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20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Tel. direct: +41 22 791 29 16
Fax direct: +41 22 791 47 30
E-mail : pqvectorcontrol@who.int
In reply please refer to: V2-447-3/ML/CS/1
Your reference: 020-006, NP2018-006

Clarke International LLC
Ms Karen J. Larson
675 Sidwell Court, St. Charles
Illinois 60174
Etats Unis d'Amérique

22 January 2019

Dear Ms Larson,

WHO Prequalification Team – Vector Control
VCP Prequalification – Letter of Prequalification

Product number: 020-006

Thank you for submitting the data and information requested and for your voluntary participation in this quality assessment procedure. The review of your company's product dossier on:

- **020-006 Cielo ULV**

has been completed and it has been found to meet the norms and standards recommended by the World Health Organization for Space Spray products and is acceptable, in principle, for procurement by UN and other international agencies and countries.

This conclusion is based on information available to WHO at the current time, i.e. the information in the submitted dossier and on the status of ISO 9001 Certification at the facilities used for the manufacture of the product. Please note, however, that this decision may change based on new information that may become available to us. Therefore, the product will now be included on the list of vector control products, which are considered to be acceptable, in principle, for procurement by UN and other international agencies and countries. This list is published by WHO at http://www.who.int/pq-vector-control/prequalified-lists/en/.

Please note that inclusion on the list cannot be construed as WHO approval or endorsement, and does not necessarily mean that the listed products will actually be procured from the suppliers mentioned. The list, and the WHO name, emblem and/or acronym may not, furthermore, be used by the applicants, manufacturers, suppliers or any other parties for commercial or promotional purposes.

The applicants and the manufacturers of prequalified products are required to communicate to WHO details of any changes in manufacture or control that may have an impact on the safety, efficacy and/or quality of the product.

cc: John Dawson, John Dawson Consulting

Finally, I should like to draw your attention to the fact that the list will be reviewed and updated at regular intervals. Consequently, WHO will, at regular intervals, arrange for the products and manufacturing sites included in the list to be re-evaluated. If, as a result of this reassessment, it is found that a product and/or specified manufacturing site no longer complies with the WHO recommended standards, such products will be removed from the list. The failure of an applicant or a manufacturer to participate in the reassessment procedure will also lead to removal from the list.

Yours sincerely,

Mr Deus Mubangizi
Coordinator
Prequalification Team
Regulation of Medicines and other Health Technologies

Prequalification Team Vector Control Decision Document

Cielo ULV Adulticide Space Spray

Prequalification Team–Vector Control Group (PQT-VC)

Access to Medicines, Vaccines and Pharmaceuticals (MVP)

World Health Organization

Prequalification Team Vector Control Decision Document

Cielo ULV Adulticide Space Spray

1 Introduction

WHO's Prequalification Team Vector Control Group (PQT- VC) ensures that vector control products and public health pesticide active ingredients are safe, effective and manufactured to a high-quality standard. This is done by assessing product dossiers and inspecting manufacturing sites. Products and manufacturing sites that meet prequalification requirements are added to (a) the WHO list of prequalified vector control products; (b) the WHO list of manufacturing sites for public health pesticide active ingredients.

WHO prequalification of vector control products primarily benefits populations most affected by major vector-borne diseases such as malaria, dengue fever and other arboviral diseases (Chikungunya, Zika virus), Chagas disease, lymphatic filariasis, visceral leishmaniasis, and human African trypanosomiasis.

This document presents the results of the safety, efficacy and quality (product chemistry and manufacturing process) assessments for the product Cielo ULV Adulticide Space Spray which provide the basis for the prequalification listing decision.

