncertainty stems from studies in the published literature that indicate that pharmacodynamics and pharmacokinetic factors, notably age-dependent maturation of key metabolic processes, may lead to increased susceptibility of the young to pyrethroid toxicity. It has also been noted that the design of a developmental neurotoxicity (DNT) study does not consider time-to-peak-effect and may miss the window of peak toxicity for the pyrethroids. However, a database uncertainty factor has not been applied in the case of etofenprox because of the minimal evidence of neurotoxicity noted in adult animals in the database, and considering the structural differences between etofenprox and other pyrethroids.

Although some limitations have been identified with the typical protocol for DNT studies when it comes to identifying neurotoxicity in the young following exposure to pyrethroids, concern for these limitations in the context of etofenprox is tempered by the available toxicokinetic evidence demonstrating exposure of the young to etofenprox through the placenta and via maternal milk. Finally, as discussed in Section 3.1.1, the *Pest Control Products Act* (PCPA) factor was retained in part to afford additional margins of safety to the effects noted in the young following exposure to etofenprox.

Two 28-day dietary immunotoxicity studies were conducted with etofenprox, one in mice and one in rats. In rats, there was no evidence of immune system dysregulation. In mice, there was no evidence that etofenprox caused immune suppression, and there was no evidence of immunotoxicity observed in females. An increase in antibody producing cells in the spleen provided possible evidence of immune system dysregulation in males at a dose level exceeding the limit dose.

An oral comparative thyroid assay in rats was conducted to assess thyroid hormones in maternal animals, fetuses, and pups. However, the thyroid hormone levels were highly variable and the study investigator concluded that the TSH data were unreliable, and that the results could not be used quantitatively or qualitatively.

The toxicology reference values for use in the human health risk assessment are summarized in Appendix I, Table 1. Results of the toxicology studies conducted on laboratory animals with etofenprox and with its associated end-use products, are summarized in Appendix I, Tables 2 and 3.

3.1.1 *Pest Control Products Act* hazard characterization

For assessing risks from potential residues in food or from products used in homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.[5]

With respect to the completeness of the etofenprox toxicity database as it pertains to the toxicity to infants and children, the database contains several studies investigating effects in the young, that together fulfill the full complement of required studies. A dietary 2-generation reproductive toxicity study in rats was available, and although it was conducted according to older test guidelines, there was a low level of concern for any missing parameters. Three oral gavage special studies assessing developmental and reproductive toxicity in rats were available, covering pre-mating, gestational, and lactational exposure. A prenatal developmental toxicity study in rats conducted according to current test guidelines was not available; however, coverage for the typical dosing scenario and fetal assessments was provided by these three non-guideline studies. Two oral gavage developmental toxicity studies were available in rabbits, as well as a dose range-finding developmental toxicity study in rabbits.

[5] SPN2008-01. The Application of Uncertainty Factors and the *Pest Control Products Act* Factor in the Human Health Risk Assessment of Pesticides.

A dietary developmental neurotoxicity study in the rat and an oral comparative thyroid assay in the rat were also available. As discussed above, a comparative oral gavage neurotoxicity study considering time-to-peak effect in pups, weanlings and adult animals was not available for etofenprox; however, overall concern for the lack of this study was low.

With respect to concerns regarding potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in rats as effects in the young occurred in the presence of parental toxicity; however, sensitivity of the young was observed in one study in rabbits in which unossified talus bone occurred in the absence of maternal toxicity. In addition, effects considered serious in nature were observed in the young in several studies. In the dietary 2-generation reproductive toxicity study in rats, increased pup mortality was observed in the presence of significant maternal toxicity (mortality, kidney and liver effects). In the special study assessing developmental and reproductive toxicity with gestational exposure in rats, malformations of the eye (microphthalmia and anophthalmia), resorptions and post-implantation loss were observed in the presence of maternal toxicity (body weight effects) at a dose level exceeding the recommended limit dose of testing. In the special study assessing developmental and reproductive toxicity in the rat with lactational exposure, pup mortality, including the loss of complete litters, was observed in the presence of maternal toxicity (body weight effects) at a dose level exceeding the recommended limit dose of testing. In the developmental toxicity study in rabbits, a malformation of the gallbladder (bifurcated) as well as spontaneous abortions and increased resorptions were observed in the presence of maternal toxicity (body weight effects, neurotoxicity). In the developmental neurotoxicity study in rats, pup mortality, evidence of neurotoxicity (changes in brain morphometry and altered acoustic startle response), and ocular abnormalities were observed in the presence of maternal toxicity (body weight effects and increased rearing). Some residual uncertainty remains with respect to the possible effects of etofenprox on the brain morphometry of the developing young, given that brain samples of offspring in the low- and mid-dose groups did not undergo morphometric analyses. However, the retention of the PCPA factor, discussed below, provides an additional margin to the effects on brain morphometry noted at the high dose and thus addresses any residual concern for the lack of brain morphometric measurements in animals from the low- and mid-dose groups.

Overall, the database is adequate for determining the sensitivity of the young. There is a low level of concern for sensitivity of the young in rats as effects in the young are well-characterized and occurred in the presence of maternal toxicity. In rabbits, sensitivity of the young was noted as a variation occurred in the absence of maternal toxicity. As such, the PCPA factor was reduced to threefold if this endpoint was used for the point of departure for risk assessment. Concern for the serious endpoints of reduced offspring survival, developmental neurotoxicity, and malformations was tempered by the fact that they occurred in the presence of maternal toxicity. Therefore, the PCPA factor was reduced to threefold if these serious endpoints were used for the point of departure for risk assessment. For exposure scenarios relying on other endpoints of concern, the PCPA factor was reduced to onefold as the risk was considered well-characterized and the endpoints selected for risk assessment provided adequate margins to these serious effects.

3.2 Toxicology reference values

3.2.1 Route and duration of exposure

For commercial handlers of RF2129 EC, exposure is characterized as short (< 30 days) to intermediate-term (30 < 180 days) in duration and is predominantly by the dermal and inhalation routes. For postapplication workers, occupational exposure to RF2129 EC is expected to be minimal. Any exposure during re-entry activities is expected to be less than that of people living in treated areas. Therefore, the occupational postapplication exposures were qualitatively assessed.

Residential exposure to RF2220 Premium Aerosol II-M Premise Spray is characterized as short- to intermediate-term in duration. Applicator exposure is predominantly by dermal and inhalation routes. Postapplication exposure for adults (16+ years) is predominantly by the dermal route and for children (1 < 2 years) by the dermal and incidental oral routes.

3.2.2 Occupational and residential toxicology reference values

Short- and intermediate-term dermal and inhalation

Children (1< 2 years old):

For short- and intermediate-term residential exposure of children via the dermal and inhalation routes, the offspring NOAEL of 57 mg/kg bw/day from the oral developmental neurotoxicity study in the rat was selected for risk assessment. At the offspring LOAEL of 169 mg/kg bw/day, toxicity was observed in this study in the form of pup deaths, ocular lesions, and changes in brain morphometry and auditory startle response in the presence of maternal toxicity. The available 28-day dermal and 90-day inhalation toxicity studies did not assess the relevant endpoints of concern (that is, developmental neurotoxicity effects and survival of the young), thus necessitating the use of an oral toxicity study for risk assessment purposes.

Since a point of departure from an oral study was selected to assess risks from dermal and inhalation exposure, consideration was given to any correction required for oral absorption in order to account for differences in bioavailability between the different routes of exposure. As noted previously, the oral absorption of etofenprox was estimated to be approximately 30% based on the results from bile duct-cannulated rats. To account for this relatively low oral absorption noted in the animal database, the offspring NOAEL was adjusted by the estimated oral absorption value of 30%. Therefore, the point of departure for use in the human health risk assessment for short to intermediate-term dermal and inhalation routes of exposure is the adjusted offspring NOAEL of 17 mg/kg bw/day.

The target margin of exposure (MOE) for these scenarios is 300, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The PCPA factor was reduced to threefold as discussed in the *Pest Control Products Act* Hazard Characterization section.

Adults (≥16 years old):

For short- and intermediate-term occupational and residential exposures of adults via the dermal and inhalation routes, the developmental NOAEL of 30 mg/kg bw/day from the oral developmental toxicity study in the rabbit was selected for risk assessment. At the developmental LOAEL of 100 mg/kg bw/day, toxicity was observed in the form of increased incidences of unossified talus bone in the absence of maternal toxicity. Populations could include pregnant people and therefore these endpoints were considered appropriate for occupational and residential risk assessments. The available 28-day dermal and 90-day inhalation toxicity studies did not assess the relevant endpoint of concern (that is, developmental effects following prenatal exposure), thus necessitating the use of an oral toxicity study for risk assessment purposes.

Since a point of departure from an oral study was selected to assess risks from dermal and inhalation exposure, consideration was given to any correction required for oral absorption in order to account for differences in bioavailability between the different routes of exposure. As noted previously, the oral absorption of etofenprox was estimated to be approximately 30% based on the results from bile duct-cannulated rats. To account for this relatively low oral absorption noted in the animal database, the developmental NOAEL was adjusted by the estimated oral absorption value of 30%. Therefore, the point of departure for use in the human health risk assessment for short to intermediate-term dermal and inhalation routes is the adjusted developmental NOAEL of 9 mg/kg bw/day.

For occupational and residential scenarios, the target MOE is 300, which includes standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. For residential scenarios, the PCPA factor was reduced to threefold as discussed in the *Pest Control Products Act* hazard characterization section. As the worker population could include pregnant people, it is necessary to afford adequate protection of the fetus that may be exposed via its parent. In light of concerns regarding prenatal toxicity, as outlined in the *Pest Control Products Act* hazard characterization section, an additional threefold factor was applied to this endpoint to protect for a sensitive subpopulation, namely females 13 to 49 years of age. The selection of this study and target MOE is considered to be protective of all populations, including nursing infants and unborn children of exposed pregnant people.

Acute-, short-, and intermediate-term incidental oral ingestion

Children (1 to < 2 years old):

For acute-, short-, and intermediate-term residential exposures via incidental oral ingestion of etofenprox by children aged 1–2 years old, the offspring NOAEL of 57 mg/kg bw/day from the oral developmental neurotoxicity study in the rat was selected for risk assessment. At the offspring LOAEL of 169 mg/kg bw/day, toxicity was observed in this study in the form of pup deaths, ocular lesions, and changes in brain morphometry and auditory startle response in the presence of maternal toxicity.

The target MOE for these scenarios is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As outlined in the *Pest Control Products Act* hazard characterization section, the PCPA factor was reduced to threefold. The selection of this study and target MOE is protective of children aged 1 to <2 years old.

3.2.3 Acute reference dose (ARfD)

Establishment of an acute reference dose is not required, as no exposure via the diet or drinking water is expected.

3.2.4 Acceptable daily intake (ADI)

Establishment of an acceptable daily intake is not required, as no exposure via the diet or drinking water is expected.

3.2.5 Cancer assessment

As previously discussed, an increased incidence of thyroid follicular cell tumours was observed in rats following chronic dosing. A MOA for tumour induction was proposed related to the induction of UDP-GT, followed by changes in thyroid hormones and thyroid cell proliferation. Despite some limitations, the MOA was deemed plausible. The overall weight of evidence was considered sufficient to conclude that a linear low-dose extrapolation (q_1*) approach to the cancer risk assessment may be overly conservative. For these reasons, a threshold approach for thyroid follicular cell tumours was applied for the cancer risk assessment. An increase in the incidence of renal cortical tumours in male mice was observed at the highest dose tested at a dose level that exceeded the MTD in the 18-month oncogenicity study in mice. Based on the observed effect on survival at the same dose level, these tumours were not determined to be relevant to the human health risk assessment. Overall, the toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of etofenprox.

3.2.6 Aggregate toxicology reference values

Aggregate exposure is the total exposure to a single pesticide that may occur from dietary (food and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). As etofenprox is not proposed for use on food crops, dietary exposure (food + drinking water) is not expected. Therefore, an aggregate assessment (dietary + residential exposure) was not required.

