Proposed Registration Document PRD2013-19

Novaluron

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Overview

Proposed Registration Decision for Novaluron

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Technical Insecticide (Novaluron) and its end-use products, Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D, containing the technical grade active ingredient novaluron, to control mosquito larvae (excluding *Mansonia* spp. and *Coquilletidia* spp.).

An evaluation of available scientific information found that, under the approved conditions of use, the products have value and do not present an unacceptable risk to human health or the environment.

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 Technical Insecticide (Novaluron) and its end-use products, Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D.

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 people 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 special precautionary measures on the product label to further reduce risk.

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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."

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) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). 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 PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management section of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on novaluron, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on novaluron, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA'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 Novaluron?

Novaluron is an insect growth regulator for control of mosquito larvae (excluding *Mansonia* spp. and *Coquilletidia* spp.) in standing bodies of water. It inhibits chitin synthesis, affecting moulting of larvae, but does not affect the adult stage after development is completed. Novaluron is also registered to control various pests in many agricultural crops.

Health Considerations

Can Approved Uses of Novaluron Affect Human Health?

Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D, containing novaluron, are unlikely to affect your health when used according to label directions.

Potential exposure to novaluron may occur when handling and applying the end-use products. When assessing health risks, two key factors are considered: the levels where no health effects occur, and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

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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*.

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

In laboratory animals, novaluron technical grade active ingredient and Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D were of low acute oral and dermal toxicity, minimally irritating to the eyes and did not cause an allergic skin reaction. Novaluron was non-irritating to the skin while the Mosquiron end-use products were minimally irritating to the skin. Novaluron was of low acute toxicity via the inhalation route; due to the use pattern and the formulation of the end-use products, exposure via the inhalation route is not expected.

Novaluron did not cause cancer in animals and did not damage genetic material. There was no indication that novaluron damaged the nervous system. Novaluron did not cause birth defects in animals and there were no effects on the animal's ability to reproduce. Health effects in animals given repeated doses of novaluron included damage to red blood cells.

When novaluron was given to pregnant or nursing animals, effects on the juvenile animal (changes in body weight and body weight gain, and increases in spleen and liver weight) were observed at doses that were toxic to the mother, indicating that the young do not appear to be more sensitive to novaluron than the adult animal.

The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

A risk assessment for residues in water and food was not required for this application as the proposed uses do not include dietary exposure.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for non-occupational exposure is not of concern.

A quantitative risk assessment conducted for homeowners applying Mosquiron 0.12CRD-D and Mosquiron 0.12P-D to standing water indicated that the risk is not of concern.

Occupational Risks From Handling Mosquiron 0.12CRD or Mosquiron 0.12P

Occupational risks are not of concern when Mosquiron 0.12CRD or Mosquiron 0.12P are used according to the proposed label directions, which include protective measures.

A quantitative risk assessment conducted for individuals handling Mosquiron 0.12CRD or Mosquiron 0.12P products, indicated that the risk for workers is not of concern when these products are used according to label directions.

Workers applying Mosquiron 0.12CRD or Mosquiron 0.12P can come in direct contact with novaluron on the skin or through inhalation. Therefore, the label will specify that workers must wear a long sleeved shirt, long pants and chemical resistant gloves when applying Mosquiron 0.12CRD or Mosquiron 0.12P to standing water.

Environmental Considerations

What Happens When Novaluron Is Introduced Into the Environment?

Novaluron is toxic to aquatic invertebrates. Marine and freshwater invertebrates are at risk.

Novaluron is used in the formulation of Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D. Once applied to water for mosquito larval control novaluron is expected to be non-persistent to slightly persistent. Novaluron is slightly persistent in sediments but is not expected to be mobile or leach into groundwater or volatilize into air.

Novaluron is very highly toxic to freshwater and marine invertebrates on an acute and chronic basis and shows negligible toxicity to freshwater and marine fish, algae and aquatic vascular plants. Novaluron presents a risk to freshwater and marine aquatic invertebrates. Therefore, hazard statements and label statements placing restrictions on potential use-sites will be required.

Value Considerations

What Is the Value of Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D?

Novaluron is an insect growth regulator used in the Mosquiron line of end-use products to control mosquito larvae (excluding *Mansonia* spp. and *Coquilletidia* spp.) in standing bodies of water for up to 90 days.

Mosquiron 0.12CRD and Mosquiron 0.12P are restricted class products that are to be applied by public health officials, mosquito abatement officials and other trained personnel. Mosquiron 0.12CRD-D and Mosquiron P-D are domestic class products. The Mosquiron line of end-use products control mosquito larvae in standing bodies of water at concentrations of 120 to 240 µg novaluron/L of water. The Mosquiron line of end-use products are compatible with current

mosquito management practices and have the potential to reduce or replace the use of organophosphates in standing bodies of water. Novaluron may be used in rotation with mosquito larvicides having a different mode of action to aid in resistance management.

Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Anyone handling Mosquiron 0.12CRD or Mosquiron 0.12P, in an occupational setting, must wear the personal protective equipment as stated on the label.

Environment

Precautionary measures are required to mitigate potential risks to non-target aquatic invertebrates. These include adding statements to the label regarding environmental hazard and the directions for use.

Next Steps

Before making a final registration decision on novaluron, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

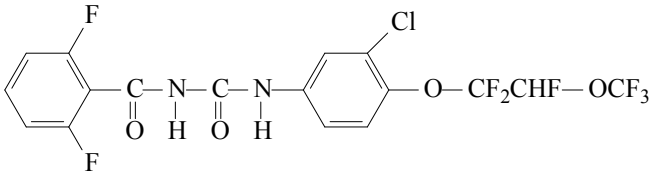
When the PMRA makes its registration decision, it will publish a Registration Decision on novaluron (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Novaluron

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	
Function	**Insecticide**
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]-3-(2,6-difluorobenzoyl)urea
2. Chemical Abstracts Service (CAS)	N-[[[3-chloro-4-[1,1,2-trifluoro-2-(trifluoromethoxy)ethoxy]phenyl]amino]carbonyl]-2,6-difluorobenzamide
CAS number	116714-46-6
Molecular formula	$C_{17}H_9ClF_8N_2O_4$
Molecular weight	492.71
Structural formula	
Purity of the active ingredient	99.2 %

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

Technical Product—Technical Insecticide (Novaluron)

Property	Result
Colour and physical state	White
Odour	None detectable
Melting range	176.5178.0 °C
Boiling point or range	N/A
Density	1.56
Vapour pressure at 20°C	1.6×10^{-5} Pascal
Henry's law constant at 20°C	N/A
Ultraviolet (UV)-visible spectrum	$\lambda_{max} = 253$ nm
Solubility in water at 20°C	3.4 ± 1.0 µg/L