2 Product Identification

Cielo ULV Adulticide Space Spray (PQ Ref. Number: 020-006) is a liquid mixture containing imidacloprid (30 g/kg; 3% w/w) and prallethrin (7.5 g/kg; 0.75% w/w). The formulation is an ultra-low volume liquid and is applied as a space spray (cold fogging) by professional users only. It is labelled for application as an ultra-low volume (ULV) non-thermal cold aerosol mist for indoor and outdoor, residential, institutional, industrial and recreational areas. Target vectors are *Aedes aegypti* and *Aedes albopictus* which are vectors of dengue, Chikungunya, yellow fever, and Zika.

The source of active ingredients and their declared minimum contents are:

- Imidacloprid, declared minimum content 970 g/kg
- Prallethrin, declared minimum content 900 g/kg

The applicant, Clarke International LLC, St. Charles, Illinois, USA submitted a dossier containing supporting data on the product to PQT-VC on April 18, 2018 and requested a PQ listing for the product. Formulating plants are located in Roselle, Illinois, USA and Puebla, Mexico.

The product is registered for use in Mexico and Iraq; and, is pending registration in multiple countries.

Cielo ULV is a ready to use insecticide for indoor and outdoor use for the control of *Aedes aegypti* and *Aedes albopictus* adult mosquitoes. According to the label provided by the manufacturer, for indoor use, Cielo ULV is sprayed using portable equipment, backpack electric or gas-powered ULV cold aerosol application at a rate of 8.8 to 14.6 mL per 1000 m^2. For outdoor use, Cielo ULV is applied undiluted through ultra-low volume cold aerosol equipment at a rate of 88 to 146 mL per hectare. Clarke International LLC has performed indoor, outdoor and environment studies for space spraying with Cielo ULV, and the target application rates provided are used in this decision document.

3 Assessment of Quality

3.1 Chemical and Physical Properties

Data on the chemical and physical properties of the active ingredients and the product Cielo ULV were provided. Product specific properties are summarized in Table 1. These data were obtained from studies conducted according to Good Laboratory Practices (GLP) and are complete.

Table 1. Chemical and Physical Properties for Cielo ULV Adulticide Space Spray

Title	Study Number	Test method ID	Result
Appearance	Product Properties Study of CMP123-004 GLP study No. AN 1056 (PC1)	Colour : SOP-C006-2 Odour : SOP-C005-1	Amber coloured clear liquid with slight mint odour
pH (1% aqueous dilution)	Product Properties Study of CMP123-004 GLP study No. AN 1056 (PC1)	CIPAC MT 75.3 P-006	7.3 to 7.7
Flash point	Product Properties Study of CMP123-004 GLP study No. AN 1056 (PC1)	SOP-C017 (Pensky-Martens closed cup tester)	117 °C (range 117 – 121°C)
Viscosity	Product Properties Study of CMP123-004 GLP study No. AN 1056 (PC1)	SOP-C018	20 °C, 41.84 centiPoise 40 °C, 20.98 centiPoise
Density	Product Properties Study of CMP123-004 GLP study No. AN 1056 (PC1)	SOP-C016 (using a pycnometer)	1.138 g/ml
Metal immersion test	Product Properties Study of CMP123-004 GLP study No. AN 1056 (PC1)	SOP-C019-1	No evidence of corrosion or weight loss after 14 days at 54 °C.
Low temperature stability	Product Properties Study of CMP123-004 GLP study No. AN 1056 (PC1)	CIPAC MT 39.3	No separated material founded for each of the five batches after storage for 7 days at a low temperature condition (0°C ±2°C).
Accelerated temperature storage	Product Properties Study of CMP123-004 GLP study No. AN 1056 (PC1)	CIPAC MT 46.3	Storage stability was conducted using simulated commercial packs- Fluorinated HDPE, and stainless steel coated with L15 phenolic film. No significant change in appearance, pH, or weight loss after 14 days. Active ingredient content remained stable after 14 days at 54 °C
Shelf life stability, 9 months storage at 30° ± 2°C in FHDPE	Product Properties Study of CMP123-004 GLP study No. AN 1056 (PC1) and Long term Stability – Interim report – Jan 2018 (PC3)	Clarke method CV-006	After 2 weeks storage at 54 ± 2°C in HDPE and in glass with metal immersion strips to simulate drums, the prallethrin and imidacloprid contents remain stable. After 9 months storage at 30º ± 2°C in FHDPE the prallethrin and imidacloprid contents remain stable.