3.3 Dermal absorption

An in vivo dermal absorption study was submitted. Sprague-Dawley rats were administered actual doses of 4.87, 59, and 184 µg/cm^2 (0.65 g/L, 6.43 g/L and 22.3 g/L) of diluted etofenprox over 12.5 cm^2. For each dose, 4 rats were exposed for 10 hours, after which the application site was washed, followed by termination at 10, 24 or 96 hours post-dosing.

Sampled matrices included skin wash, feces, urine, blood, cage wash, cage wipe, residual carcass, non-occlusive cover (filter paper), enclosure, skin at application site and spreader rinse and wipe. Mean total radioactivity recoveries ranged from 93% to 134% across the three dose levels (Appendix I, Tables 5, 6 and 7). Recoveries for the rats in the low and mid-dose groups were within the acceptable OECD (2011) range of 100% ± 10% but recoveries for rats in the high dose group, terminated at 10, 24 and 96 hours, were 131%, 134% and 119%, respectively. The majority of the administered dose for all rats was recovered from the skin wash with mean recoveries of 79.6% to 100.6% across all three doses. Skin at the test site was the matrix with the

next highest dose recovered and the primary route of excreta was feces. Systemic absorption (blood, carcass and excreta) increased as both monitoring time and dose increased (96-hour means of 4.26% at 5 µg/cm^2, 5.96% at 59 µg/cm^2, to 6.16% at 184 µg/cm^2). The mean dermal absorption values, as percentage of applied dose, were the sum of skin test site, blood, carcass, urine, feces, cage wash and cage wipe, with values of 14%, 16% and 33% in the 5, 59, and 184 µg/cm^2 doses, respectively, for rats sacrificed at 96 hours.

There are major limitations in the study which preclude its use to establish a single dermal absorption value for all use scenarios, formulations and product types. The active ingredient was not administered in a blank formulation similar to one proposed for registration. The choice of vehicle is similar to water and so the applied dose can be considered as technical grade active ingredient applied in water. Given the high percentage of either solvents or other active ingredients in the proposed formulations, the technical grade active ingredient in water may underestimate dermal absorption. There is also an increase in absorption between the low and mid-dose groups but the unreliable results of the high dose group make it difficult to determine with certainty if that trend continues. The high dose group concentration is lower than the emulsifiable concentrate formulation and, given that absorption increases with dose, the high dose group absorption value may not adequately reflect absorption of both end-use products.

The dermal absorption value of the mid-dose group at 96 hours (16%) is adequate to estimate dermal absorption for end-use products which have a similar concentration (g/L) and contain water as the main diluent in the formulation. This value is therefore relevant for the following scenarios: 1) postapplication exposure to the emulsifiable concentrate formulation and 2) applicator and postapplication exposure to the aerosol formulation. The dermal absorption value of 16% was used for the residential applicator exposure assessment to RF2220 Premium Aerosol II-M Premise Spray and postapplication risk assessments for adults and children when exposed to etofenprox from either end-use product. However, for commercial applicators handling the RF2129 EC formulation, a dermal absorption value of 50% is applied. As the unit exposure (UE) values for handheld equipment are derived from worker exposure studies where exposure from mixing/loading was not monitored separately from application exposure, the 50% is applied to all commercial applicator exposure scenarios. This is not expected to underestimate exposure as it is expected that the majority of exposure to etofenprox occurs during application.

3.4 Occupational and residential exposure assessment

3.4.1 Acute hazards of the end-use products and mitigation measures

3.4.1.1 RF2129 EC

The acute hazard assessment of RF2129 EC concluded that it is of slight acute toxicity to rats via the oral route, and of low acute toxicity to rats via the dermal and inhalation routes. It was mildly irritating to the eyes and skin of rabbits, and was not a dermal sensitizer in guinea pigs according to the Buehler method. This classification requires that CAUTION – EYE AND SKIN IRRITANT be added to the principal panel. The proposed PPE are protective of acute toxicity hazards for workers mixing, loading, applying, and during clean-up and repair activities. For good hygiene practices, it is recommended that when applying overhead and in confined spaces, appropriate eye, head and respiratory protection is worn.

3.4.1.2 RF2220 Premium Aerosol II-M Premise Spray

The acute hazard assessment of RF2220 Premium Aerosol II-M Premise Spray concluded that it is of low acute toxicity to rats via the oral, dermal and inhalation routes. It was not irritating to the eyes of rabbits, was slightly irritating to the skin of rabbits, and was not a dermal sensitizer in guinea pigs according to the Buehler method. This classification does not require any signal words or hazard statements on the principal panel.

3.4.2 Occupational exposure and risk assessment

3.4.2.1 Mixer, loader and applicator exposure and risk assessment

Individuals have the potential for exposure to etofenprox during mixing, loading, application, clean-up and repair activities. Dermal and inhalation exposure estimates for mixers, loaders and applicators applying indoor surface treatments were generated from a previously reviewed worker exposure study representative of manually and mechanically pressurized and backpack sprayers. The risk assessment was based on handlers wearing the proposed PPE of a single layer with chemical-resistant gloves and the standard amount handled per day of 40 L/day. As risks of concern were identified, restrictions were placed on the amount of product handled per day and the PPE was increased to allow greater amounts of product to be handled (Appendix I, Table 8).

Dermal exposure was estimated by combining the unit exposure values with the amount of product handled per day and the dermal absorption value of 50%. Inhalation exposure was estimated by combining the unit exposure values with the amount of product handled per day and 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the selected toxicological reference value to obtain the margin of exposure (MOE). Dermal and inhalation MOEs were combined since the dermal and inhalation reference values are based on the same toxicological effects. Calculated MOEs are greater than the target MOE of 300 when limiting the amounts of product handled according to the level of PPE (Appendix I, Table 9). When following all label directions, including limiting the amount handled and wearing appropriate PPE, there are no health risks of concern.

3.4.2.2 Postapplication exposure and risk assessment

Postapplication risk to workers entering treated areas was assessed qualitatively. Exposure is expected to be less than that of an adult resident entering a residence treated with RF2129 EC as duration of exposure, exposed body surface area and contact with treated surfaces would be greater for the resident. As such, the postapplication exposure of a residential adult to surfaces treated with RF2129 EC is not expected to underestimate exposure to postapplication worker exposure.

3.4.3 Residential exposure and risk assessment

3.4.3.1 Handler exposure and risk

RF2220 Premium Aerosol II-M Premise Spray is a domestic class product. The dermal and inhalation estimates of exposure to residential applicators during broadcast application of the pressurized aerosol product was calculated based on the algorithm and standard parameter values from the USEPA 2012 Residential Standard Operating Procedure (SOP), Section 7 Indoor Environments.

Using the default values in combination with toxicological reference values, applicator exposure is not expected to result in risks of concern when etofenprox is used according to label directions as the calculated MOEs exceeded the target MOE 300 (Appendix I, Table 10).

3.4.3.2 Postapplication exposure and risk

Adults and children will be exposed to surfaces treated with etofenprox after the application of either RF2129 EC or RF2220 Premium Aerosol II-M Premise Spray. The end-use products are proposed for use on hard and soft surfaces such as carpets, floors, closets, furniture (excluding mattresses), storage areas and other areas where indoor pests hide. Dermal exposure was calculated for adults (16+ years) and dermal and incidental oral exposures were calculated for children (1 < 2 years). Only exposure for children 1 < 2 years was calculated as this lifestage represents the most appropriate index lifestage. Children in this age group have a higher body surface area to body weight ratio and engage in more mouthing exposure events compared to other lifestages; and as such, have the highest possible exposure among all children and youth less than 16 years old. Incidental oral exposures include hand-to-mouth and object-to-mouth exposures after a hand or toy comes into contact with surfaces treated with etofenprox. Inhalation exposure is not expected as etofenprox is not volatile and when standard label statements to ventilate treated areas are followed.

Except for the application rate, all parameter values were derived from the USEPA 2012 Residential SOP, Section 7 Indoor Environments for broadcast application.

The calculated dermal and incidental oral MOEs for broadcast treatment on hard and soft surfaces were above the target MOE of 300 (Appendix I, Tables 11 to 13). Therefore, the use of the end-use products in residential settings does not result in risks of concern.

As the toxicological reference values for all routes of exposure are derived from the same toxicological study, all dermal, inhalation and incidental oral routes of exposure are combined for the relevant lifestages. As RF2220 Premium Aerosol II-M Premise Spray is a domestic end-use product, adults can be exposed through inhalation and dermal routes during application (Appendix I, Table 10) and through the dermal route when in contact with treated surfaces (Appendix I, Table 11). For children, dermal exposure to treated surfaces (Appendix I, Table 11) is combined with object-to-mouth exposure (Appendix I, Table 13), as the latter is the greater of the two incidental oral routes of exposure. Combined assessments were conducted to determine overall risk for both lifestages and no risks of concern where identified (Appendix I, Table 14).

3.4.4 Bystander exposure and risk assessment

Bystander exposure to RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray is expected to be minimal as the proposed labels require indoor treatment areas to be vacated by humans and pets during application.

3.5 Aggregate exposure and risk assessment

As etofenprox is not proposed for use on food crops, dietary exposure (food + drinking water) is not expected. Therefore, an aggregate assessment (dietary + residential exposure) was not required.

3.7 Cumulative assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Etofenprox is classified as a pyrethroid-like ether compound with a mode of action against insects similar to that of pyrethroids. Etofenprox also showed evidence of neurotoxicity, a common effect within pyrethroid insecticides.

As noted in the Cumulative Health Risk Assessment Operational Planning Framework, the pyrethroid cumulative health risk assessment is currently in the initial planning phase and will consist of a complex standalone quantitative assessment. As part of that assessment, an evaluation will be undertaken to determine whether etofenprox shares a common mechanism of mammalian toxicity with other pyrethroids, and if so, a cumulative assessment for etofenprox and relevant pyrethroids will be conducted.

3.8 Health incident reports

As of 8 August 2025, 6 human and 627 domestic animal incidents involving etofenprox were submitted to the PMRA. For the domestic animal incidents, only incidents reporting etofenprox products registered for use around homes were evaluated further (17 incidents). The remaining domestic animal incidents involving companion animal products were not considered further in this review.

The human and domestic animal etofenprox incidents involved products registered in the US that were co-formulated with other active ingredients such as s-methoprene, tetramethrin, piperonyl butoxide, pyrethrins or pyriproxyfen. In the human incidents, the reported exposure scenarios involved hands coming in contact with the etofenprox product when applying it to pets or to indoor residential sites; suspected accidental ingestion in a child; as well as oral exposure during application to an indoor residential site. The severity of the reported effects in these incidents were mainly minor. Symptoms reported in individuals following exposure to etofenprox and other active ingredients included numbness, hypoesthesia, or the non-specific symptom of spitting.

In the domestic animal incidents, exposure to etofenprox and other active ingredients in animals occurred as a result of the animal licking treated sites in the home or following the animal contact with product residues on treated pet beddings. Symptoms in animals (mainly cats) were seen relatively quickly (within 24 hours) following product exposure and included effects such as lethargy, abnormal behaviour, difficulty walking, seizures or death.

Overall, the majority of the incidents involving etofenprox products co-formulated with other active ingredients occurred in the US. The number of reported serious US incidents (classified as major or death) involving the use of etofenprox products at residential sites is low (2 human and 17 domestic animal incidents over 18 years (2007–2025)). Therefore, no trends relating to either the reported exposure scenario or adverse effects were identified in this incident evaluation. No additional mitigation measures are being recommended.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

Etofenprox is stable to hydrolysis. It is practically insoluble in water. Etofenprox breaks down through aerobic biotransformation. It is considered to be non-persistent with a maximum half-life of 22.8 days. Etofenprox is not expected to be found in the air near the application site as it has low volatility and the Henry's law constant indicates that it has low potential to volatilize from water or moist soil. Etofenprox is immobile and has a strong tendency to bind to sediment/soil based on its high K_{oc} value. It has potential to accumulate in the tissues of fish. Based on the use pattern, etofenprox is not expected to leach to groundwater.

4.2 Environmental risk characterization

Etofenprox is for use as broadcast, spot, crack and crevice, perimeter void, and furniture treatments in and on non-food/non-feed areas of buildings, structures and modes of transportation to control a wide variety of arthropod pests. With limited outdoor use proposed and with application methods including low-pressure sprayer, void injector or as an aerosol spray where the product is applied directly to the target pests, exposure to non-target organisms is expected to be negligible. As such, a characterization of the risk to non-target organisms in the environment is not required.