Property	Result
Solubility in organic solvents at 20°C (g/L)	Solvent — Solubility acetone 198.5 ethylacetate 113.0 methanol 14.5 1,2-dichloroethane 2.85 xylene 1.88 n-octanol 0.98 n-heptane 0.00839
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} = 4.3
Dissociation constant (pK_a)	Not investigated due to the low water solubility of the test material (OECD method No. 112)
Stability (temperature, metal)	Photochemical degradation half-life = 2.4 hours. Chemically stable on contact with aluminium, aluminium acetate, iron, iron acetate, zinc and zinc acetate at 54°C for 14 days

End-Use Products—Mosquiron 0.12CRD, Mosquiron 0.12P, Mosquiron 0.12P-D, Mosquiron 0.12CRD-D

Property	Result
Colour	light yellow
Odour	slight organic
Physical state	solid
Formulation type	pellet
Guarantee	Novaluron 0.12 %
Container material and description	lined cardboard boxes
Density	1.071 g/cm^3
pH of 1% dispersion in water	4.24
Oxidizing or reducing action	Not an oxidizer, slight reducing activity
Storage stability	Storage stability study is in progress
Corrosion characteristics	Corrosion characteristics study is in progress
Explodability	Product does not contain any explosive components

1.3 Directions for Use

The Mosquiron line of end-use products consist of four products which are used to control mosquito larvae (excluding *Mansonia* spp. and *Coquilletidia* spp.) in standing bodies of water for up to 90 days when applied according to label directions. The period of mosquito larvae control may be reduced in areas of high water turnover or high organic matter content. The first application should be made at the start of the mosquito breeding season. The product may be re-applied every 90 days as dictated by monitoring for mosquito larvae. The retreatment interval may be shorter than 90 days in areas with high turnover or in areas with high organic matter.

Mosquiron 0.12CRD and Mosquiron 0.12P are restricted class products that are to be applied by public health officials, mosquito abatement officials and other trained personnel. Mosquiron 0.12CRD-D and Mosquiron 0.12P-D are domestic class products.

Mosquiron 0.12CRD and Mosquiron 0.12CRD-D are formulated into 20 gram rods that are to be applied into standing bodies of water containing more than 100 litres at a concentration of 0.1–0.2 grams product/L water or at a rate of 20–30 grams product per m^2 for shallow pools up to 15 cm deep.

Mosquiron 0.12P and Mosquiron 0.12P-D are formulated into a 0.2 gram pellet that may be applied to any size of standing bodies of water at a concentration of 0.1–0.2 grams product/L water or 15 to 30 g product per m^2 for shallow pools up to 15 cm deep.

1.4 Mode of Action

Novaluron is classified as a Group 15 Insecticide by the Insecticide Resistance Action Committee. It is an insect growth regulator that inhibits chitin synthesis, affecting moulting which results in the mortality of the mosquito larvae. This active ingredient does not affect the adult stage of mosquitoes after development is completed. Novaluron does not represent a new mode of action for mosquito larvicides because another active ingredient is registered as a mosquito larvicide with the same mode of action (i.e. diflubenzuron).

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

Validated methods have been provided previously for the analysis of the active ingredient and the impurities in Technical Insecticide (Novaluron), and were assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

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

2.3 Methods for Residue Analysis

Validated methods have been provided previously for determination of the parent compound and transformation products in soil, sediment, water and biota.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for novaluron was previously published under Proposed Registration Decision PRD2006-05, *Novaluron*. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. Due to change of ownership of the toxicology database, the applicant was not able to confirm that Good Laboratory Practice (GLP) was followed during the conduct of some of the toxicology studies. Furthermore, several studies were conducted with batches of chemical of unknown purity. Despite these factors, the scientific quality of the data is satisfactory and the database is considered adequate to define the majority of the toxic effects that may result from exposure to novaluron.

The main toxicological effect noted in studies conducted via the oral route was oxidative stress, resulting in the formation of methemoglobin (Met-Hb) and sulphemoglobin (Sulph-Hb) in the blood, and destruction of red blood cells. As a result of erythrocyte destruction, secondary effects were observed in associated blood tissues/organs and included pigmentation in Kupffer cells in the liver as well as macrophages in the spleen. At higher doses, the effect on red blood cell parameters was of a sufficient magnitude to result in hemolytic anaemia and provoke a regenerative response. Adverse haemolytic effects observed in the toxicology database did not progress in magnitude or severity with prolonged dosing. Following repeated dermal dosing in rats, blood findings consisting of marginal increases in Met-Hb as well as slight effects on body weight were also observed and recorded down to the lowest dose level tested.

Long term dietary studies in both rats and mice provided no evidence of treatment-induced oncogenicity at any dose level tested. There was no evidence to suggest that novaluron was genotoxic, or neurotoxic. No adverse effects of treatment were observed in either the rat or rabbit oral gavage developmental toxicity studies, which may, in part, reflect poor uptake from the GI tract as a result of novaluron's low solubility in aqueous vehicles. In a two-generation dietary reproduction study, offspring effects (changes in body weight/body weight gain, liver and kidney weights) were noted at dose levels which also elicited toxicity in maternal animals (increased body weight gain and spleen weight), indicating that the young animal was not more sensitive than the adult animal to novaluron toxicity.

The four end-use products containing novaluron (Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D) are of low acute oral and dermal toxicity in rats, minimally irritating to the eyes and skin of rabbits, and, based on the Buehler method of testing, are not expected to be dermal sensitizers. Due to the physical form of the end-use products (hard wax) and low acute toxicity profile, as well as the low volatility of the active ingredient, the requirement for an acute inhalation study was waived.

Results of toxicology studies conducted on laboratory animals with the end-use products are summarized in Appendix I, Table 1 of this document. Results of toxicology studies conducted on laboratory animals with technical grade novaluron are summarized in Appendix 1 of PRD2006-05. However, PRD2006-05 contains a typographical error with regards to the results for the reproductive toxicity study. The entry for this study (see page no. 44 of PRD2006-05) should indicate that sexual maturation in F1 male offspring was delayed at the mid-dose of 297.5 mg/kg bw/day and above, and not 74.2 mg/kg bw/day and above as was reported previously. The updated entry for this study is included in this document under Appendix I, Table 2. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 3.

Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website. Incidents from were searched and reviewed for the active ingredient novaluron.

As of 8 July 2013, the PMRA has not received any human or domestic animal incident reports related to novaluron.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* 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.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for novaluron. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a two-generation reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in either the reproductive or developmental toxicity studies. Although no adverse effects due to treatment were noted in the developmental toxicity studies, a water-based vehicle was employed for gavage dosing, and it is known that novaluron is poorly soluble in water. There is concern that the lack of adverse findings reflects minimal systemic uptake of the test material by the treated dams. Consequently, there remains some residual uncertainty with respect to the characterization of prenatal toxicity.