3.2 **Manufacturing, Composition and Formulant Information**

Data on the manufacturing process and product composition has been provided and are adequate. A summary is presented in Table 2. Detailed information on the manufacturing process and product formulation is considered Confidential Business Information (CBI) and is presented in Appendix A.

Table 2. Data Submitted for the Cielo ULV Adulticide Space Spray

Data Requirement	Study Number	Details
Description of Starting Material	Confidential Business Information Cielo ULV	Prallethrin 98.4-98.9 % purity, minimum prallethrin content 90.0%. Manufacturer: Sumitomo Chemical Co. Japan Imidacloprid 98.5 % purity, minimum imidacloprid content 97.0 %. Manufacturer: UPL Limited, India Inert ingredients
Production / Formulation Process	Confidential Business Information Cielo ULV	Included in the Confidential Business Information. Appendix A (Internal use only).
Discussion of Impurities	Confidential Business Information Cielo ULV	There are no known relevant impurities in the inert ingredients and in the product.
Control Product Specification Form / Confidential Statement of Formula	Chemistry Dossier	Included in the Confidential Business Information. Appendix A (Internal use only).
Certification of Limits	Product Properties Study of CMP123-004 GLP study No. AN 1056	Prallethrin: 0.75 % w/w certified limits 0.675 to 0.825% Imidacloprid: 3 % w/w certified limits 2.7 to 3.3% w/w
Preliminary Analysis	Study No. AN 1054	The Clarke analytical method, CV-006, "HPLC Determination of Imidacloprid and Prallethrin Contents in CMP123-003", was used to determine ingredient content of the test substance.
Enforcement Analytical Method	Study No. AN 1054	“HPLC Determination of Imidacloprid and Prallethrin Contents in CMP123-003”, Clarke method CV-006. This method was independently validated.

3.3 Enforcement Analytical Method

A validated analytical method was submitted and is summarized in Table 3.

Table 3. Details of the analytical method used to determine prallethrin and imidacloprid in Cielo ULV	
Method ID	Clarke analytical method, CV-006, "HPLC Determination of Imidacloprid and Prallethrin Contents in CMP123-003"
Sample preparation	Weigh to the nearest 0.1mg, 1.0g of CIELO ULV sample into a 25 mL volumetric flask. Dilute to volume with ACN. Make further dilutions for the necessary concentration.
Instrument	HPLC system: pump, auto sampler, UV/Vis detector, column oven, degasser
Detector	UV-Vis detector
Column	Allsphere ODS-2, 100 mm x 4.6 mm, 3µm
Mobile phase (for LC)	Acetonitrile/Water (gradient)
Column temperature	30 ºC
Flow rate	1.0 ml/min
Injection volume	10 µL
Wavelength	225 nm
Quantitation	calibration
Retention time, prallethrin	10.7 min
Retention time, imidacloprid	1.9 min
Total run time	15 min
Chromatograms	available

The method validation data are shown in Table 4. The method is suitable for the determination of the active ingredient content of the product.

Table 4. Validation data for prallethrin and imidacloprid in Cielo ULV.

Method ID	Method type	Linearity	Recovery (%)	RSD (%)	Method
Clarke analytical method, CV-006, "HPLC Determination of Imidacloprid and Prallethrin Contents in CMP123-003", Report AN 1054	HPLC	Calibration range: 0.024-0.12 mg/mL for prallethrin 0.048-0.24 mg/mL for imidacloprid	102.9 for prallethrin 101.6 for imidacloprid	0.13 for prallethrin 0.35 for imidacloprid	CV-006

3.4 Specifications

The sources of active ingredients are supported by existing WHO specifications.