4.2.1 Risks to non-target terrestrial and aquatic organisms

Based on the use pattern, the potential exposure of non-target terrestrial and aquatic organisms is not expected to be significant. Therefore, the risk to non-target terrestrial and aquatic organisms is expected to be negligible.

4.2.2 Incident reports related to the environment

Etofenprox is a new active ingredient pending registration for use in Canada. As of 8 August 2025, no environmental incident reports involving etofenprox have been submitted to the PMRA.

5.0 Value

Efficacy trials and rationales were reviewed to support the claims for both products. Direct contact sprays and residual assessments were considered.

Efficacy trials tested RF2129 EC as a direct-contact and residual spray against many different insect species, including ticks, ants, wasps, beetles, spiders, earwigs, house flies, and other pests. The submitted value information was sufficient to support claims to knockdown the tested pests. Claims for residual control were supported for up to 28 days on non-porous surfaces for crickets and cockroaches and for up to 14 days on non-porous surfaces for other pests. Claims for ants and stink bugs were supported for direct contact knockdown only.

Efficacy studies tested the direct application of RF2220 Premium Aerosol II-M Premise Spray against adult cat fleas, four different species of ticks, two different species of cockroaches, and two different species of ants, which was sufficient to support claims for fleas, ticks, cockroaches, and ants, except carpenter ants, by broadcast, crack and crevice, void, or spot treatment or by direct application to exposed pests. Additional scientific information supported use of this product against juvenile stages of fleas.

6.0 Pest Control Product Policy considerations

6.1 Toxic Substances Management Policy considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, in other words, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, etofenprox was assessed in accordance with the PMRA Regulatory Directive DIR99-03[6] and evaluated against the Track 1 criteria. Health Canada has reached the conclusion that etofenprox does not meet all of the TSMP Track 1 criteria.

Please refer to Appendix I, Table 15, for further information on the TSMP assessment.

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the active ingredient as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.[7] The list is

[6] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

[7] SI/2005-114, last amended on June 24, 2020. See Justice Laws website*, Consolidated Regulations, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

used as described in the PMRA Science Policy Note SPN2020-01[8] and is based on existing policies and regulations, including the Toxic Substance Management Policy and Formulants Policy, and taking into consideration the *Ozone-depleting Substances and Halocarbon Alternatives Regulations* under the *Canadian Environmental Protection Act, 1999* (substances designated under the *Montreal Protocol*).

Health Canada has reached the conclusion that etofenprox and its end-use products, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray, do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02

7.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Etofenprox Technical, RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray, containing the technical grade active ingredient etofenprox, tocontrol arthropod pests in and on various structures, including buildings, modes of transportation, kennels, and pet bedding, by broadcast, spot, crack and crevice, perimeter, void, and furniture treatments.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

[8] PMRA's Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under paragraph 43(5)(b) of the *Pest Control Products Act*

List of abbreviations

↑	increased
↓	decreased
♂	male
♀	female
λ	wavelength
µg	microgram(s)
µPa	microPascal
4-MUGT	4-methylumbelliferone glucuronosyltransferase
°C	degrees centigrade
a.i.	active ingredient
abs	absolute
AD	administered dose
ADI	acceptable daily intake
AHPD	amount handled per day
ALK	alkaline phosphatase
ALT	alanine aminotransferase
AOPWIN	Atmospheric Oxidation Program for Windows
ARfD	acute reference dose
ASR	auditory startle response
AST	aspartate aminotransferase
AUC	area under the curve
BAF	bioaccumulation factor
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAR	constitutive androstane receptor
C_{max}	maximum concentration
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
cm	centimetres
cm^2	square centimetre
CR	chemical-resistant
DE	3-phenoxybenzyl 2-(4-hydroxyphenyl)-2-methylpropyl ether
DEN	N-diethylnitrosamine
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
DP	3-hydroxybenzyl 2-(4-ethoxyphenyl)-2-methylpropyl ether
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
EC	emulsifiable concentrate
ET	exposure time
F0	parental generation
F1	first filial generation
F2	second filial generation
$F_{a.i.}$	fraction of active ingredient on hands

fc	food consumption
fe	food efficiency
FOB	functional observational battery
g	gram(s)
GD	gestation day
GLP	good laboratory practice
GST-P	glutathione S-transferase placental form
h	hour
HDPE	high density polyethylene
HGB	hemoglobin
IRAC	Insecticide Resistance Action Committee
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC_{50}	concentration estimated to be lethal to 50% of the test population
LD	lactation day
LD_{50}	dose estimated to be lethal to 50% of the test population
LDH	lactate dehydrogenase
LOAEL	lowest observed adverse effect level
m	metre
m^2	square metre
m^3	cubic metre
MAS	maximum average score for 24, 48 and 72 hours
MCV	mean corpuscular volume
MIS	maximum irritation score
mg	milligram
min	minute
mL	millilitre
M/L	mixer/loader
MOA	mode of action
MOE	margin of exposure
MPHG	mechanically pressurized handgun
MPHW	manually pressurized handwand
MTD	maximum tolerated dose
n	sample size
ND	not detectable;
nm	nanometres
NOAEL	no observed adverse effect level
Nrf2	nuclear factor erythroid 2-related factor 2
NZW	New Zealand white
OECD	Organisation for Economic Co-operation and Development
OtM	object to mouth
Pa	Pascal
PCPA	*Pest Control Products Act*
PCV	packed cell volume
PEG	polyethylene glycol

pH	log10 hydrogen ion concentration
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PNGT	p-nitrophenol glucuronosyltransferase
PPE	personal protective equipment
ppm	parts per million
q_1*	cancer potency factor
RBC	red blood cells
rel	relative
ROS	reactive oxygen species
SD	standard deviation
T3	tri-iodothyronine
T4	thyroxine
TBARS	thiobarbituric acid reactive substances
TSH	thyroid stimulating hormone
TSMP	Toxic Substances Management Policy
UDP-GT	uridine diphosphate glucuronyltransferase
UE	unit exposure
UV	ultraviolet
WBC	white blood cells
wc	water consumption
wt	weight

Appendix I Tables and figures

Table 1 Toxicology reference values for use in health risk assessment for etofenprox

Exposure scenario	Study	Point of departure and endpoint	CAF[1] or Target MOE
Short- and intermediate-term dermal and inhalation[2] children 1<2 years old	Oral DNT study in rats	Offspring NOAEL = 57 mg/kg bw/day (Corrected for 30% oral absorption = 17 mg/kg bw/day) Pup deaths, ocular lesions, and changes in brain morphometry and ASR in the presence of maternal toxicity	300
Short- and intermediate-term dermal and inhalation [2] Adults (≥16 years old)	Oral developmental toxicity study in rabbits	Developmental NOAEL = 30 mg/kg bw/day (Corrected for 30% oral absorption = 9 mg/kg bw/day) Unossified talus bone in the absence of maternal toxicity	300
Acute, short-, and intermediate-term non-dietary oral ingestion children 1<2 years old	Oral DNT study in rats	Offspring NOAEL = 57 mg/kg bw/day Pup deaths, ocular lesions, and changes in brain morphometry and ASR in the presence of maternal toxicity	300
Cancer	Evidence of thyroid follicular cell tumours (adenomas) in rats. Toxicology reference values selected for non-cancer risk assessment are protective of any residual concerns regarding carcinogenic potential.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE (margin of exposure) refers to a target MOE for occupational and residential assessments.

[2] Since an oral NOAEL was selected, a dermal absorption factor of either 16% or 50% (see Section 3.3 Dermal Absorption) and an inhalation absorption factor of 100% (default value) were used in route-to-route extrapolation. The oral dose administered in the toxicity studies was corrected by a factor of 30% to account for low oral absorption in order to extrapolate to the dermal and inhalation routes.

Table 2 Toxicity profile of technical etofenprox

Effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Note: unless otherwise specified, studies listed in this table are considered acceptable according to Information Note: Determining Study Acceptability for use in Pesticide Risk Assessments.

Study Type/Animal/PMRA No.	Study results
Toxicokinetic studies	
Absorption, distribution, metabolism and excretion (gavage, single dose) Wistar rat PMRA No. 3060745	**Acceptable with limitations** Study involved single gavage dose administration of 30 mg/kg bw of [α-^{14}C-benzyl]-Etofenprox in PEG 400 to intact rats (♂ only) to assess absorption, distribution, metabolism, and elimination. Excretion via urine and feces was measured at 24 and 48 hours after dosing. Animals were sacrificed at 48 hours and radioactivity in selected organs/tissues was determined. **Absorption:** The absorption of etofenprox at 48 hours post-dosing, as a sum of radioactivity in the urine, cage wash, tissues (excluding intestines), and carcass, was 23% of the AD. **Excretion:** Excretion occurred rapidly mainly via the feces (50% of the AD). Low amounts were found in urine (14% of the AD). **Metabolism:** Unchanged etofenprox accounted for 12% of the AD in feces collected from 0-48 hours. The following metabolites were also identified in feces: 2-(4-ethoxyphenyl)-2-methylpropyl 3-(4-hydroxyphenoxy) benzyl ether (4'-OH) (11.6% of the AD); 3-phenoxybenzyl 2-(4-hydroxyphenyl)-2-methylpropyl ether (DE) (11.3% of the AD); 3-hydroxybenzyl 2-(4-ethoxyphenyl)-2-methylpropyl ether (DP) (5.4% of the AD); and 3-phenoxybenzyl alcohol (m-PB-alc) (0.45% of the AD). In the liver, unchanged etofenprox accounted for 3.9% of the radioactivity recovered in the liver. The following metabolites were also identified (% radioactivity in liver): 3-phenoxybenzyl 2-(4-hydroxyphenyl)-2-methylpropyl ether (DE) (1.0%); 3-hydroxybenzyl 2-(4-ethoxyphenyl)-2-methylpropyl ether (DP) (0.9%), 3-phenoxybenzoic acid (m-PB-acid) (1.5%), 3-phenoxybenzyl alcohol (m-PB-alc) (0.8%) and 3-(4-hydroxyphenoxy)benzoic acid (4'-OH-PB-acid) (1.3%).

Study Type/Animal/PMRA No.	Study results
	In the fat, exclusively unchanged etofenprox was identified (96% of the radioactivity in fat). In urine, no unchanged etofenprox was detected. Metabolites 3-phenoxybenzoic acid (m-PB-acid) and 3-(4-hydroxyphenoxy)benzoic acid (4'-OH-PB-acid) were identified at 1.5% and 0.2% of the radioactivity recovered in urine, respectively. **Limitations:** Overall recovery was low (84.3% of the AD); biliary elimination was not evaluated; not conducted according to GLP; no Quality Assurance statement.
Absorption, distribution, metabolism and excretion (gavage, single and repeat dose) Sprague-Dawley rat PMRA No. 3060747	**Acceptable with limitations** A single gavage dose of 30 or 180 mg/kg bw was administered to intact and bile duct-cannulated rats, and repeat gavage dose of 30 mg/kg bw/day. A 1:1 mixture of [1-^{14}C-propyl] etofenprox and [α-^{14}C-benzyl] etofenprox in PEG 400 was used for all rats, except for bile duct-cannulated rats that received ^{14}C-propyl etofenprox in PEG 400. **Absorption:** Plasma C_{max} values of 5.2 µg/mL (♂) and 5.0 µg/mL (♀) at 5 and 3 hours respectively after single low dose, and 17.3 µg/mL (♂) and 16.4 µg/mL (♀) at 5 hours after a single high dose. Thereafter, concentrations declined in an apparent biphasic manner. After a single high dose, AUC values were 3.3/3.8-fold higher for ♂/♀ than following a single low dose (compared to a sixfold difference in dose level). Based on radioactivity levels in urine, tissues, and bile collected up to 48 hours post-dose, absorption following a single low dose was 20/39% of the AD and following a single high dose was 14/13% of the AD in ♂/♀. **Excretion:** After single oral doses at the low or high levels, 86–90% of the AD was eliminated via the feces and 6–11% of the AD was excreted in urine. Excretion patterns in animals given the separate labelled forms were similar. Concentrations excreted in expired air was minimal, at ≤ 0.2% of the AD. In animals with cannulated bile ducts, excretion of radioactivity in bile amounted to 15/30% of the AD for ♂/♀ after a single low dose and 9.9/10% of the AD for ♂/♀ after a single high dose, while elimination via in feces decreased to 76/50% of the AD for ♂/♀ following a single low dose and 78/75% of the AD for ♂/♀ following a single high dose. Fat concentrations declined in a relatively linear fashion with apparent half-lives of approximately 5/8.5 days in ♂/♀.