Notwithstanding this uncertainty, it is evident from the effects noted in the database that systemic exposure occurred following dietary dosing. Therefore, the evaluation of offspring in the 2-generation rat reproduction study, a dietary study, would likely capture any serious prenatal effects that could have occurred following exposure to novaluron. In the reproductive toxicity study, increased spleen and liver weight as well as changes in body weight and body weight gain were noted in pups at dose levels also eliciting maternal toxicity (increased body weight gain, and spleen weight). Delayed sexual maturation of F1 males was observed at the next highest dose level. Since systemic toxicity was achieved in the offspring from the reproduction study, and it only occurred in the presence of maternal toxicity, the uncertainty with respect to characterizing pre-natal toxicity is mitigated. The endpoints selected for the risk assessment were considered to afford protection of the developing young. Based on these considerations, the PCPA factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose

An acute reference does is not required as the proposed uses do not include dietary exposure.

3.3 Determination of Acceptable Daily Intake

An acceptable daily intake is not required as the proposed uses do not include dietary exposure.

Cancer Assessment

There was no evidence of carcinogenicity and therefore a cancer risk assessment was not necessary.

3.4 Occupational and Residential Risk Assessment

Occupational exposure to the end-use products will occur predominately via the dermal and inhalation routes, and is characterized as being of intermediate-term duration.

Residential exposure to the end-use products will occur via the dermal, inhalation and incidental oral route (toddler), and is characterized as being of intermediate-term duration.

3.4.1 Toxicological Endpoints

Short- and Intermediate-term Dermal

Dermal exposure may occur during application (occupational) and postapplication (occupational and residential) activities. For the short to intermediate-term dermal risk assessment, the lowest observed adverse effect level (LOAEL) of 75 mg/kg bw/day from the 28-day dermal study in rats was selected. Effects at the LOAEL included increases in Met-Hb and decreased body weight gain in males. There was no NOAEL (no observed adverse effect level) identified for this study as the effects noted above occurred at the lowest dose tested. This study addressed the endpoint of concern (increases in Met-Hb) and was of the appropriate route.

In PRD2006-05, an additional 3-fold factor was applied to account for the use of a LOAEL for risk assessment. However, the effects noted at the LOAEL were considered to be slight, consisting of non-statistically significant changes in Met-Hb and minor decreases in body weight gain in males. As such, the LOAEL is likely approaching a threshold for treatment-related effects in this study. Due to these considerations as well as the fact that the critical endpoint was demonstrated at the LOAEL, no additional factor for the use of a LOAEL was warranted for the current risk assessment.

For occupational and residential risk assessments, the target Margin of Exposure (MOE) is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. There was some residual uncertainty regarding potential sensitivity of the young in the developmental toxicity studies due to solubility issues and poor uptake from the gut. However, there was no indication of sensitivity of the young in the rat dietary reproductive toxicity study. When the dermal absorption of novaluron (approximately 24%) is used to estimate systemic exposure, the short- and intermediate-term dermal endpoint provides a margin of 400 to the dose at which effects were observed in the young animals in the rat dietary reproductive toxicity study. For these reasons, the endpoint and target MOE are considered to be protective of all populations, including nursing infants and the unborn children of exposed adult females.

Non-Dietary Oral Ingestion (Children, all durations)

There is potential for incidental oral exposure to toddlers via-hand-to-mouth activities. For this exposure scenario, the NOAEL of 4.2 mg/kg bw/day from the 90-day mouse dietary study was selected for risk assessment. In this study, increases in inclusion bodies and bilirubin were noted in both sexes, increased Sulph-Hb was noted in males and decreased red-blood cell parameters were observed in females at the LOAEL of 12.8 and 15.2 mg/kg bw/day, for males and females, respectively.

The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The PCPA factor was reduced to 1-fold as outlined in the PCPA Hazard Characterization section.

3.4.1.1 Dermal Absorption

A dermal absorption value of 24% was established at the time of the initial registration decision for novaluron (PRD2006-05; RD2007-04). However, since the most recent endpoint was established from a dermal toxicity study, the dermal absorption value was not required for use in the current risk assessment.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Applicator Exposure and Risk Assessment

Mosquiron 0.12CRD and Mosquiron0.12P are ready-to-use control rods and pellets added to standing water for mosquito larvae control. Hence, individuals have potential for exposure to Mosquiron 0.12CRD or Mosquiron 0.12P during loading and application and during postapplication monitoring. The end-use products may be used throughout the mosquito season, thus workers have a potential for intermediate-term exposure to Mosquiron 0.12CRD or Mosquiron 0.12P. Exposure estimates for workers treating standing water were generated from the Pesticide Handlers Exposure Database (PHED v.1.1) and Outdoor Residential Exposure Task Force (ORETF, 1999) data.

Dermal and inhalation exposure estimates were derived for workers loading and applying Mosquiron 0.12CRD or Mosquiron 0.12P to standing water sites using hand dispersion, belly grinder and push type spreader equipment and wearing a long-sleeved shirt, long pants and chemical resistant gloves.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted. Therefore, exposure estimates, generated from PHED (v.1.1) and ORETF data (1999) were based on the application of granules, which are not expected to underestimate the exposure from applying the wax control rods or pellets.

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

Exposure estimates were compared to the toxicological endpoints to obtain the MOE; the target MOE is 100.

Table 1 Loader/Applicator Dermal & Inhalation Exposure Estimates and MOE

PPE Scenario	Application Method	Daily Dermal Exposure[a] (mg/kg bw/day)	Daily Inhalation Exposure[b] (mg/kg bw/day)	Dermal MOE[c]	Inhalation MOE[d]
Single layer with gloves	Hand Dispersion, Granules	0.011	6.5×10^{-5}	7060	64 700
	Belly Grinder, Granules	0.046	2.3×10^{-4}	1640	18 400
	Commercial Push Type Spreader, Granules	0.0043	1.5×10^{-4}	17 600	28 300

PPE = personal protective equipment
[a] Dermal Exposure Estimates = (PHED or ORETF Exposure (µg /kg a.i. handled) × Application Rate × Area Treated per Day) ÷ bw (80 kg)
[b] Inhalation Exposure Estimates = (PHED or ORETF Exposure (µg /kg a.i. handled) × Application Rate × Area Treated per Day) ÷ bw (80 kg)
[c] Short-Intermediate Term Dermal LOAEL of 75 mg/kg bw/day; Target MOE = 100
[d] Short-Intermediate Term Inhalation NOAEL of 4.2 mg/kg bw/day; Target MOE = 100

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

There is potential for exposure to workers re-entering areas treated with Mosquiron 0.12CRD and Mosquiron 0.12P for postapplication monitoring purposes. Exposure potential would occur primarily via the dermal route and is expected to be of intermediate-term duration. Postapplication inhalation exposure is not expected to be of concern based on the low volatility of novaluron (1.6×10^{-5} Pa). Postapplication monitoring is expected to occur with the aid of a dip stick to visually inspect water. Dermal contact is expected to be limited; however, consideration is given to hands contacting water bodies treated with Mosquiron end-use products, as a worst-case scenario.