The proposed specification for the formulated product was evaluated and established through the procedures of the WHO/FAO Joint Meeting on Pesticide Specifications (JMPS).

3.5 Impurities of Toxicological Concern

No impurities of toxicological concern were found in the technical active ingredients and inert ingredients.

3.6 Quality conclusions

According to the studies presented all physical-chemical properties of the product were in accordance with the specifications. The proposed methods for assessing the physical-chemical properties of the product were CIPAC methods and/or validated methods. The physical-chemical data was generated in accordance with GLP.

The quality component of the dossier is complete. The assessment of the submitted information supports the prequalification of the product.

4 Assessment of Safety

The existing toxicology database is adequate to support the proposed labelled uses of Cielo ULV.

4.1 Product Specific Toxicity Data-Acute Toxicity

A summary of acute toxicity data is provided in Table 5. All acute studies (mammalian and ecotoxicity) were conducted at Stillmeadow Lab., Sugar Land, Texas, USA following OECD guidelines and conducted in compliance with all GLP standards. Under the GHS classification, Cielo ULV Adulticide Space Spray has low acute oral and dermal toxicity (Category 5), and moderate acute inhalation toxicity (Category 3). It is a minimal eye irritant, but neither a skin irritant nor a dermal sensitizer. The results of the studies are summarized as below:

Table 5: Toxicity Data for Cielo ULV Adulticide Space Spray

Route of Exposure	Species	Results	GHS Classification	Study Reference
Oral	Rat	LD50 > 2000 mg/kg	Category 5	Stillmeadow Lab. # 19943-16, October 2016
Dermal	Rat	LD50 > 2000 mg/kg	Category 5	Stillmeadow Lab. # 19944-16, October 2016
Inhalation	Rat	LC50 > 5.15 mg/L/4 hours	Category 3	Stillmeadow Lab., # 19945-16, October 2016
Eye Irritation	Rabbit	Minimally Irritating; Irritation score not provided.	Not Classified	Stillmeadow Lab. #19946-16, October 2016
Skin Irritation	Rabbit	Non-irritating; Irritation score not provided.	Not Classified	Stillmeadow Lab. #19947-16, October 2016
Dermal sensitization	Guinea Pig	Not a sensitizer	Not Applicable	Stillmeadow Lab. # 19948-16, October 2016

The acute toxicity package generated with Cielo ULV Adulticide Space Spray demonstrated that the combination of both insecticides, prallethrin and imidacloprid, did not potentiate the toxicological profile of the individual active substances. Therefore, it can be concluded that the combination of both insecticides in the same product does not impact the human risk assessment.

4.2 Summary of Available Toxicity Data on Active Ingredients: Prallethrin and Imidacloprid

There is sufficient information on the toxicity of the two active ingredients to assess the human health safety of Cielo ULV. This information was provided through the submission of human safety evaluations conducted by the US EPA. For imidacloprid, the primary effects as indicated by the toxicity database are on the nervous system. Evidence of neurotoxicity was observed in several species (rats and dogs) and consisted of decreased motor and locomotor activities such as tremors and gait abnormalities. Prallethrin is a member of the pyrethroid chemical class which have been classified into two groups, Type I and Type II, based on chemical structure and toxicological effects. Pyrethroids disrupt the voltage-gated sodium channels in the nervous system, resulting in neurotoxicity. Prallethrin is a Type I pyrethroid. Neurotoxicity was observed throughout the database and clinical signs characteristic of Type I pyrethroids, such as increased salivation, altered mobility/gait, and tremors, were the most common effects observed. There is no evidence for carcinogenic, genotoxic, developmental, reproductive, or immunotoxic potential.

Points of Departures (PODs) based on the most sensitive endpoints in the toxicity database are available for both prallethrin and imidacloprid. The PODs and toxicological endpoints of concern selected for dietary and non-dietary risk assessment are considered protective of any potential adverse effects, including neuro- and developmental toxicity, reproductive effects, and immunotoxicity for all populations.