Study Type/Animal/PMRA No.	Study results
	Distribution: Retention of radioactivity in tissues/carcass at 120 hours after dosing was in the range of 2.8–3.8% of the AD. Tissues with the highest concentrations, from highest to lowest concentrations, in the low and high dose groups 120 hours after a single dose were as follows: fat, liver, kidneys, muscle. Tissue radioactivity concentrations were increased in animals given repeated low doses compared to those given single low doses. After seven daily oral low doses, highest tissue radioactivity concentrations were found at 4 hours after the last dose and, in general, tissue concentrations declined progressively with time. At most sacrifice times, tissues containing the highest levels were as follows: fat, adrenal glands, ovaries, liver, and thyroid. Quantitative measurements suggested that the pancreas contained high levels of radioactivity, but whole-body autoradiography indicated that these high levels were probably due to associated fatty tissue. **Metabolism:** In feces collected during 0–72 hours after single doses, unchanged etofenprox accounted for 6.6/14% of the AD in ♂/♀ following a single low dose, and 23/29% of the AD in ♂/♀ following a single high dose. Two major metabolites (designated 3A and 3B) were present which together accounted for 28-39% of the AD in feces. These were identified as resulting from O-demethylation of the ethoxyphenyl moiety (3A = desethyletofenprox) and ring-hydroxylation of the phenoxybenzyl moiety of etofenprox (3B = 4'-hydroxyetofenprox). Metabolites 3A and 3B were also excreted in bile (~70% of biliary radioactivity) and urine (0.6-1.7% of the AD) as glucuronide or sulphate conjugates. **Limitations**: Some methodology details lacking.
Metabolism (gavage, single dose) Sprague-Dawley rat PMRA No. 3137425	**Acceptable with limitations** A single gavage dose of 30 mg/kg bw (α-^{14}C-ethofenprox in PEG) was administered to determine if α-CO (2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzoate) was a metabolite in the rat. Approximately 67–69% of the AD was recovered in feces and 11–14% in urine collected up to 23 days after dosing. In urine, α-CO was detected at up to 0.002% of the AD. Metabolic products of α-CO were detected, including PB-acid (3-phenoxybenzoic acid; 4% of the AD in feces) and 4'OH PB-acid (3-(4-hydroxyphenoxy)benzoic acid) in conjugated form (0.05/0.006% of the AD in feces/urine).

Study Type/Animal/PMRA No.	Study results
	On the basis of these observations, it was concluded that α-CO was one of the metabolites in rats. **Limitations:** Small group size, not conducted according to GLP; no Quality Assurance statement, limitations in reporting, inadequate metabolite identification according to current test guidelines.
Transplacental and lactational transfer (gavage, repeat dose) Sprague-Dawley rat PMRA No. 3060747	Study involved gavage dosing of 30 mg/kg bw (all rats given 1:1 mixture of [1-^{14}C-propyl] etofenprox and [α-^{14}C-benzyl] etofenprox in PEG 400). To assess tissue distribution during pregnancy, pregnant ♀ were dosed from GD 10 to 16, and sacrificed at intervals up to 120 hours after the final dose. Maternal tissues (mammary glands, adrenals, kidneys, heart, liver, plasma), fetuses, and placentae were sampled. The transfer of radioactivity into the milk of nursing dams was also assessed (dosing from GD 18 to LD 9). Following seven daily oral doses to pregnant rats, concentrations of radioactivity were highest at 4 hours after the final dose on GD 16, and were lower in fetuses (1.6–1.7 µg/g) and placentae (4.6–4.8 µg/g) compared to concentrations in maternal tissues such as the liver (27.2 µg/g) and adrenal glands (61.5 µg/g). The highest maternal tissue concentrations were present in mammary glands (87.4 µg/g at 4 hours, declining to 32.4 µg/g at 120 hours), followed by adrenals, liver, and kidneys. The secretion of radioactivity into the milk of nursing rat mothers was investigated via measurement of the stomach contents of suckling pups. During repeated daily dosing to the mothers, pup stomach contents contained radioactivity concentrations in the range of 40–90 µg/g compared to maternal plasma concentrations of 1.9–3.6 µg/mL. Concentrations in pup stomach contents were highest at approximately LD 4, 6, and 9. Total intake of radioactivity by pups was equivalent to 13–47 µg per pup after suckling for 1 hour. At 30 hours after cessation of dosing, radioactivity concentrations in pup stomach contents had declined to 1.6–1.8 µg/g. Approximately 95% of the radioactivity ingested by the pups was associated with unchanged etofenprox.
Biokinetics and metabolism (gavage, single dose) Beagle dog PMRA No. 3060746	**Acceptable with limitations** A single gavage dose of 30 mg/kg bw (1:1 mixture of [1-^{14}C-propyl] etofenprox and [α-^{14}C-benzyl] etofenprox in PEG 400) was administered to assess biokinetics and metabolism. Urine, feces and blood samples were collected up to 120 hours post-dosing.

Study Type/Animal/PMRA No.	Study results
	Excretion: At 120 hours post-dosing, 89% and 6.2% of the AD was excreted in feces and urine, respectively. The majority of the radioactivity was excreted in the first 24 hours. **Kinetics:** Plasma C_{max} values occurred at 0.25 to 3 hours post-dosing and were in the range of 4.4 to 7.2 µg equivalent/mL. Following the peak, concentrations declined with half-lives in the range of 8.6 to 17 hours. **Distribution:** In animals sacrificed at 2 or 4 hours after dosing, highest tissue concentrations (approximately three times higher than plasma concentrations) were found in liver (up to 0.9% of the AD). Concentrations in kidneys and fat were similar to that in plasma. High concentrations of radioactivity were found in bile suggesting that this was an important route of elimination of absorbed radioactivity. **Metabolism:** Unchanged etofenprox accounted for more than 90% of the radioactivity extracted from feces collected from 0 to 24 hours feces, and represented 49/59% of the AD in ♂/♀. The two most prominent metabolites in feces, together accounting for about 3% of the AD in the 0 to 24 hour feces were metabolites 3A (desethyletofenprox) and 3B (4'-hydroxyetofenprox), resulting from O-demethylation of the ethoxyphenyl moiety and ring-hydroxylation of the phenoxybenzyl moiety of etofenprox, respectively. Radioactivity in bile and urine appeared to be entirely associated with polar conjugated metabolites. Enzymic hydrolysis released the two metabolites found in feces (metabolites 3A and 3B) as major components and a number of minor metabolites. Metabolites 3A and 3B were detected at 1.2% and 1.8% of the AD in urine, respectively. The metabolite desethyl-4'-hydroxyethofenprox was also identified in bile and urine. Most of the radioactivity recovered in fat (>80%) was associated with unchanged etofenprox. Radioactivity in liver was mainly associated with conjugates of metabolites 3A and 3B. Unchanged etofenprox was present in liver at concentrations of 0.6/1.7 µg/g in ♂/♀. **Limitations:** Small group sizes, biliary elimination was not evaluated, low recovery (15% of the AD) in one dog, inadequate metabolite identification according to current test guidelines.

Study Type/Animal/PMRA No.	Study results
Acute toxicity studies	
Acute Oral Toxicity Beagle dog PMRA 1547422	LD_{50} > 5000 mg/kg bw (♂/♀) Clinical signs of toxicity included green coloured feces (♂). **Low acute oral toxicity**
Acute oral toxicity Sprague-Dawley rat PMRA No. 3137417	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity. **Low acute oral toxicity**
Acute toxicity – oral and dermal (non-guideline) Sprague-Dawley rat PMRA No. 1547423	Oral: LD_{50} > 42.88 g/kg bw (♂/♀) Dermal: LD_{50} > 2.14 g/kg bw (♂/♀) Clinical signs of toxicity (oral) included reduction in spontaneous movement; ochre coloured, glossy and muddy feces; oily dirty hair; blood-look substance from nostrils and eyelids; diarrhea. **Low acute oral and dermal toxicity**
Acute toxicity – oral and dermal (non-guideline) IRC mouse PMRA No. 1547424	Oral: LD_{50} > 107.2 g/kg bw (♂/♀) Dermal: LD_{50} > 2.14 g/kg bw (♂/♀) Clinical signs of toxicity (oral) included death, watery diarrhea, reduction in spontaneous movements, oiling of hair, yellow soft stool, abdominal swelling, piloerection, facial edema. **Low acute oral and dermal toxicity**
Acute dermal toxicity Sprague-Dawley rat PMRA No. 164720	LD_{50} > 2000 mg/kg bw (♂/♀) No clinical signs of toxicity. **Low acute dermal toxicity**
Acute inhalation toxicity (whole body) Wistar rat PMRA No. 1597797	LC_{50} > 5.9 g/m^3 (♂/♀) Clinical signs of toxicity included abnormal body posture, closing/partial closing of the eyes, abnormal respiratory movements, lethargy (♂/♀); hair loss and hyperactivity (♀). **Low acute inhalation toxicity**
Eye irritation Japanese white rabbit PMRA No. 1547426	MAS = 0.89/110 MIS = 2/110 (1 hour) **Minimally irritating to the eyes**
Skin irritation	MAS = 0.11/8

Study Type/Animal/PMRA No.	Study results
Japanese white rabbit PMRA No. 1547427	MIS = 0.167/8 (48 hours) **Minimally irritating to the skin**
Dermal sensitization (maximization test) English Hartley guinea pig PMRA No. 1547428	**Negative**
Short-term toxicity studies	
90-day oral toxicity (diet) CD-1 mouse PMRA No. 3060760	NOAEL = 375/390 mg/kg bw/day (♂/♀) LOAEL = 1975/2192 mg/kg bw/day (♂/♀) Effects at LOAEL: piloerection, hunched posture, emaciated appearance, anaemic appearance, body tremors, respiratory distress, death (2♂, 6♀), ↓ fc, ↓ fe, ↓ bw, ↓ bwg, ↑ wc, ↓ HGB, ↓ RBC, ↑ cholesterol, ↓ urine specific gravity, ↑ rel. liver wt, ↑ kidney wt, gross pathology findings (cortical scarring of the kidneys, pale kidneys, enlarged kidneys, cystic kidneys, minimal adipose tissue, small thymus), cortical and medullary tubular basophilia, tubular dilation and dilation of the renal pelvis (frequently cystic), centrilobular hepatocyte enlargement, increased cellularity of splenic white pulp, reactive changes in lymph nodes, reduced thymic cellularity (♂/♀); ↓ glucose, ↓ ALT (♂); lethargy, unsteady gait, ↑ BUN, ↑ WBC, ↓ ALK, ↓ abs. thymus wt, misshapen kidneys (♀).
90-day oral toxicity (diet) Sprague-Dawley rat PMRA No. 3060785	NOAEL = 20/23 mg/kg bw/day (♂/♀) LOAEL = 120/142 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ number of microfollicles in the thyroid (♂/♀); ↓ T4, ↑ cholesterol, ↑ ALT, ↑ AST, ↑ LDH, enlarged liver, ↑ thyroid wt (♂); ↑ liver wt, enlargement of centrilobular hepatocytes, ↓ MCV, enlarged adrenal glands (♀).
12-month oral toxicity (diet) Beagle dog PMRA No. 3060784	NOAEL = 33/32 mg/kg bw/day (♂/♀) LOAEL = 352/339 mg/kg bw/day (♂/♀) Effects at LOAEL: ↓ PCV, ↓ RBC, ↓ serum total protein, ↓ albumin, ↓ cholesterol, ↑ ALK, ↑ liver wt, ↑ kidney wt, ↑ pancreas wt, ↑ lung wt, ↑ adrenal wt, lobular markings of the liver (♂/♀); ↓ HGB (♂); swelling of centrilobular liver cells (♀). Recovery group: no apparent persistence in recovery group animals, although group sizes were limited.
28-day dermal toxicity	Systemic NOAEL = 1000 mg/kg bw/day (♂/♀) Systemic LOAEL not established