Dermal exposure to workers entering treated areas is estimated based on the United States Environmental Protection Agency (USEPA) Superfund Risk Assessment (USEPA, 2004). In the absence of a chemical specific study for this scenario, it was determined that this approach for estimating postapplication dermal exposure was acceptable. For the purpose of this exposure assessment, it is assumed that the surface area which may be exposed for re-entry workers includes hands only (975 cm^2; USEPA Exposure Factors Handbook [EFH], 2011). Though it is not expected that re-entry workers' hands will be submerged continuously for 8 hours, it is assumed that contact or immersion of hands with treated water occurs throughout a work day.

The equation used to estimate re-entry worker dermal exposure was derived as follows:

$$\mathbf{E = [FA \times K_p \times SA \times PF \times C_w \times CF \times (t/(1+B) + 2\tau(1 + 3B + 3B^2/(1 + B)^2)] / bw}$$

where,

E = total dermal exposure (mg/kg bw/day)
FA = fraction of absorbed water (dimensionless, default = 1)
K_p = permeability coefficient (cm/hr); see Appendix II for calculation
SA = surface area exposed; assumed hands (975 cm^2, USEPA EFH, 2011)
PF = protection factor from clothing; assume 1 as hands may not be protected by clothing
C_w = concentration of a.i. in water (maximum approved application rate; 0.24 mg/L)
CF = conversion factor to convert cm^3 to L; 0.001L = 1 cm^3
t = duration of work day (hours/event); 8 hours/day
B = dimensionless ratio of two permeability coefficients (one for stratum corneum and one for the epidermis); see Appendix II for calculation
τ = lag time per event (hours/event); see Appendix II for calculation
bw = body weight; 80 kg

Exposure estimates were compared to the toxicological endpoint to obtain the MOE; the target MOE is 100.

Table 2 Postapplication Estimated Dermal Exposure and Margin of Exposure

Total Dermal Exposure (mg/kg bw/day)[a]	Margin of Exposure[b]
0.000729	103 000

[a] Refer to Appendix II for calculation of dermal exposure
[b] Based on an intermediate-term dermal LOAEL of 75 mg/kg bw/day; Target MOE = 100

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Residential Handler Exposure and Risk

Mosquiron 0.12CRD-D and Mosquiron0.12P-D are domestic class ready-to use control rods and pellets to be added to standing water sites around the home for mosquito larvae control. Homeowners have potential for exposure to these end-use products during loading and application and postapplication. The end-use products may be used throughout the mosquito season, thus homeowners have a potential for intermediate-term exposure to Mosquiron 0.12CRD-D or Mosquiron 0.12P-D via dermal and inhalation routes. Exposure estimates were derived for homeowners applying Mosquiron 0.12CRD-D or Mosquiron 0.12P-D to standing water sites using hand dispersion, spoon, cup belly grinder and push-type spreader. Chemical-specific data for assessing exposures during pesticide handling activities were not submitted. Exposure estimates, generated from the USEPA Residential SOP (USEPA, 2012), were based on the application of granules which are not expected to underestimate the exposure from applying the wax control rods or pellets.

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

Exposure estimates were compared to the toxicological endpoints to obtain the MOE; the target MOE is 100.

Table 3 Residential Loader/Applicator Dermal & Inhalation Exposure Estimates and MOE

Application Method	Daily Dermal Exposure[a] (mg/kg bw/day)	Daily Inhalation Exposure[b] (mg/kg bw/day)	Dermal MOE[c]	Inhalation MOE[d]
Hand Dispersion, granules (CRD & Pellets)	1.77×10^{-2}	4.21×10^{-5}	4.24×10^{3}	9.97×10^{4}
Spoon (CRD & Pellets)	6.86×10^{-4}	9.53×10^{-6}	1.09×10^{5}	4.41×10^{5}
Cup (CRD & Pellets)	1.20×10^{-5}	1.45×10^{-6}	6.23×10^{6}	2.89×10^{6}
Belly Grinder (Pellets)	3.32×10^{-2}	3.60×10^{-6}	2.26×10^{3}	1.17×10^{6}
Push-type Spreader (Pellets)	1.61×10^{-3}	5.13×10^{-6}	4.66×10^{4}	8.19×10^{5}

[a] Refer to Appendix III: Dermal Exposure = (Unit Exposure × Application Rate × Area Treated per Day) ÷ bw (80 kg)
[b] Refer to Appendix III: Inhalation Exposure = (Unit Exposure × Application Rate × Area Treated per Day) ÷ bw (80 kg)
[c] Short-Intermediate Term Dermal LOAEL of 75 mg/kg bw/day; Target MOE = 100
[d] Short-Intermediate Term Inhalation NOAEL of 4.2 mg/kg bw/day; Target MOE = 100

3.4.3.2 Postapplication Residential Exposure and Risk

There is potential for homeowners to contact areas treated with Mosquiron 0.12CRD-D, and Mosquiron 0.12P-D. Like occupational workers, exposure to homeowners is expected to be primarily via the dermal route and of intermediate term duration. Postapplication residential exposure is most likely to occur when homeowners are cleaning areas such as ornamental ponds, gutters, flower pots or bird baths that may have been treated with the proposed product. However, considering that postapplication residential exposure is not likely to exceed the postapplication exposure of occupational workers, the risk assessment conducted for re-entry workers adequately addresses postapplication adult residential exposure.

3.4.3.3 Postapplication Toddler Dermal Exposure and Risk

Although the occupational scenario addresses adult homeowners, a separate risk assessment was necessary to address the potential postapplication exposures to toddlers (ages 1 to <2 years old). Two postapplication scenarios exist for toddlers: dermal exposure and incidental oral exposure via hand-to-mouth activities.