The existing toxicology database is adequate to support the labelled uses of Cielo ULV for control of mosquitoes that may transmit vector borne diseases. Toxicity data are available on the active ingredients prallethrin and imidacloprid contained in the formulated product, Cielo ULV.

4.2.1 Mammalian Toxicity

a) Prallethrin

- **Acute Toxicity**

Prallethrin is moderately toxic by oral ingestion (oral LD50 in rats was 640 mg/kg and 460 mg/kg in males and females, respectively – Globally Harmonized System (GHS) Category 4) and by inhalation (acute inhalation LC50 was > 0.288 mg/L - GHS Category 2). It is not toxic by dermal application (acute dermal LD50 > 5000 mg/kg in rats – GHS Category 5) and is not a skin sensitizer in guinea pigs (GHS Category = Not Applicable). It is not irritating to the skin after dermal application and minimally irritating to the eyes (irritation score = 3.7 at 1 hr.; 0.0 at 48 hours; GHS Category = Not Classified) (USEPA 2003, 2016).

- **Subchronic Toxicity**

In 90-day feeding studies, the NOAEL was 79.1 mg/kg/day for male rats and the LOAEL was 230 mg/kg/day based on alopecia, decreased body weight, changes in blood chemistry, and increased small follicles in thyroid.

In a 90-day subchronic study, dogs were given capsules containing prallethrin. The NOAEL was 3 mg/kg/day and the LOAEL was 10 mg/kg/day based on tremors, enlarged livers, and changes in blood chemistry (USEPA 2003, 2016).

In a 21-day dermal study with rats, the NOAEL was 30 and the LOAEL was 150 mg/kg/day based on clinical signs of toxicity and decreased body weights (USEPA 2016).

In a 28-day inhalation with rats, the NOAEL was 0.0010 mg/L with irregular respiration, decreased spontaneous activity, salivation and nasal discharge noted at 0.0044 mg/L (USEPA 2016).

- **Genotoxicity**

The genotoxic potential of prallethrin was investigated in both *in vitro* and *in vivo* assays using bacterial and mammalian system. In a Chinese hamster ovary cell test, the *in vitro* chromosomal aberration test was positive but only in the presence of metabolic activation. All other gene mutation, chromosomal aberration, and unscheduled DNA synthesis (UDS) studies were negative. Using a weight of evidence approach, there is no evidence to suggest that prallethrin is mutagenic or clastogenic (USEPA 2014).

- **Reproductive/Developmental Toxicity**

In a 2-generation reproduction study with rats, the reproductive NOEC was established at 600 mg a.i./kg-diet and the reproductive LOEC was 3000 mg a.i./kg diet based on decreased pup weight.

In a reproductive toxicity study with rats, the parental systemic NOAEL was 31 mg/kg/day and 37 mg/kg/day for male and female rats, respectively. The parental systemic LOAEL was 156 and 185 mg/kg/day, respectively, for male and female rats. No adverse reproductive effects were noted up to the highest dose tested, and the reproductive NOAELs for males and females were 329 and 375 mg/kg/day, respectively. Offspring NOAEL was 31 mg/kg/day with decreased pup body weights noted during lactation at higher dose levels (USEPA, 2016).

In oral developmental toxicity studies, no adverse developmental effects were noted in rats up to the highest dose tested of 300 mg/kg/day and in rabbits up to the highest dose tested of 200 mg/kg/day. The maternal NOAEL in rats was 25 mg/kg/day whereas that in rabbits was 30 mg/kg/day.

In subcutaneous developmental toxicity and reproductive study in rats, the systemic maternal NOAEL and LOAEL were, respectively, 25 and 50 mg/kg/day based on tremors and exaggerated reflexes noted at the 50 mg/kg dose level. No developmental effects were noted up to the highest dose tested of 50 mg/kg/day.