Study Type/Animal/PMRA No.	Study results
NZW rabbit PMRA No. 3060782	≥ 400 mg/kg bw/day: ↑ dermal lesions (epidermal hyperplasia, dermal inflammation, dermal heterophil infiltrates), ↑ erythema (♂/♀). No adverse treatment-related findings indicative of systemic toxicity. Recovery animals: After a 2-week recovery period, histological skin lesions were observed with lower incidence, severity and distribution compared to main study animals.
90-day dermal toxicity – waiver request PMRA No. 3137421	A request to waive the requirement for a 90-day dermal toxicity study was submitted, focusing on the argument that the 28-day dermal study is adequate to assess hazards from the repeated dermal exposure. Overall, based on the absence of adverse systemic effects in the 28-day dermal toxicity study up to the limit dose, and the noted endpoints of concern in the database, particularly those in the young, it was determined that a guideline 90-day dermal toxicity study is unlikely to provide additional information critical to the human health assessment.
90-day inhalation toxicity (whole body) Wistar rat PMRA No. 3060781	NOAEL = 33/8.8 mg/kg bw/day (♂/♀) LOAEL = 161/43 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ thyroid microfollicles, ↑ height of follicular epithelium in the thyroid, ↑ liver wt, ↑ adrenal wt (♂/♀); enlargement of centrilobular hepatocytes, vacuolated hepatocytes (♂); ↑ kidney wt (♀).
Chronic toxicity/Oncogenicity studies	
18-month oncogenicity (diet) CD-1 mouse PMRA No. 3060765, 3060766, 3060770, 3060767, 3060768, 3060769, 3060771, 3060764, 3650953	NOAEL = 3.1/12 mg/kg bw/day (♂/♀) LOAEL = 10/81 mg/kg bw/day (♂/♀) Effects at LOAEL: pale kidneys, ↑ severity of dilated/basophilic renal cortical tubules (♂); renal cortical cyst(s) lined by columnar epithelium (♀). Incidence of total renal cortical adenoma and carcinoma (♂): 0%, 0%, 0%, 2%, 5.8%. **Evidence of tumourigenicity at a dose exceeding MTD (survival in high-dose ♂ at study termination was 19%).**
24-month chronic toxicity/oncogenicity (diet) Sprague-Dawley rat PMRA No. 3060774, 3060775, 3060779,	NOAEL = 3.7/4.8 mg/kg bw/day (♂/♀) LOAEL = 26/34 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ urine volume, ↑ thrombotest time, ↑ abs. thyroid wt, ↑ abs. kidney wt, foci/areas of eosinophilic hepatocytes (♂); centrilobular vacuolated hepatocytes (♀).

Study Type/Animal/PMRA No.	Study results
3060776, 3060777, 3060778, 3060780, 3060773, 3650952	Incidence of thyroid follicular cell adenomas (♂/♀): Adenomas: 12%, 12%, 8%, 10%, 22% / 0%, 6%, 4%, 0%, 18% (♂/♀) Carcinomas: 0%, 0%, 2%, 6%, 4% / 0%, 0%, 0%, 4%, 2% (♂/♀) Combined: 12%, 12%, 10%, 16%, 26% / 0%, 6%, 4%, 4%, 18% (♂/♀) **Evidence of tumourigenicity**
Developmental/Reproductive toxicity studies	
2-generation reproductive toxicity (diet) Sprague-Dawley rat PMRA No. 3060763	**Acceptable with limitations** F0 and F1b generations were mated twice. F1a and F2b offspring were maintained on test diet for 13 weeks after weaning before sacrifice. F2a offspring were sacrificed at weaning. **Parental and F2 post-weaning toxicity:** NOAEL = 7.1/58 mg/kg bw/day (♂/♀) LOAEL = 50/420 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ abs. thyroid wt (F0), early progressive glomerulonephrosis (F1b), occasional basophilic tubules (F1b) (♂/♀); centrilobular hepatocyte vacuolization (F1b) (♂); deaths (F1b, 1♀ week 14; related to renal toxicity), ↓ post-weaning bw (F1a, F1b, F2b; carry-over from pre-weaning effect), ↑ wc (F1a, F1b, F2b), ↑ kidney wt (F1b, F2b), ↑ liver wt (F0, F1b, F2b), ↑ abs. thyroid wt (F2b), gross kidney pathology (enlarged, swollen, misshapen kidney with or without irregular cortical scarring) (F1a, F1b, F2b), cystic collecting ducts in the kidney (F1b), foreshortened renal papilla (F1b), renal focal medullary fibrosis (F1b), mineral deposits in kidney (F1b), vascular congestion/hemorrhage in the renal medulla (F1b), acute inflammatory cells in renal collecting ducts (F1b), dilated renal cortical tubules (F1b), early progressive glomerulonephrosis (F1b), centrilobular hepatocyte enlargement (F1b), ↑ abs. spleen wt (F1b), ↑ pituitary wt (F2b), ↑ spleen wt (F2b), ↑ height of thyroid follicular epithelium, pyelonephritis (F1b), renal papillary necrosis (F1b), epithelial hyperplasia in renal pelvis (F1b) (♀). **Offspring toxicity:** NOAEL = 58 mg/kg bw/day (♀) LOAEL = 420 mg/kg bw/day (♀) Effects at LOAEL: ↑ pup mortality (PND 12–21) (F1a, F1b, F2a), ↓ lactation index (F1a, F1b, F2a), ↓ pup wt (F1a, F1b, PND 4-21; F2a, F2b PND 8–21), ↓ litter wt (F1a, F1b, F2a, F2b), body tremors (F1a,

Study Type/Animal/PMRA No.	Study results
	F1b, F2a), distended abdomen (F1a, F2a), abnormal gait (F1a, F1b), kidney pathology (enlarged, swollen, pale, cystic, misshapen, irregular cortical scarring) (F1a, F1b, F2a, F2b), ↑ kidney wt (F1a, F1b, F2a, F2b), ↑ rel. heart wt (F1a, F1b, F2a, F2b), ↑ rel. liver wt (F2a), ↑ rel. spleen (F1a) (♂/♀); ↑ rel. liver wt (F1b) (♀). **Reproductive toxicity:** NOAEL = 347/420 mg/kg bw/day (♂/♀) LOAEL not established No treatment-related findings on reproductive performance or reproductive organs assessed. No evidence of sensitivity of the young. Serious endpoint (pup mortality) in the presence of parental toxicity. **Limitations:** No assessment of estrous cyclicity (except during mating), sperm parameters, or sexual maturation. No data on achieved intake of test material during the gestation or lactation periods.
Special study assessing developmental and reproductive toxicity (gavage) (non-guideline) Pre-mating exposure Sprague-Dawley rat PMRA No. 3137422	Dosing of ♂ for 9 weeks prior to mating and during mating and of ♀ for 2 weeks prior to mating until GD 7. Sacrifice of ♂ after mating and of ♀ on GD 20 followed by cesarian section to assess embryo-fetal development. **Parental toxicity** NOAEL = 250 mg/kg bw/day (♂/♀) LOAEL = 5000 mg/kg bw/day (♂/♀) Effects at LOAEL: staining/wetness around the anogenital region, white crystalline appearance of feces, renal pelvic dilation (♂/♀); unkempt hair coat, skin lesions (♂). **Developmental and reproductive toxicity** NOAEL = 250 mg/kg bw/day (♂/♀) LOAEL = 5000 mg/kg bw/day (♂/♀) Effects at LOAEL: ↑ pre-implantation loss, ↑ resorptions (total and early), ↑ post-implantation loss. **No evidence of sensitivity of the young** **No evidence of treatment-related malformations**
Special study assessing developmental and reproductive toxicity (gavage) (non-guideline)	**Acceptable with limitations** Pregnant F0 ♀ dosed from GD 6 to 17; 2/3 sacrificed on GD 20 and underwent cesarian section to assess embryo-fetal development; 1/3

Study Type/Animal/PMRA No.	Study results
Gestational exposure Sprague-Dawley rat PMRA No. 3060757	allowed to deliver their litters and sacrificed on LD 21. F1 generation offspring were mated at approximately 82 days old to yield the F2 generation, but were not directly dosed. **Maternal (F0) toxicity** NOAEL = 250 mg/kg bw/day LOAEL = 5000 mg/kg bw/day Effects at LOAEL: wet/yellow staining of fur around the anogenital region, ↓ bwg (GD 6-17, F1), ↑ resorptions (early and total), ↑ post-implantation loss. **Developmental toxicity** NOAEL = 250 mg/kg bw/day LOAEL = 5000 mg/kg bw/day Effects at LOAEL: ↓ ♂ sex ratio of fetuses, ↑ resorptions (early and total), ↑ post-implantation loss, ↑ incidence of microphthalmia and anophthalmia, left renal pelvic dilation, intra-abdominal hemorrhage, subcutaneous hemorrhage. **Offspring and reproductive toxicity** NOAEL = 5000 mg/kg bw/day LOAEL not established No treatment-related findings in animals, which were not directly dosed, in the F1 (pre-weaning, pre-mating, gestation or lactation) or F2 (pre-weaning) generations. **No evidence of sensitivity of the young.** **Evidence of treatment-related malformations in the presence of maternal toxicity at a dose level exceeding the recommended limit dose of testing.** **Limitations:** no assessment of estrous cycle, sperm parameters, or preputial separation.
Special study assessing developmental and reproductive toxicity (gavage) (non-guideline) Lactational exposure Sprague-Dawley rat	**Acceptable with limitations** Pregnant F0 ♀ dosed from GD 7 to LD 21; F1 generation offspring were mated at approximately 84 days old to yield the F2 generation, but were not directly dosed. F1 animals underwent assessment of behaviour and developmental landmarks. **Maternal (F0) toxicity** NOAEL = 250 mg/kg bw/day

Study Type/Animal/PMRA No.	Study results
PMRA No. 3137426	LOAEL = 5000 mg/kg bw/day Effects at LOAEL: yellow staining of fur around anogenital region (gestation), ↓ bwg (GD 17-20), ↑ total litter loss. **Offspring (F1) toxicity** NOAEL = 250 mg/kg bw/day LOAEL = 5000 mg/kg bw/day Effects at LOAEL: ↑ pup mortality (PND 12-21), ↑ total litter loss, tremors, subcutaneous hemorrhage around the nose, general incoordination (occurring antemortem, PND 16-20), ↓ litter wt (PND 12 and 21), ↓ pup wt (PND 12 and 21), ↑ abs. kidney wt, gross lesions of the kidney (enlarged, pale, scarred cortices), cystic collecting ducts of the kidney, acute inflammatory cells in renal collecting ducts (♂/♀); mineral cast in renal medulla, early renal cortical scarring (♂). **Offspring (F2) toxicity** NOAEL = 5000 mg/kg bw/day LOAEL not established No treatment-related findings in F2 offspring (F1 parents were not directly dosed). **Parental (F1) toxicity** NOAEL = 250 mg/kg bw/day LOAEL = 5000 mg/kg bw/day Effects at LOAEL: ↓ bw (early post-weaning period), ↑ wc, ↑ kidney wt, gross lesions of renal cortex (pale, scarred, misshapen), cystic collecting ducts of the kidney, acute inflammatory cells in renal collecting ducts, mineral casts in renal medulla, focal fibrosis of renal papilla, vascular congestion of renal medulla, renal papillary necrosis, pyelitis and foreshortening of renal papilla (♂/♀); ↓ bw (♂). **Reproductive (F1) toxicity** NOAEL = 5000 mg/kg bw/day LOAEL not established No treatment-related reproductive findings in the F1 offspring (not directly dosed) that were mated.