Postapplication toddler dermal exposure was estimated using the same method for occupational workers, taking into consideration assumptions specific to toddlers: hands could contact treated water; therefore, the surface area for toddler hands is 302 cm^2 (based on 5.7% of total body surface area as provided in the EFH (2011); an exposure duration of 1.1 hours; and a body weight of 11 kg. Based on the maximum application rate of 0.24 mg/L, and the assumptions listed above, the following dermal exposure has been derived for toddlers contacting water treated with Mosquiron CRD-D or Mosquiron P-D:

Table 4 Postapplication Toddler Dermal Exposure Estimate and MOE

Dermal Exposure (mg/kg bw/day)[a]	Dermal MOE[b]
0.0016	48 100

[a] Refer to Appendix II for calculation of dermal exposure
[b]Based on a LOAEL of 75 mg/kg bw/day; Target MOE = 100.

3.4.3.4 Postapplication Toddler Incidental Oral Exposure and Risk

The potential for incidental oral ingestion of Mosquiron domestic products exists for toddlers. This scenario is likely to occur via hand-to-mouth activity or direct ingestion of treated standing waters. However, chemical-specific data for assessing postapplication incidental oral exposure were not submitted. Hence, exposure estimates, generated from the USEPA Residential SOP (2012), were based on the direct ingestion of granules which are not expected to underestimate the exposure to incidental oral ingestion of standing water treated with Mosquiron CRD-D or Mosquiron P-D.

Incidental oral exposure was estimated by coupling the default ingestion rate from the USEPA Residential SOP (2012) with the fraction of active ingredient in the formulation. Exposure was normalized to mg/kg bw/day by using 11 kg toddler body weight.

Table 5 Postapplication Toddler Incidental Oral Exposure Estimate and MOE

Incidental Oral Exposure (mg/kg bw/day)	Oral MOE[a]
0.0304	138

[a] Incidental Oral Exposure = $\frac{\text{Ingestion Rate} \times \text{Fraction of a.i. in Formulation}}{\text{Body Weight}}$

[b] Based on a NOAEL of 4.2 mg/kg bw/day; target MOE = 100

3.4.3.5 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

The properties and environmental fate characterization of novaluron have been previously reviewed and reported in the Proposed Decision Document PRD2006-05, *Novaluron*.

Briefly, novaluron is considered to be non-persistent to moderately persistent in soils and sediments. Phototransformation of novaluron on soil surfaces is not an important route of transformation in the environment. Novaluron dissipates primarily due to microbial biotransformation. Laboratory and field data indicate that novaluron is unlikely to leach into groundwater or volatize into air. Transformation products are not considered to be a concern.

Once applied to water, novaluron is expected to be non-persistent to slightly persistent in aerobic systems. The solubility of novaluron is 3.4 µg/L, suggesting it's practically insoluble in water. The Henry's law constant predicts novaluron to be volatile from a water surface. However, novaluron is expected to dissipate into the sediment, because it is insoluble in water and strongly sorbs onto particles. It is stable to hydrolysis and photolysis in water. Considering these properties, novaluron residues are not expected in the air, and very little expected in the water phase. Rapid transformation is expected to occur in aerobic water/sediment systems with half-lives ranging from 6 to 26 days.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental concentrations are concentrations of pesticide in various environmental media, such as food, water, soil and air. The estimated environmental

concentrations are estimated using standard models that take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

The potential environmental impacts of novaluron on terrestrial organisms have been previously reviewed and reported in PRD2006-05. Due to the aquatic use-sites proposed for this product there is negligible exposure or risk anticipated for terrestrial organisms.

4.2.2 Risks to Aquatic Organisms

The potential environmental impacts of novaluron on aquatic organisms have been previously reviewed and reported in PRD2006-05. However, the risk assessment for aquatic biota was reassessed taking into consideration new information submitted by the registrant.

Novaluron is very highly toxic to freshwater and marine invertebrates on an acute and chronic basis, but shows negligible toxicity to freshwater and marine fish, algae and aquatic vascular plants. Bioaccumulation is not expected due to proposed use sites, label restrictions, and a relatively short half-life in fish of 11–14 days.

There is no risk expected for freshwater fish, freshwater algae, freshwater vascular plants or marine fish. However, there is a risk to freshwater invertebrates (*Daphnia*), freshwater pelagic and benthic invertebrates, and marine invertebrates (mollusk and Mysid shrimp).

To protect at risk species, restrictions on potential use-sites will be specified on the label.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

One study conducted in 5 locations demonstrated the effectiveness of the Mosquiron line of end-use products at 120–240 µg a.i./L against *Culex* and/or A*ede*s mosquitoes for up to 90 days. In addition, use history information from the World Health Organization supported the use of novaluron against various mosquito genera (i.e., *Aedes*, *Culex*, *Anophele*s) for up to 90 days. Both the efficacy data and use history supported control of mosquito larvae (excluding *Mansonia* spp. and *Coquilletidia* spp.) for up to 90 days using concentrations of 120–240 µg novaluron/L of water.

5.2 Sustainability

5.2.1 Survey of Alternatives

Alternatives for control of mosquito larvae include *Bacillus sphaericus* 2362 (Mode of action [MOA] 11); *Bacillus thuringiensis* subsp. *israelensis* (MOA 11); s-methoprene (MOA 7A); diflubenzuron (MOA 15); chlorpyrifos (MOA 1B) and malathion (MOA 1B). These active ingredients are registered in commercial class or restricted class products. S-methoprene and *Bacillus thuringiensis* subsp. *israelensis* are the only active ingredients registered in domestic class products.

Proposed Re-evaluation Decision PRVD2010-18, *Malathion* proposes phase-out of malathion for this use. The Mosquiron products represent a potential alternative to malathion and chlorpyrifos as mosquito larvicides.

5.2.2 Compatibility with Current Management Practices Including Integrated Pest Management

The Mosquiron line of products are compatible with current mosquito management practices and have the potential to further reduce or replace the use of organophosphates in standing bodies of water as mosquito larvicides.

Monitoring for mosquito larvae is necessary to ensure that the products are applied to target the susceptible stages of mosquitoes.

5.2.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Resistance in mosquitoes has been reported for most of the active ingredients currently registered in Canada for this use (*Bacillus sphaericus* 2362; *Bacillus thuringiensis* subsp. *israelensis*; s-methoprene; chlorpyrifos and malathion). One other registered active ingredient, diflubenzuron, has the same MOA as novaluron. Since diflubenzuron is registered only as a commercial class product, novaluron represents a new mode of action for the domestic class market. In order to delay or avoid the development of resistance, resistance management recommendations are included on the labels of the restricted class products for novaluron.

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 [those that meet all four criteria outlined in the policy, i.e., 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*].