In a subcutaneous developmental toxicity study in rabbits, dose levels of 1, 3, and 10 mg/kg/day were administered and no maternal and developmental effects were noted at 10 mg/kg/day (USEPA 2016). Collectively, there is no evidence to indicate that prallethrin is a reproductive or developmental toxicant.

- **Neurotoxicity**

In an acute neurotoxicity study in rats, the NOAEL was 100 mg/kg/day and the LOAEL was 300 mg/kg/day based on reduced motor activity in both sexes and tremors and death in females.

In an additional acute neurotoxicity comparison study with rats (WIL Laboratories; non-guideline study), the NOAEL was 150 mg/kg/day and the LOAEL was 250 mg/kg/day based on findings of chronic convulsions, splayed hind legs, impaired mobility, coarse tremors, ataxia and impaired gait.

However, in a 13 week study in rats, there is no evidence of neurotoxicity up to the highest dose tested of 363 mg/kg/day (males) and 420 mg/kg/day (females). The systemic NOAELs were 74 and 88 mg/kg/day for males and females, respectively (USEPA 2016).

- **Chronic and Carcinogenicity**

Chronic and carcinogenicity studies were conducted with mice and rats. The chronic systemic NOELs in rats were 83.5 mg/kg/day (highest dose tested) in males and 19.1 mg/kg/day in females. In female rats, decreased body weight gains and histiocytic infiltration in the liver were noted at LOAEL=103.4 mg/kg/day (USEPA 2016).

In mice, the systemic NOAEL in males was 68 mg/kg/day with kidney effects noted at LOAEL=347 mg/kg/day whereas in females, the systemic NOAEL was 778 mg/kg/day (highest dose tested) and the LOAEL not determined (USEPA 2016).

In a 1-year chronic study, dogs were treated with capsules containing prallethrin. At 10 mg/kg/day tremors, increased serum cholesterol and phospholipids, and increased alkaline phosphatase activity were noted. The systemic LOAEL was established at 5 mg/kg/day as evidenced by clinical signs of neurotoxicity: tremors, convulsions, salivation and the systemic NOAEL was established at 2.5 mg/kg/day (USEPA, 2014, 2016).

There is no evidence to suggest that prallethrin is carcinogenic in either rats or mice.

b) Imidacloprid

- **Acute Toxicity**

Imidacloprid given orally as a single dose was moderately toxic to rats (LD_{50} = 424–650 mg/kg bw; GHS Category 3). The acute dermal LD50 was > 5000 mg/kg in rats (GHS Category 5). The LC_{50} for a single exposure to a dust aerosol for 4 hours was > 5.32 mg/L (GHS Category 5). Imidacloprid (purity, 94.2%) did not irritate the eyes or skin of New Zealand white rabbits (GHS Category: Non-irritating) and was not a skin sensitizer in guinea pigs (GHS Category: Not Applicable).

- **Subchronic Toxicity**

In a 90-day subchronic feeding study, groups of male and female rats were exposed to imidacloprid at 0, 150, 600, or 2400 ppm corresponding to 0, 14, 61 and 300 mg/kg/day for males and 0, 20, 83 and 420 mg/kg/day for females. Adverse effects on the liver were noted in males at 300 mg/kg/day, but these effects reversed within 4 weeks. The systemic NOAEL was 14 mg/kg/day with decreased weight gain noted at 61 mg/kg/day (LOAEL).

In a 90-day feeding study with dogs, the animals were exposed to 0, 200, 600, 1800/1200 ppm, corresponding to 0, 7.7, 22.1 and 45.0 in males and 8.0, 24.8 and 45.7 mg/kg/day in females. The NOAEL was 8 mg/kg/day (200 ppm) based upon findings of tremors noted within one week of treatment at 22.1/24.8 mg/kg/day (600 ppm; LOAEL).

Groups of four male and four female pure-bred beagles were given diets containing imidacloprid at a concentration of 0, 200, 500 or 1250/2500 ppm for 52 weeks. At 1250/2500 ppm, clinical chemical examination revealed a slight increased plasma cholesterol concentration in females after 13 and 26 weeks, increased hepatic cytochrome P450 activity and slightly increased liver weights in males and females after 52 weeks. These slight effects were not of biological significance. The NOAEL was 2500 ppm, equivalent to 72 mg/kg bw per day (USEPA 2017).