Study Type/Animal/PMRA No.	Study results
	No evidence of sensitivity of the young **Serious endpoint (pup mortality) in the presence of maternal toxicity at a dose level exceeding the recommended limit dose of testing.** **Limitations:** non-guideline study; no assessment of estrous cycle, sperm parameters, or preputial separation; the timing of clinical signs was not provided.
Developmental toxicity – dose range-finding (gavage) NZW rabbit PMRA No. 3060755	**Acceptable with limitations** **Maternal toxicity** ≥250 mg/kg bw/day: spontaneous abortions (1 on GD 27 at 250 mg/kg bw/day; 3 on GD 23, 24, and 27 at 500 mg/kg bw/day). 500 mg/kg bw/day: bw loss (throughout study), ↓ bw/bwg, ↓ fc, thin appearance, few or no feces, pale liver. **Developmental toxicity** ≥250 mg/kg bw/day: spontaneous abortions. Fetal assessments were limited to bw and external abnormalities. **Limitations:** dose range-finding study with limited group sizes and fetal assessments.
Developmental toxicity (gavage) NZW rabbit PMRA No. 3060756	**Acceptable with limitations** **Maternal toxicity** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day Effects at LOAEL: spontaneous abortion (GD 25), thin and pale appearance, cold to the touch, few or no feces, bw loss (GD 6-9, 27-29), ↓ bwg GD 6-29, dark area on stomach, pale liver. **Developmental toxicity** NOAEL and LOAEL not established due to limited fetal assessment. **Limitations:** fetal assessments not conducted in full due to procedural issues.
Developmental toxicity (gavage) NZW rabbit	**Maternal toxicity** NOAEL = 100 mg/kg bw/day LOAEL = 300 mg/kg bw/day

Study Type/Animal/PMRA No.	Study results
PMRA No. 3207865	Effects at LOAEL: spontaneous abortions (GD 26 and 28), deaths or early sacrifice (GD 16 and 26), thin appearance, few or no feces, bw loss (GD 6-9, GD 6-29), ↓ bw, ↓ bwg, ↓ fc, ↑ resorptions, ↑ post-implantation loss. **Developmental toxicity** NOAEL = 30 mg/kg bw/day LOAEL = 100 mg/kg bw/day Effects at LOAEL: unossified talus bone. **Evidence of sensitivity of the young** **No evidence of treatment-related malformations**
Developmental toxicity (gavage) NZW rabbit PMRA No. 3207864	**Maternal toxicity** NOAEL = 50 mg/kg bw/day LOAEL = 250 mg/kg bw/day Effects at LOAEL: ↓ fecal output, ↓ wc, orange-coloured urine, piloerection, hunched posture, spontaneous abortion (1GD 23, 26, 28, 29), bw loss (GD 6-8, 6-10), ↓ bw, ↓ bwg, ↓ fc, ↓ litter size, ↑ resorptions (early and total), ↑ post-implantation loss. **Developmental toxicity** NOAEL = 50 mg/kg bw/day LOAEL = 250 mg/kg bw/day Effects at LOAEL: bifurcated gall bladder, unossified talus bone, spontaneous abortion, ↑ resorptions. **No evidence of sensitivity of the young** **Evidence of treatment-related malformations (bifurcated gallbladder) in the presence of maternal toxicity**
Genotoxicity Studies	
Bacterial reverse mutation assay S. typhimurium TA98, TA100, TA1535, TA1537, TA 1538 PMRA No. 3060754	**Negative ± metabolic activation** Tested up to a limit concentration.
In vitro unscheduled DNA synthesis Human HeLa S3 cell line PMRA No. 3137423	**Negative ± metabolic activation** Tested up to cytotoxic or precipitating concentrations.

Study Type/Animal/PMRA No.	Study results
In vitro mutation assay in mammalian cells Chinese hamster V79 cells PMRA No. 3060752	**Acceptable with limitations** **Negative ± metabolic activation** Tested up to cytotoxic concentrations. **Limitations:** Controls in the confirmatory assay (Experiment II) showed a higher than expected spontaneous background mutant frequency. However, since the test material groups were similar to controls, failed to show the required fivefold increase over controls, and the positive controls produced a strong response in both experiments, the combined results of both experiments are considered reliable and support a negative finding.
In vitro chromosomal aberration assay Human peripheral blood lymphocytes PMRA No. 3060751	**Negative ± metabolic activation** Tested up to cytotoxic concentrations.
In vivo micronucleus assay (gavage) CD-1 mouse PMRA No. 3060749	**Negative** No clinical signs of toxicity
In vitro micronucleus assay Human peripheral blood lymphocytes PMRA No. 3137424	**Negative ± metabolic activation** Tested up to cytotoxic concentrations
Neurotoxicity studies	
Acute oral neurotoxicity (gavage) Sprague-Dawley rat PMRA No. 3060761	**Acceptable with limitations** NOAEL = 500 mg/kg bw (♂/♀) LOAEL = 2000 mg/kg bw (♂/♀) Effects at LOAEL: axonal degeneration (cervical ventral funiculus in both sexes; cervical dorsal root ganglion in ♂; lumbar dorsal funiculus in ♀) (not assessed in lower dose groups) (♂/♀). **Evidence of potential neurotoxicity**

Study Type/Animal/PMRA No.	Study results
	Limitation: no positive control data, neuropathology not assessed in all dose groups.
90-day neurotoxicity (diet) Sprague-Dawley rat PMRA No. 3060762	**Acceptable with limitations** NOAEL = 149 mg/kg bw/day/not established (♂/♀) LOAEL = 299/174 mg/kg bw/day (♂/♀). Effects at LOAEL: ↓ bwg (♂); ↓ bw, ↓ bwg, ↓ fc, ↑ barbering (♀). **No evidence of neurotoxicity.** **Limitation:** no positive control data.
Developmental neurotoxicity (diet) Sprague-Dawley rat PMRA No. 3060759, 3060758	**Acceptable with limitations** **Maternal toxicity** NOAEL = 57 mg/kg bw/day LOAEL = 169 mg/kg bw/day Effects at LOAEL: ↑ rearing activity. **Offspring toxicity** NOAEL = 57 mg/kg bw/day LOAEL = 169 mg/kg bw/day Effects at LOAEL: ↓ bwg, ↑ deaths PND 14-21, ocular abnormalities (large/prominent/dark eyes and opacity; clinically observed mostly PND 16-21), ↑ amplitude and ↓ habituation in auditory startle response (PND 23 and 58), ↑ corpus callosum thickness (PND 21) (♂/♀); ↓ bw (PND 7), ↓ total motor activity (PND 58), ↑ pre-impulse inhibition in auditory startle response (PND 58), shorter latency to peak startle response (PND 58), bilateral renal pelvic dilatation, lenticular degeneration with associated retinal folds and minimal accumulation of macrophages in the iris or the uvea, ↑ hippocampus thickness (PND 65) (♂); ↓ hippocampus thickness (PND 65) (♀). **No evidence of sensitivity of the young.** **Evidence of serious endpoints (pup mortalities, neuropathology and altered neurobehaviour) in the presence of maternal toxicity.** **Limitations:** descriptions of behavioural equipment used were lacking; deficiency in memory assessment in offspring (platform not removed during Morris water maze testing); brain morphometric measurements limited to offspring of control and high-dose groups; positive control data available for FOB assessment only; conducted

Study Type/Animal/PMRA No.	Study results
	according to 1998 USEPA test guideline (prior to adoption of OECD test guideline in 2007).
Other studies	
28-day immunotoxicity study (diet) CD-1 mouse PMRA No. 3060815	NOAEL = 239/284 mg/kg bw/day (♂/♀) LOAEL = 1116/1528 mg/kg bw/day (♂/♀) Effects at LOAEL: bw loss (days 1-4), ↓ bwg, ↑ wc, ↑ abs. spleen wt (♂/♀); ↓ fc, ↑ total spleen activity (IgM PFC/spleen), ↑ cells/spleen (♂). No suppression of anti-sRBC T-cell dependent humoral antibody response. Increased total spleen activity (IgM PFC/spleen) and cells/spleen in ♂ at LOAEL may provide an indication of perturbation/dysregulation of the immunologic response. **Possible evidence of immune system dysregulation at dose level exceeding the limit dose.**
28-day immunotoxicity study (diet) Sprague-Dawley rat (♂) PMRA No. 3060814	NOAEL = 213 mg/kg bw/day (♂) LOAEL = 1053 mg/kg bw/day (♂) Effects at LOAEL: ↓ bw, ↓ bwg, ↓ fc (♂). No treatment-related effect on anti-sRBC T-cell dependent humoral antibody response. **No evidence of immune system dysregulation.**
28-day mechanistic study investigating thyroid function and hepatic microsomal enzyme induction (diet) (non-guideline) Sprague-Dawley rat PMRA No. 3060748	**Acceptable with limitations** Different groups of animals were dosed for either 14 days or 28 days and then sacrificed, or for 14 days or 28 days and then sacrificed after a 28-day recovery period. ≥94/102 mg/kg bw/day (♂/♀): ↑ TSH (14 and 28 days of dosing) (♂/♀); ↑ rel. liver wt (14 days of dosing) (♂). ≥371/399 mg/kg bw/day (♂/♀): ↑ 4-MUGT (14 days of dosing), ↑ abs. liver wt (14 days of dosing) (♂); ↑ rel. liver wt (28 days of dosing) (♀). 1598/1620 mg/kg bw/day (♂/♀): ↑ PNGT (14 days of dosing), multinucleated hepatocytes (14 and 28 days of dosing), centrilobular hepatocellular hypertrophy (14 days of dosing) (♂/♀); ↓ T4 (14 days of dosing), ↑ protein yield in hepatic microsomal fractions (28 days of dosing), mild ↑ thyroid cell proliferation rate (14 and 28 days of dosing), ↑ rel. liver wt (28 days of dosing) (♂); ↑ 4-MUGT (14 days of dosing), ↑ liver wt (14 days of dosing), ↑ abs. liver wt (28 days of

Study Type/Animal/PMRA No.	Study results
	dosing), centrilobular hepatocellular hypertrophy (28 days of dosing) (♀). **Recovery groups:** ≥371/399 mg/kg bw/day (♂/♀): ↑ 4-MUGT (14 days of dosing (♂/♀); ↑ protein yield in hepatic microsomal fractions (14 days of dosing), ↑ PNGT (14 days of dosing) (♂). 1598/1620 mg/kg bw/day (♂/♀): multinucleated hepatocytes (14 and 28 days of dosing) (♂/♀); ↑ protein yield in hepatic microsomal fractions (14 days of dosing), ↑ PNGT (14 days of dosing), centrilobular hepatocellular hypertrophy (28 days of dosing) (♀). Notes: effect on TSH was reversible in ♂; dosing for 28 days did not result in marked changes in UDP-GT; there was a general trend for a decrease in thyroid peroxidase activity in both sexes; effect on thyroid cell proliferation rate was reversible.
Oral comparative thyroid assay (gavage) Sprague-Dawley rat PMRA No. 3586447	**Acceptable with limitations** Maternal animals were dosed GD 6-20 or GD 6-LD 21. Thyroid hormones assessed in maternal animals on GD 20 and LD 21, in fetuses on GD 20, and in pups on PND 4 and 21. **Maternal toxicity** NOAEL not established LOAEL = 25 mg/kg bw/day Effects at LOAEL: ↑ incidence and severity of epithelial hyperplasia and hypertrophy of the thyroid gland (LD 21), ↓ T3 (LD 21). **Developmental toxicity** NOAEL = 450 mg/kg bw/day. LOAEL not established. No treatment-related effects on fetal body weights, fetal thyroid hormone levels, or cesarian section parameters. **Offspring toxicity** NOAEL = 450 mg/kg bw/day. LOAEL not established. No treatment-related effects on pup body weights, liver or thyroid gland weights, gross necropsy or histopathology findings, or thyroid hormone levels.