During the review process, novaluron and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Novaluron does not meet all Track 1 criteria and is not considered a Track 1 substance.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies

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

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette,* Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

and regulations including DIR99-03 and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions

- Technical Insecticide (Novaluron) and its end-use products, Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D, do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for novaluron is adequate to define the majority of toxic effects that may result from human exposure. Novaluron was not neurotoxic or genotoxic and there was no evidence of carcinogenicity in rats or mice after longer-term dosing. In a two generation rat reproduction study, increased spleen and liver weight as well as changes in pup body weight and body weight gain were noted at dose levels eliciting maternal toxicity. Delays in male sexual maturation were observed at a higher dose level. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. The primary effect of treatment with novaluron in laboratory animals was an adverse effect on the hematopoietic system, as demonstrated by the destruction of circulating red blood cells. This effect did not progress in magnitude or severity with prolonged dosing. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Workers handling Mosquiron 0.12CRD or Mosquiron 0.12P and re-entering treated areas are not expected to be exposed to levels of novaluron that will result in an unacceptable risk when Mosquiron 0.12 CRD or Mosquiron 0.12P are used according to label directions.

Residential exposure to individuals handling Mosquiron 0.12 CRD-D or Mosquiron 0.12P-D and contacting treated areas is not expected to result in unacceptable risk when these products are used according to label directions.

7.2 Environmental Risk

Technical Insecticide (Novaluron) and its end-use products, Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D, present a risk to freshwater and marine aquatic invertebrates. To protect at risk species, restrictions on use-sites will be specified on the label.

[8] DIR2006-02, Formulants Policy and Implementation Guidance Document.

7.3 Value

An efficacy study conducted in five locations and use history from the World Health Organization support the use of Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P and Mosquiron 0.12P-D to control mosquito larvae in standing bodies of water at concentrations of 120 to 240 µg novaluron/L of water. Applications must be made according to the use instructions identified on the label.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use Technical Insecticide (Novaluron) and its end-use products, Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D, containing the technical grade active ingredient novaluron, to control mosquito larvae (excluding *Mansonia* spp. and *Coquilletidia* spp.).

An evaluation of available scientific information found that, under the approved conditions of use, the products have value and do not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
τ	lag time per event
a.i.	active ingredient
ATPD	area treated per day
B	ratio of two permeability coefficients (stratum corneum:epidermis)
bw	body weight
bwg	body weight gain
CAS	Chemical Abstracts Service
CF	conversion factor to convert cm^3 to L
cm	centimetres
cm^2	square centimetre
cm^3	cubic centimetre
CRD	control rod
Cw	concentration of a.i. in water
DA_{event}	absorbed dose per event
E	total dermal exposure
EFH	Exposure Factors Handbook
F0	parental generation
F1	first generation
F2	second generation
FA	fraction of absorbed water
g	gram
GI	Gastrointestinal
GLP	Good Laboratory Practice
hr	hour
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{ow}	Octanol-water partition coefficient
Kp	permeability coefficient
L	litre
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
LOC	Level of Concern
m^2	square metre
MAS	maximum average score for 24, 48 and 72 hours
Met-Hb	methemoglobin
mg	milligram(s)
MIS	maximum irritation score
MOA	Mode of Action
MOE	margin of exposure
MW	molecular weight
N/A	not applicable
nm	nonametre
NOAEL	no observed adverse effect level

NZW	New Zealand white
OECD	Organization for Economic Cooperation and Development
ORETF	Outdoor Residential Exposure Task Force
Pa	Pascals
PCPA	*Pest Control Product Act*
P_{cw}	steady-state permeability coefficient of the stratum corneum
PF	protection factor from clothing
PHED	Pesticide Handlers Exposure Database
pK_a	Dissociation constant
PMRA	Pest Management Regulatory Agency
RBC	red blood cell
RQ	Risk Quotient
SA	surface area
SOP	standard operating procedure
Sulph-Hb	sulphhemoglobin
t	time, duration of work day
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
UE	Unit Exposure
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WHO	World Health Organization
wt	weight

Appendix I Tables and Figures

Table 1 Toxicity Profile of Mosquiron 0.12CRD, Mosquiron 0.12CRD-D, Mosquiron 0.12P, and Mosquiron 0.12P-D Containing Novaluron
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Sprague-Dawley rats, female PMRA #2042872	LD_{50} > 5000 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA #2042873	LD_{50} > 5050 mg/kg bw Low toxicity
Acute inhalation toxicity Waiver request PMRA #2024874	Waiver accepted based on low acute toxicity profile, low volatility of the TGAI, and non-friability of wax units. Low toxicity.
Dermal irritation NZW rabbits PMRA #2042876	MAS = 0.44 MIS = 1, at one hour Minimally irritating
Eye irritation NZW rabbits PMRA #2042875	MAS=0.89 MIS=8.67, at one hour Minimally irritating
Dermal sensitization (Buehler test) Hartley-Albino guinea pigs PMRA #2042877	Not a dermal sensitizer

Table 2 Revised Table Entry for Technical Insecticide (Novaluron)
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Two-generation reproductive toxicity (diet) CD Rats PMRA# 686907, 836776, 836778, and 836780	**Parental** **LOAEL =** 74.2 mg/kg bw/day **NOAEL** < 74.2 mg/kg bw/day **≥74.2/84.0 mg/kg bw/day:** ↑bwg, spleen wt (F0, F1 ♂,♀) **Offspring** **LOAEL =** 74.2 mg/kg bw/day **NOAEL** < 74.2 mg/kg bw/day **≥74.2/84.0 mg/kg bw/day**: ↑ mean litter pup bw at birth (F1 & F2), ↓ pup bwg during lactation, ↓ litter wt during lactation (F1 & F2) ↑spleen wt, liver wt (F1/2 ♂, F2♀) **Reproductive:** **NOAEL =** 74.2 mg/kg bw/day **LOAEL** = 297.5 mg/kg bw/day **≥297.5 mg/kg bw/day:** ↓epididymal sperm count and delayed sexual maturation (F1 ♂)

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Novaluron

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE[1]
Short- to Intermediate-term dermal	Rat 28-day dermal	LOAEL = 75 mg/kg bw/day Increases in Met-Hb and decreased body weight gain in males.	100
Non-dietary oral ingestion (all durations)	Mouse 90-day dietary	NOAEL = 4.2 mg/kg bw/day Increases in inclusion bodies, bilirubin, and sulph-Hb in males and decreases in RBC, hematocrit, and hemoglobin in females at the LOAEL of 12.8/15.2 mg/kg bw/day, respectively	100

[1] MOE refers to a target MOE for occupational and residential assessments

Appendix II

Dermal Exposure Input Calculations for Postapplication Workers and Toddlers

To estimate dermal exposure, the approach taken relies on using theoretically derived values for skin permeability coefficients. The equations used to calculate skin permeability coefficients (K_p) are adapted from correlation of Potts and Guy (1992) which is based only on human in vitro data (USEPA, 2004). The equation addresses non-steady state exposure using the Cleek and Bunge Approach (1993). This approach was recommended by the USEPA (1992) for estimating exposure to organic compounds in water.