Imidacloprid (purity, 95.3%) was administered as a dust in a nose-only inhalation to groups of 10 male and 10 female Wistar rats at analytically determined concentrations of 0, 5.5, 30 and 190 mg/m^3 for 6 h/day, 5 days per week for 4 weeks. Body weight gain was decreased in males at the two higher concentrations. Increased mixed-function oxidase activities were found in liver homogenate from females at these concentrations and in males at 190 mg/m^3 air. Increased alanine aminotransferase and glutamate dehydrogenase activities were seen in both sexes at the highest concentration, and alanine aminotransferase activity was increased in females at 30 mg/m^3 air. The females had increased alkaline phosphatase activity at the two higher concentrations and increased liver weights at 190 mg/m^3 of air. The serum *alpha*1-globulin fraction was reduced in both sexes at the two higher concentrations. The NOAEL was 5.5 mg/m^3 air (JMPR 2001).

- **Genotoxicity**

The genotoxic potential of Imidacloprid was tested in various assays using bacterial and mammalian cells. No genotoxic effects were noted in reverse mutation assays with *Salmonella typhimurium* and Chinese hamster ovary cells. Tests for mitotic, DNA damage in the *rec* assay and unscheduled DNA synthesis also gave negative results. All tests for chromosomal damage *in vivo* (micronucleus formation and cytogenetic effects in bone marrow and spermatogonia) were negative (USEPA, 2014). There is no evidence to suggest that imidacloprid is mutagenic or clastogenic.

- **Reproductive/Developmental Toxicity**

In a 2-generation reproduction study with rats, imidacloprid was mixed in the diet at 0, 100, 250 or 700 ppm, equivalent to 6.6, 16.5 and 47.3 mg/kg bw per day, for 84 days before mating and throughout mating, gestation and lactation of the F1a and F1b litters. Reduced body weights and body-weight gains were observed in all generations (F1a, F1b, F2a, F2b) at 700 ppm during lactation. The parental systemic NOAEL was 16.5 mg/kg/day with decreased body weights noted at higher concentrations. The reproductive NOAEL was 47.3 mg/kg/day (highest dose tested) and the offspring NOAEL was 16.5 mg/kg/day. Decreased pup body weights were found in both litters of both generations at 47.3 mg/kg/day (offspring LOAEL; USEPA 2017).

Developmental toxicity studies with imidacloprid were conducted in rats and rabbits. Rats were dosed by gavage from days 6-15 of gestation with 0, 10, 30 or 100 mg/kg bw/day. Skeletal examination of the pups

showed a slightly increased incidence of wavy ribs at 100 mg/kg bw per day. The NOAEL for maternal effects was 100 mg/kg bw/day and the NOAEL for developmental effects was 100 mg/kg bw/day (USEPA 2017).

Imidacloprid was administered by gavage to groups of 16 female Chinchilla rabbits at a dose of 0, 8, 24 or 72 mg/kg bw/day on days 6–18 of gestation. Decreased food intake and body-weight gain were observed at doses greater than 24 mg/kg bw/day, and an increased mortality rate was observed at 72 mg/kg bw per day, two females dying on days 18 and 19. A female in this group aborted on day 26 post coitum, and two females showed total resorption at terminal necropsy. The dose at 72 mg/kg bw/day had slightly increased post-implantation loss. The body weights of the fetuses were reduced and the incidence of fetuses with retarded ossification was increased at 72 mg/kg bw per day. The NOAEL for maternal effects was 24 mg/kg bw/day, and that for developmental effects was 24 mg/kg bw/day. The developmental LOAEL was established at 72 mg/kg/day based on total litter resorptions, increased post implantation loss, decreased fetal weights and low incidences of skeletal alterations (USEPA 2017).