Study Type/Animal/PMRA No.	Study results
	No evidence of sensitivity of the young. Limitation: The TSH data in this study were too variable to be reliable and could not be used qualitatively or quantitatively.
Literature studies	
Liver tumour promoting effect on etofenprox in rats and its possible mechanism of action (8-week dietary) Literature study: Hojo, Yuri et al. (2012) F344 rat (♂) PMRA No. 3764322	Acceptable with limitations. Rats were initiated with DEN and 2 weeks later were fed diets containing etofenprox for 8 weeks. To enhance hepatocellular proliferation, animals were subjected to a partial hepatectomy 3 weeks after DEN initiation. Under the conditions of this study, it was reported that treatment with DEN + etofenprox showed liver tumour-promoting activity in rats, demonstrated by an increase in the number and area of GST-P positive foci in the liver in rats treated with DEN + ≥223 mg/kg bw/day etofenprox, and an upregulation of certain genes considered to promote liver tumours and ROS. GST-P is a pre-neoplastic marker for hepatocarcinogenesis in rats. The results of the study suggest a mechanism of action in which etofenprox activates CAR translocation to the nucleus and enhances microsomal ROS production, resulting in the upregulation of Nrf2 gene batteries, and such oxidative stress subsequently induces liver tumour-promoting effects by increased cellular proliferation. ≥0.25% (105 mg/kg bw/day): upregulated Cyp2b1/2, microsomal ROS production, ↓ CAR, translocation of CAR into the nuclei of hepatocytes, ↑ Nqo1 (Nrf2 gene battery). ≥0.50% (223 mg/kg bw/day): ↑ number and area of GST-P positive foci, ↑ TBARS content (marker of lipid peroxidation), ↓ Sult2al (CAR related protein), ↑ Gsta5 (Yc2) (Nrf2 gene battery). 1.0% (445 mg/kg bw/day): ↑ Ugt1a6 (Nrf2 gene battery), ↑ 8-OHdG (oxidative guanine). **Limitations:** no negative or vehicle control groups.

Table 3 Toxicity Profile of RF2129 EC and RF2220 Premium Aerosol II-M Premise Spray Containing Etofenprox

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, effects observed in both sexes are presented first followed by sex-specific effects in males, then females, each separated by semi-colons.

Study type/Animal/PMRA No.	Study results
RF2129 EC	
Acute toxicity studies	
Acute oral toxicity Sprague-Dawley rat PMRA No. 3059941	LD_{50} = 1750 mg/kg bw (♀) No clinical signs of toxicity **Slight acute oral toxicity**
Acute dermal toxicity Sprague-Dawley rat PMRA No. 3059942	LD_{50} > 5000 mg/kg bw (♂/♀) No clinical signs of toxicity **Low acute dermal toxicity**
Acute inhalation toxicity Sprague-Dawley rat PMRA No. 3059943	LC_{50} > 2.07 mg/L (♂/♀) No clinical signs of toxicity **Low acute inhalation toxicity**
Eye irritation New Zealand albino rabbit PMRA No. 3059944	MAS = 11.8/110 MIS = 20.7/110 at 24 hours **Mildly irritating to the eye**
Dermal irritation New Zealand albino rabbit PMRA No. 3059945	MAS = 1.6/8 MIS = 3/8 at 24 hours **Mildly irritating to the skin**
Dermal sensitization (Buehler method) Hartley albino guinea pig PMRA No. 3059946	**Negative**
RF2220 Premium Aerosol II-M Premise Spray	
Acute toxicity studies	
Acute oral toxicity	LD_{50} > 5000 mg/kg bw (♀)

Study type/Animal/PMRA No.	Study results
Sprague-Dawley rat PMRA No. 3114738	No clinical signs of toxicity **Low acute oral toxicity**
Acute dermal toxicity Sprague-Dawley rat PMRA No. 3114739	LD_{50} > 5000 mg/kg bw (♂/♀) No clinical signs of toxicity **Low acute dermal toxicity**
Acute inhalation toxicity Sprague-Dawley rat PMRA No. 3114740	LC_{50} > 2.05 mg/L (♂/♀) No clinical signs of toxicity **Low acute inhalation toxicity**
Eye irritation New Zealand albino rabbit PMRA No. 3114741	MAS = 0/110 MIS = 0 **Non-irritating to the eye**
Dermal irritation New Zealand albino rabbit PMRA No. 3114742	MAS = 1.33/8 MIS = 2/8 at 24 hours **Slightly irritating to the skin**
Dermal sensitization (Buehler method) Hartley albino guinea pig PMRA No. 3114743	**Negative**

Table 4 Proposed personal protective equipment and amount handled restrictions

Application equipment	Personal protective equipment		Restriction on the amount of diluted product handled per day per person
	Mixing/Loading, clean-up and repair	Application[1]	
Handheld and backpack sprayers (all droplet sizes) - Indoor surface spray[2]	Long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.		21 L
	Coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and shoes.		30 L

Application equipment	Personal protective equipment		Restriction on the amount of diluted product handled per day per person
	Mixing/Loading, clean-up and repair	Application[1]	
	Chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks and chemical-resistant boots.		34 L

1 In addition, wear eye, head and respiratory protection when applying above waist height, including overhead, and in confined spaces.
2 Includes broadcast, perimeter, spot, crack & crevice and void application.

Table 5 Distribution of the actual radioactive dose of 5 µg/cm^2 (0.65 g/L), at specified post-dose intervals in male rats following a single dermal dose of ^{14}C-Etofenprox

Monitoring interval (hours post-dose)	Residue in matrix (% of applied dose)[1]					
	10 h		24 h		96 h	
Matrix analyzed	Mean	SD	Mean	SD	Mean	SD
Non-occlusive cover	0.11	0.08	0.11	0.01	0.24	0.22
Enclosure rinse	0.28	0.10	0.47	0.17	0.68	0.29
Skin wash[2]	80.63	7.30	88.76	2.70	81.48	6.68
Skin test site	13.50	5.79	10.43	2.91	9.42	5.55
Blood	ND	NA	ND	NA	ND	NA
Carcass	0.28	0.33	0.84	0.05	0.42	0.49
Cage wash	0.04	0.01	0.09	0.08	0.13	0.16
Cage wipe	ND	NA	ND	NA	ND	NA
Total urine	0.26	0.08	0.50	0.17	1.08	0.17
Total feces	ND	NA	0.49	0.03	3.44	0.45
Systemic absorption[3]	0.58	0.25	1.91	0.11	5.07	1.16
Total recovery (sum of above)	95.1	2.3	101.7	0.2	96.9	3.2
Dermal absorption value[4] (%)	14.1	5.7	12.3	2.8	14.5	6.0

NA – Not applicable; ND - Not detectable; SD - Standard deviation; h - hour
1. Mean (n = 4, unless otherwise noted).
2. Skin wash was conducted at 10 hours for all monitoring groups.
3. Sum of blood + carcass + cage wash and wipe + urine + feces.
4. Sum of skin test site + blood + carcass + cage wash and wipe + urine + feces.

Table 6 Distribution of the actual radioactive dose of 59 µg/cm^2 (6.43 g/L), at specified post-dose intervals in male rats following a single dermal dose of ^{14}C-Etofenprox

Monitoring interval (hours post-dose)	Residues in matrix (% of applied dose)[1]					
	10 h*		24 h		96 h	
Matrix analyzed	Mean	SD	Mean	SD	Mean	SD
Non-occlusive cover	0.05	0.02	0.19	0.14	0.14	0.05
Enclosure rinse	0.56	0.37	0.81	0.39	0.87	0.22
Skin wash[2]	83.57	2.84	79.65	10.56	81.58	6.87
Skin test site	17.73	3.18	18.14	9.34	9.85	2.82
Blood	0.02	0.00	0.02	0.00	ND	NA
Carcass	0.53	0.11	1.21	0.17	0.85	0.32
Cage wash	0.03	0.02	0.07	0.04	0.17	0.12
Cage wipe	0.03	0.01	0.08	0.03	0.16	0.06
Total urine	0.18	0.09	0.48	0.25	1.03	0.25
Total feces	0.00	0.00	0.35	0.13	3.89	1.13
Systemic absorption[3]	0.79	0.19	2.19	0.31	6.10	1.83
Total Recovery (sum of above)	102.7	0.7	101.0	6.4	98.5	5.0
Dermal absorption value[4] (%)	18.5	3.1	20.3	9.4	15.9	4

NA – Not applicable; ND - Not detectable; SD - Standard deviation; h – hour.
1. Mean (n = 4, unless otherwise noted).
2. Skin wash was conducted at 10 hours for all monitoring groups.
3. Sum of blood + carcass + cage wash and wipe + urine + feces.
4. Sum of skin test site + blood + carcass + cage wash and wipe + urine + feces.
* One rat (#23972) was excluded from analysis as it died before the 10 h skin wash.

Table 7 Distribution of the actual radioactive dose of 184 µg/cm^2 (22.3 g/L), at specified post-dose intervals in male rats following a single dermal dose of ^{14}C-Etofenprox

Monitoring interval (hours post-dose)	Residues in matrix (% of applied dose)[1]					
	10 h		24 h		96 h	
Matrix analyzed	Mean	SD	Mean	SD	Mean	SD
Non-occlusive cover	0.29	0.43	0.20	0.13	2.19	3.79
Enclosure rinse	0.55	0.13	0.62	0.45	0.87	0.38
Skin wash[2]	100.85	6.95	100.18	4.57	83.85	10.95
Skin test site	29.20	1.87	30.30	5.97	26.40	11.35
Blood	0.02	0.00	0.02	0.01	ND	NA
Carcass	0.50	0.11	1.29	0.22	0.87	0.21
Cage wash	0.05	0.03	0.07	0.02	0.13	0.06
Cage wipe	0.03	0.04	0.05	0.04	0.20	0.06
Total urine	0.15	0.11	0.40	0.17	1.24	0.12
Total feces	ND	NA	0.31	0.07	4.32	0.36
Systemic absorption[3]	0.74	0.20	2.14	0.21	6.58	0.35

Monitoring interval (hours post-dose)	Residues in matrix (% of applied dose)[1]					
	10 h		24 h		96 h	
Matrix analyzed	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Total Recovery (sum of above)	131.6	8.3	133.43	5.64	119.9	8.0
Dermal absorption value[4] (%)	29.9	1.9	32.4	6.1	33.0	11.4

NA – Not applicable; ND - Not detectable; SD - Standard deviation; h - hour
1. Mean (n = 4, unless otherwise noted).
2. Skin wash was conducted at 10 hours for all monitoring groups.
3. Sum of blood + carcass + cage wash and wipe + urine + feces.
4. Sum of skin test site + blood + carcass + cage wash and wipe + urine + feces.

Table 8 Unit exposure estimates for commercial handlers of RF2129

Exposure Scenario and PPE	Dermal (mg/kg a.i. handled)	Inhalation[1] (mg/kg a.i. handled)
PPE: Single layer and chemical-resistant (CR) gloves		
Liquid, Open M/L, Manually-Pressurized Handwand (MPHW) / Mechanically-Pressurized Handgun (MPHG) / Backpack	85.84	0.3285
PPE: Coveralls over a single layer and CR gloves		
Liquid, Open M/L, MPHW/MPHG/Backpack	60.69	0.3285
PPE: CR Coveralls over a single layer and CR gloves		
Liquid, Open M/L, MPHW/MPHG/Backpack	53.05	0.3285

PPE = personal protective equipment; M/L = mixing and loading; CR = chemical-resistant, MPHW = manually-pressurized handwand; MPHG = mechanically-pressurized handgun.
1 Light inhalation rate for all application equipment.

Table 9 Mixer/Loader/Applicator risk assessment

Exposure scenario	Unit exposure (mg/kg a.i. handled)[1]		AHPD (L/day)[2]	Rate (kg a.i./L)	Exposure (mg/kg bw/day)[3]		MOE[5]		Combined MOE[6]
	Dermal	Inhalation			Dermal[3]	Inhalation[4]	Dermal	Inhalation	
PPE: Single layer and CR gloves									
MPHW / MPHG / Backpack	85.84	0.32852	40	0.0026	0.0558	0.0004	**160**	21000	**160**
			21		0.0293	0.00022	310	40000	300
PPE: Coveralls over a single layer and CR gloves									
MPHW / MPHG / Backpack	60.69	0.32852	40	0.0026	0.0394	0.0004	**230**	21000	**230**
			30		0.0296	0.00032	300	28000	300
PPE: CR coveralls over a single layer and CR gloves									
MPHW / MPHG / Backpack	53.05	0.32852	40	0.026	0.0345	0.0004	**260**	21000	**260**
			34		0.0293	0.00036	310	25000	300

Bolded values indicate risks of concern.

AHPD = amount handled per day; MOE = margin of exposure; MPHW = manually-pressurized handwand; MPHG = mechanically-pressurized handgun; PPE = personal protective equipment; CR = chemical-resistant;

[1] Unit exposure based on a previously reviewed worker exposure study from Table 8.