Uncertainties exist with the application of these equations to estimate dermal exposure to active ingredients. The uncertainties include the following:

- The use of K_p for formulated insecticide end-use products may over- or underestimate exposure as the formulation may result in increased or decreased dermal absorption potential compared to the K_p value, which is based on data from novaluron in pure form.

- The equation used to derive K_p values are based on in vitro data rather than in vivo data. The use of in vitro data is problematic because the relationship between in vivo and in vitro test results have not been reliably established. Different interlaboratory experimental conditions (for example, skin sample characteristics, temperature, flow-through or static diffusion cells, concentration of chemicals in solution) in the data used to derive K_p introduces a considerable amount of uncertainty in this approach.

- This model assumed that the chemical concentration in the water contacting skin is constant.

- The Risk Assessment Guidance for Superfund, Part E (USEPA, 2004) model also relies on parameters B and τ. Calculations for these parameters depend upon many assumptions and limited, surrogate data.

The first step in the estimate of dermal dose is to calculate the value of K_p, which is calculated based on the following equation, using the USEPA's Empirical Predictive Correlation for Permeability Coefficients of Organics (USEPA, 2004) which is based on a dataset examining absorption of about 90 chemicals from water through human skin in vitro. The equation is as follows:

$$\mathbf{Log\ K_p = -2.80 + 0.66\ log\ \mathit{K}_{ow} - 0.0056\ MW}$$

where,

MW = molecular weight; 492.71
Log K_{OW} = octanol-water coefficient; 4.3
(Values from PRD2006-05)

$$\mathbf{K_p = 0.0019\ cm^2/hr}$$

The second step is the calculation of B, the dimensionless ratio of two permeability coefficients, one for the stratum corneum and one for the epidermis. The permeability coefficient for the epidermis is difficult to determine, therefore, B is estimated without knowing epidermal permeability and is, instead, based on empirical data and theory. B is estimated from Method 4 in Bunge and Cleek (1995a) as follows:

$$\mathbf{B = P_{cw}\ [(MW)^{0.5}/(2.6cm/hr)]}$$

where P_{cw} is the estimated steady-state permeability of the stratum corneum from water containing ISL, calculated as follows (Bunge and Cleek, 1995b):

$$\mathbf{Log\ P_{cw} = -2.8 - 0.006\ (MW) + 0.74\ log\ \mathit{K}_{ow}}$$
$$\mathbf{P_{cw} = 0.00267}$$

therefore,

$$\mathbf{B = 0.02275}$$

τ is the lag time per event (hours) or the time it takes for a chemical to cross the skin, including both the stratum corneum and the epidermis. τ is calculated as follows (USEPA, 2004):

$$\mathbf{\tau = 0.105 \times 10^{\ (0.0056\ MW)}}$$
$$\mathbf{\tau = 60.3067\ hours}$$

The equation for dermal exposure per event DA_{event} in the USEPA Risk Assessment Guidelines for Superfund – Part E (USEPA, 2004) is as follows (modified from Equation 3.3 in USEPA (2004), surface area exposure and body weight were added to the equation to achieve results in mg/kg bw/day rather than mg/cm^2):

$$\mathbf{E = [FA \times K_p \times SA \times PF \times C_w \times CF \times (t/(1+B) + 2\tau(1 + 3B + 3B^2/(1 + B)^2)] / bw\ (Results\ reported\ in\ Table\ 2\ \&\ 4)}$$

where,

E = total dermal exposure (mg/kg bw/day)
FA = fraction of absorbed water (dimensionless, default = 1)
K_p = permeability coeffiecient (cm/hr)
SA = surface area exposed; assumed hands (975 cm^2 for adults based on 5% of total body surface area; 302 cm^2 for toddlers ages 1 to <2 years old based on 5.7% of total body surface area; Surface area recommendations provided in the USEPA EFH, 2011)
PF = protection factor from clothing; assume 1 as hands may not be protected by clothing
C_w = concentration of a.i. in water (maximum supported application rate; 0.24 mg/L)
CF = conversion factor to convert cm^3 to L; 0.001L = 1 cm^3
t = duration of work day (8 hours/event or day for re-entry workers; 1.1 hours/event or day for toddlers ages 1 to <2 years as recommended in the USEPA Residential SOP (2012) for postapplication default duration to gardens/trees
B = dimensionless ratio of two permeability coefficients (one for stratum corneum and one for the epidermis)
τ = lag time (time for chemical to cross the skin) per event or day (hours/event or day)
bw = body weight; 80 kg for adults and 11 kg for toddlers ages 1 to <2 years

Residential Applicator Exposure Output Using the USEPA General Residential Handler SOP Calculator

Exposure scenario	Application Rate (kg a.i./m^2)	ATPD (m^2/day)	Amount a.i. Handled (kg a.i./ day)	Dermal Unit Exposure (mg/kg a.i.) [1]	Inhalation Unit Exposure (mg/kg a.i.) [1]	Dermal Exposure[2] (mg/kg bw/day)	Inhalation Exposure[2] (mg/kg bw/day)	Dermal MOE[3] (Target = 100)	Inhalation MOE[3] (Target = 100)
PPE: none									
Hand Dispersion, granules (CRD & Pellets)	0.000036	111.48	0.00401	352.74	0.84	1.77×10^{-2}	4.21×10^{-5}	4.24×10^{3}	9.97×10^{4}
Spoon (CRD & Pellets)	0.000036	111.48	0.00401	13.67	0.19	6.86×10^{-4}	9.53×10^{-6}	1.09×10^{5}	4.41×10^{5}
Cup (CRD & Pellets)	0.000036	111.48	0.00401	0.24	0.029	1.20×10^{-5}	1.45×10^{-6}	6.23×10^{6}	2.89×10^{6}
Belly Grinder (Pellets)	0.000036	93	0.00335	793.66	0.086	3.32×10^{-2}	3.60×10^{-6}	2.26×10^{3}	1.17×10^{6}
Push-type Spreader (Pellets)	0.000036	2000	0.072	1.79	0.0057	1.61×10^{-3}	5.13×10^{-6}	4.66×10^{4}	8.19×10^{5}

PPE = personal protective equipment

[1] Unit Exposure (UE) values taken from the USEPA Residential SOP (2012).

[2] Exposure = (Dermal UE or Inhalation UE × Amount a.i. Handled) ÷ (80 kg bw)

[3] Dermal endpoint based on LOAEL = 75 mg/kg bw/day, target MOE = 100; Inhalation endpoint based on NOAEL of 4.2 mg/kg bw/day, target MOE = 100.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA#	Reference
2042868	2010, Mosquiron Controlled Release Mosquito Larvacide: Product Properties, DACO: 3.1.1,3.1.2,3.1.3,3.1.4,3.2.1,3.2.2,3.2.3,3.3.1,3.4.1 CBI
2042870	2010, Final report for "Physical and Chemical Characteristics of Novaluron Pastille 0.1", DACO: 3.5.1,3.5.2,3.5.3,3.5.6,3.5.8 CBI
2097275	2010, Determination of Novaluron by [CBI removed], DACO: 3.4.1 CBI
2097274	2011, CRD-Mosquiron-letter of intent-08september2011-clarification, DACO: 0.8
2117941	2011, CRD-Mosquiron-letter of intent-24oct2011-clarification, DACO: 0.8
2117942	2011, Final Report for "Accuracy of Analytical Method for Mosquiron 0.12CRD, DACO: 3.4.1 CBI
2042870	2010, Final report for "Physical and Chemical Characteristics of Novaluron Pastille 0.1", DACO: 3.5.1,3.5.2,3.5.3,3.5.6,3.5.8 CBI
2042869	2011, PART 3 Chemistry DACOs 3.1-3.15, DACO: 3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3,3.5.4,3.5.5,3.5.6,3.5.7,3.5.8,3.5.9

2.0 Human and Animal Health

PMRA#	Reference
2042872	2010, Acute Oral Toxicity Study (UDP) in Rats, DACO: 4.6.1
2042873	2010, Acute Dermal Toxicity Study in Rats, DACO: 4.6.2
2042874	2010, Novaluron Controlled Release Formulations (Mosquiron 0.12 CDR, Mosquiron 0.12 P) Request for Waiver of Acute Inhalation Toxicity, DACO: 4.6.3
2042875	2010, Acute Eye Irritation Study in Rabbits, DACO: 4.6.4
2042876	2010, Acute Dermal Irritation Study in Rabbits, DACO: 4.6.5
2042877	2010, Skin Sensitization Study in Guinea Pigs, DACO: 4.6.5
208917	Use Description/Exposure Scenarios and Exposure Assessment, DACO: 5.2,5.3,5.4,5.5
883972	2002, DACO 5 Exposure, DACO: 5.2,5.3,5.4,5.5
1103003	Mixer/Loader/Applicator-PHED/Passive Dosimetry/Biological Monitoring, DACO: 5.3,5.4,5.5
2042879	2011, Mosquiron Use Description Scenario, DACO: 5.2
2163138	2012, Mosquiron -Exposure-5.2,5.6,5.7-deficiency, DACO: 5.2,5.6,5.7

3.0 Environment

2042885	2010, Characterization of Three controlled Release Formulation of Novaluron Pastille 0.1, DACO: 8.2.4.6

4.0 Value

PMRA#	Reference
884015	2002, Mode of Action: Novaluron, DACO: 10.2.1
2042865	2011, Field Efficacy of Novaluron as a Mosquito Larvacide, DACO: 10.1,10.2.3.1,10.2.3.4(E)
2042867	2011, DACO PART 10 Value DACOs 10.2.2, 10.3.1, 10.3.2, DACO: 10.2.2,10.3.1,10.3.2
2086075	2011, Letter with formula-09aug2011, DACO: 0.8.1
2093209	2011, Field Efficacy of Novaluron as a Mosquito Larvacide-Egg data-CRD mosquiron-27august2011, DACO: 10.2.3.3(C)
2093210	2011, Field Efficacy of Novaluron as a Mosquito Larvacide-Pupa data-FTN WI-1CRD Mosquiron clarification-27aug2011, DACO: 10.2.3.3(C)
2093211	2011, Field Efficacy of Novaluron as a Mosquito Larvacide-Pupa data-transfer events- FTN MB-1-CRD Mosquiron clarification-27aug2011, DACO: 10.2.3.3(C)
2093212	2011, Field Efficacy of Novaluron as a Mosquito Larvacide-Pupa data-transfer events-FTN GA-1-CRD Mosquiron clarification-27aug2011, DACO: 10.2.3.3(C)
2163139	2012, Mosquiron -Value-10.2.1,10.2.3.3-deficiency, DACO: 10.2,10.2.3.3(C)
2163141	2011, Pupa data-transfer events- BC Form-12-CRD Mosquiron clarification-26 aug2011, DACO: 10.2.3.3(C)
2163131	2012, 2011-1678-CRD-Mosquiron-letter of intent-21feb2012-deficiency, DACO: 0.8
2163162	2012, 2011-1678-CRD-Mosquiron-letter of intent-16feb2012-label deficiency, DACO: 0.8
2163164	2012, Mosquiron -Value-10.1-deficiency, DACO: 10.2, 10.2.3.3(C)
2196008	2012, Clarification Request for Mosquiron Products 053112, DACO: 10.2.3.1
2203789	2012, PMRA clarification request 26june2012, DACO: 10.2.3.1
2220209	2012, CRD-Mosquiron-letter of intent-28august2012-clarification, DACO: 10.2.3.1

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

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Bunge AL, Cleek RL and Vecchia BE. 1995b. A New Method for Estimating Dermal Absorption from Chemical Exposure; 3: Compared with Steady-State Methods for Prediction and Data Analysis. Pharm Res 12: 972-982.

Cleek RL and Bunge AL. 1993. A New Method for Estimating Dermal Absorption from Chemical Exposure; 1: General Approach. Pharm Res 10:497-506.

Potts RO and Guy RH. 1992. Predicting Skin Permeability. Pharm Res 9:663-669.

Proposed Registration Decision PRD2006-05, *Novaluron*. December 22, 2006.

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USEPA. 2004. Risk Assessment Guidance for Superfund (RAGS), Volume 1: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). EPA/540/R/99/005. July 2004. http://www.epa.gov/oswer/riskassessment/ragse/pdf/part_e_final_revision_10-03-07.pdf

USEPA. 2011. Exposure Factors Handbook 2011 Edition (Final). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/052F.

USEPA. 2012. Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessments. Washington (DC): US Environmental Protection Agency, Office of Pesticides Programs, Health Effects Division. October, 2012.

2.0 Value

PMRA#	Reference
2179260	World Health Organization. 2005. Report of the Eighth WHOPES Working Group Meeting, Review of Novaluron 10% EC, 42 pages, December 1–3, 2004. DACO: 10.6

ii) Unpublished Information

1.0 Human and Animal Health

PMRA#	Reference
1563670	ORETF. 1999. A Generic Evaluation of Homeowner Exposure Associated with Granular Turf Pesticide Handling and Application to Residential Lawns. Sponsor/Submitter: Outdoor Residential Exposure Task Force. OMA003. Sub. No. 2006-4038. Unpublished, 3 February 1999. EPA MRID # 44972201.