[2] 40 L/day is the default amount handled per day for commercial pest control officers and other values are those required to reach the target MOE of 300.

[3] Dermal Exposure (mg/kg bw/day) = (Dermal unit exposure (mg/kg a.i. handled) × dermal absorption (50%) × AHPD (ha/day) × Rate (kg a.i./L)) / (80 kg bw).

[4] Inhalation Exposure (mg/kg bw/day) = (Inhalation unit exposure (mg/kg a.i. handled) × AHPD (ha/day) × Rate (kg a.i./L)) / (80 kg bw).

[5] NOAEL of 9 mg/kg bw/day ÷ Exposure (mg/kg bw/day); Target MOE = 300 (Table 1).

[6] Combined MOE = $1 \div (1/MOE_{Dermal} + 1/MOE_{Inhalation})$; Target MOE = 300 (Table 1).

Table 10 Residential applicator risk assessment for etofenprox

Exposure scenario	Total unit exposure (mg/kg a.i. handled)[1]	Amount handled per day (AHPD) (kg a.i./day)[2]	Total exposure (mg/kg bw/day)[3]	MOE[4]
Clothing: Short-sleeved shirt, shorts, no gloves				
Aerosol - Broadcast	822.32	0.00624	0.011	840

MOE = margin of exposure

1 This is a combination of dermal and inhalation unit exposure (UE) values. The UE values for an aerosol end-use product were taken from the USEPA 2012 Residential SOP, Section 7.

2 Amount Handled per Day (kg a.i./day) = maximum can size (624 g) × guarantee (1.0%) × 0.001 kg/g; assuming 1 can per day for broadcast treatment (standard value from Res. SOP 2012, Section 7).

3 Total Exposure = (Total unit exposure × AHPD × Rate) / (80 kg bw); 16% dermal absorption applied to the dermal exposure value.

4 MOE = NOAEL ÷ Total Exposure. Based on NOAEL = 9 mg/kg bw/day; Target MOE = 300 (Table 1).

Table 11 Postapplication dermal exposure and risk estimates to etofenprox on day 0

	Surface type	Life stage	Transferable residue (µg/cm^2)[1]	TC (cm^2/h)[2]	Exposure Time (hours/day	Dermal exposure (mg/kg bw/day)[3]	Dermal MOE[4]
RF2129 EC							
Broadcast	Soft Surface	Adult	0.168	6800	8	0.01828	490
		Child		1800	4	0.01759	970
	Hard Surface	Adult	0.224	6800	2	0.00609	1500
		Child		1800	2	0.01173	1400
RF2220 Premium Aerosol II-M Premise Spray							
Broadcast	Soft Surface	Adult	0.146	6800	8	0.01593	560
		Child		1800	4	0.01534	1100
	Hard Surface	Adult	0.195	6800	2	0.00531	1700
		Child		1800	2	0.01022	1700

TC = Transfer Coefficient; h = hour; ET = Exposure Time; MOE = Margin of Exposure

1 Calculated using the proposed application rate of 2.8 µg a.i./cm^2 for the EC product and 2.44 µg a.i./cm^2 for the aerosol product (assuming 100% deposition for broadcast treatment coupled with the fraction transferred (6% carpets; 8% hard surface)).

2 Transfer coefficients obtained from the USEPA Residential SOP (updated 2012).

3 Exposure = (Transferable Residue [µg/cm^2] × TC [cm^2/h] × ET hours/day) x DA (16%) / (bw × 1000 µg/mg); where adult bw = 80 kg and child (ages 1 to <2 yrs) = 11 kg.

4 Dermal MOE = NOAEL ÷ Dermal Exposure. For TRVs, refer to Table 1.

Table 12 Postapplication hand-to-mouth exposure and risk estimates to etofenprox on day 0 for children (1 < 2 years)

Application type	Surface type	$F_{a.i.\ hands}$	Dermal exposure (mg/h)[1]	Hand residue loading (mg/h)[2]	Fraction of hand mouthed	Exposure Time (hours/day)	Number of replenishment intervals per hour (intervals/h)	Fraction saliva extraction	Number of hand-to-mouth contacts events per hour (events/h)	Oral exposure (mg/kg bw/day)[3]	Oral MOE[4]
RF2129 EC											
Broadcast	Soft Surface	0.15	0.3	0.0227	0.13	4	4	0.48	20	0.001031	55 000
	Hard Surface	0.15	0.4	0.0302	0.13	2	4	0.48	20	0.000688	83 000
RF2220 Premium Aerosol II-M Premise Spray											
Broadcast	Soft Surface	0.15	0.3	0.0198	0.13	4	4	0.48	20	0.000899	63 000
	Hard Surface	0.15	0.4	0.0264	0.13	2	4	0.48	20	0.000599	95 000

$F_{a.i.\ hands}$= fraction of active ingredient on hands; h = hour; MOE = margin of exposure

[1] Calculated based on dermal exposure (mg/day)/exposure time (h/day) (Table 11).

[2] Calculated based on dermal exposure x Fai hands/2.

[3] Calculated based on [Hand Residue (mg/h) x Fraction of hand mouthed/event (0.13) x Exposure Time (h) x (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour/Replenishment Intervals (4/h)}}$)]/ bw (11 kg).

[4] Oral MOE = NOAEL ÷ Oral Exposure. Based on a NOAEL of 57 mg/kg bw/day; Target MOE of 300 (Table 1).

Table 13 Postapplication object-to-mouth exposure and risk estimates to etofenprox on day 0 for children (1 < 2 years)

Application type	Surface type	Fraction of residue transferred to object	Object residue (ug/cm^2)[1]	Object surface area mouthed / event (cm^2/event)	Exposure time (h/day)	Replenishment interval (min)	Number of replenishment intervals per h	Extraction by saliva	Number of object-to-mouth contacts events per h	Oral exposure (mg/kg bw/day)[2]	Oral MOE[3]
RF2129 EC											
Broadcast	Soft Surface	0.06	0.168	10	4	15	4	0.48	14	0.0022	26 000
	Hard Surface	0.08	0.224	10	2	15	4	0.48	14	0.0015	39 000
RF2220 Premium Aerosol II-M Premise Spray											
Broadcast	Soft Surface	0.06	0.146	10	4	15	4	0.48	14	0.0019	30 000
	Hard Surface	0.08	0.195	10	2	15	4	0.48	14	0.0013	45 000

h = hour; min = minute; MOE = margin of exposure

[1] Calculated based on deposited residue (µg/cm^2) (2.80 for EC product and 2.44 for aerosol product) × fraction of residue transferred.

[2] Calculated based on [object residue (µg/cm^2) × surface area of object mouthed (10 cm^2) × (ET (h) × replenishment interval (4/h)) × (1-(1-saliva extraction factor (0.48)) $^{\text{Number events per hour/replenishment interval (4/h)}}$]/bw (11 kg).

Oral MOE = NOAEL ÷ Oral Exposure. Based on a NOAEL of 57 mg/kg bw/day; Target MOE of 300 (Table 1).

Table 14 Combined exposure and risk estimates to etofenprox on day 0

Exposure Scenario		Lifestage	Applicator[1]	Postapplication		Combined MOE[4]
			Dermal + Inhalation MOE	Dermal MOE[2]	OtM MOE[3]	
RF2129 EC						
Broadcast	Soft surface	Children 1 <2 years	NA	970	26 000	940
	Hard surface	Children 1 <2 years	NA	1400	39 000	1250
RF2220 Premium Aerosol II-M Premise Spray						
Broadcast	Soft surface	Adults	840	560	NA	340
		Children 1 <2 years		1100	30 000	1100
	Hard surface	Adults	840	1700	NA	560
		Children 1 <2 years		1700	45 000	1600

MOE = margin of exposure; NA – Not applicable; OtM = object-to-mouth
[1] Based on Table 10
[2] Based on Table 11
[3] Based on Table 13
[4] Calculation based on Combined MOE = 1 ÷ ($1/MOE_{App}$ + $1/MOE_{Postapp}$) or Combined MOE = 1 ÷ ($1/MOE_{Dermal}$ + $1/MOE_{OtM}$); Target MOE of 300 (Table 1).

Table 15 Toxic Substances Management Policy Considerations - Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]	Soil	Half-life ≥ 182 days	No; DT_{50} = 22.8 days[5]
	Water	Half-life ≥ 182 days	No; Whole system DT_{50} = 6.5 and 20.1 days (aerobic water sediment system)[5]
	Sediment	Half-life ≥ 365 days	
	Air	Half-life ≥ 2 days, or evidence of atmospheric transport to remote regions such as the Arctic	Not determined. The AOPWIN (v1.92) model is not suited for predicting the atmospheric half-life of etofenprox given the large fraction expected to be sorbed to airborne particles.
Bioaccumulation[4]	Log K_{ow} ≥ 5		Yes, Log K_{ow} = 6.9
	BCF ≥ 5000		No, BCF = 3951 L/kg (2565 L/kg – corrected for a whole-body lipid content of 5%)[5]
	BAF ≥ 5000		No, BAF (earthworm) = 0.734[5]
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?	No, does not meet all of the TSMP Track 1 criteria.		

1 All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (in other words, all other TSMP criteria are met).
2 The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
3 The pesticide and/or the transformation product(s) is considered persistent when the criterion is met in any one medium.
4 Bioaccumulation describes the process by which a substance accumulates in a living organism – either from the surrounding medium or through food containing the substance. A substance's potential to bioaccumulate can be expressed by the bioaccumulation factor (BAF), the bioconcentration factor (BCF), or the octanol-water partition coefficient (Log Kow). The BAF and the BCF measure the concentration of a substance in a living organism relative to its concentration in the surrounding medium. The BAF accounts for substance intake from both food and the surrounding medium, while the BCF accounts for intake from the surrounding medium only. The Log Kow estimates a substance's tendency to partition from water to organic media, such as lipids present in living organisms. In the absence of BAF or BCF data, the log Kow may be used.
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List of supported uses

RF2129 EC (Commercial)

Pests: Ants, cockroaches, centipedes, crickets, darkling beetles, earwigs, firebrats, millipedes, pill bugs, silverfish, sowbugs, spiders, stink bugs, ticks, paper wasps, western yellow jackets

Use sites: Homes, attics and crawlspaces, apartment buildings, hotels, schools, day cares, nursing homes, hospitals, office buildings, correctional facilities, commercial and industrial buildings, residential settings, warehouses, non-food/non-feed handling establishments, rail cars, marine vessels, and institutions.

Application: Broadcast (general surface), spot (not more than 0.2 m^2 spots), void, indoor perimeter (less than 0.1 m wide along edges of room) or crack and crevice treatment. Apply to areas where target pests hide, such as baseboards, corners, storage areas, closets, around water pipes, doors and windows, attics and eaves, behind and under refrigerators, cabinets, sinks, furnaces, and stoves, the underside of shelves, drawers and similar areas. Pay particular attention to cracks and crevices.

Rate: Apply a 0.25% Etofenprox solution (15.6 mL product per L of water) per 93 m^2.

Residual control (non-porous surfaces): Up to 28 days for cockroaches and crickets; 14 days for all other listed pests except ants and stink bugs (direct contact knockdown only).

Re-application interval: Repeat treatment as necessary but not more than once every 14 days after the initial treatment.

RF2220 Premium Aerosol II-M Premise Spray (Domestic)

Pests: Fleas (including immature stages), ticks, cockroaches, ants (except carpenter ants).

Sites: In and on buildings, structures, and modes of transport, including homes, apartments, veterinary clinics, automobiles, garages, kennels, pet bedding, barns, out buildings, sheds, private residences, RVs, trucks and trailers.

Application: Broadcast, crack and crevice, void, or spot treatment or by direct application to exposed pests.

Rate: For broadcast application, from a distance of 90 cm (3 feet), using a sweeping motion, apply a light, uniform spray to all surfaces. For application as a crack and crevice spray, spray at a rate of 6.5 seconds per linear meter (2 seconds per linear foot). For application as a spot spray, treat surface until slightly wet.

Re-application Interval: Repeat treatment not more than once every 14 days or two weeks.

References

A. List of studies/Information submitted by Registrant

1.0 Chemistry

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B. Additional information considered

i) Published information

1.0 Chemistry

None

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None