Collectively, the data suggested that imidacloprid is not a selective developmental toxicant (i.e., developmental toxicity occurs only in the presence of maternal toxicity) and it is not a reproductive toxicant.

- **Neurotoxicity**

In an acute neurotoxicity screening battery, imidacloprid was administered by gavage to groups of 18 male and 18 female Sprague-Dawley rats at a single dose of 0, 42, 150 or 310 mg/kg bw. Four males and 10 females at the highest dose died and these deaths were attributed to treatment. In males at 150 mg/kg bw, the effects were limited to tremors while males at the highest dose also had uncoordinated gait, decreased activity and urine staining and were cool to touch. The treatment-related effects in females at the highest dose consisted of tremors, uncoordinated gait, decreased activity, increased reactivity and red nasal staining. Clinical signs of toxicity were generally observed on day 0 and resolved in surviving males and females within 1–5 days after treatment. The LOAEL for neurotoxicity was 42 mg/kg bw based on decreased motor and locomotor activities observed in females (USEPA 2017).

Groups of 18 male and 18 female Fischer 344 rats were given diets containing imidacloprid at a concentration of 0, 150, 1000 or 3000 ppm for 13 weeks, equal to 0, 9.3, 63.3 and 196 mg/kg bw/day for males and 0, 10, 69 and 213 mg/kg bw per day for females. In the 'functional observational battery', treatment-related effects were seen in males at the highest concentration but not in treated females. Motor activity was not affected in males or females at any concentration. The systemic NOAEL was 140 ppm, equal to 9.3 mg/kg bw/day and the systemic LOAEL was 63.3 mg/kg/day based on decreased body weight gains. The neurotoxicity NOAEL was established at the highest dose tested (196/213 mg/kg/day for males and females, respectively; USEPA 2017).

In a developmental neurotoxicity study with rats, imidacloprid was fed at 0, 100, 250, or 750 ppm from gestation throughout lactation which is equivalent to 0, 8, 20 and 55 mg/kg/day. The maternal systemic NOAEL was 55 mg/kg/day (highest dose tested). In the offspring, the NOAEL and LOAEL were 20 and 55 mg/kg/day, respectively, with decreased motor activity noted at the 55 mg/kg dose level (USEPA 2017).

- **Chronic/Carcinogenicity**

In a chronic/carcinogenicity study, groups of 50 male and 50 female Charles-River B6C3F1 mice received diets containing imidacloprid at a concentration of 0, 100, 330 or 1000 ppm for 24 months. The NOAEL was 330 ppm, equal to 65.5 mg/kg bw/day with decreased food and water intake and decreased weight gain at 1000 ppm. There was no evidence of carcinogenicity.

Groups of 50 male and 50 female Wistar rats received diets containing imidacloprid at a concentration of 0, 100, 300 or 900 ppm for 24 months. The mean intake of imidacloprid was equal to 5.7, 17, or 51.3 mg/kg bw per day for males and 7.6, 25, or 73 mg/kg bw per day for females. The systemic NOAEL was 51.3 mg/kg/day for males and 73 mg/kg/day for females. There was no evidence of carcinogenicity.

In a combined chronic/carcinogenicity with rats, imidacloprid was given at 0 or 1800 ppm corresponding to 102.6 mg/kg/day for males and 143.7 mg/kg/day for females. There was no evidence of carcinogenicity (USEPA 2017).

4.3 Development of the Risk Assessment

A risk assessment for Cielo ULV Adulticide Space Spray was conducted according to the WHO "Generic risk assessment model for indoor and outdoor space spraying of insecticides, Second edition, August 2018". Risk assessment involves three steps: Hazard assessment, Exposure assessment and Risk characterization.

1. **Hazard assessment** is the identification of the possible toxic effects of a substance, the dose/exposure levels at which those effects occur, and the dose/exposure levels below which no adverse effects are observed. Authoritative evaluations may be used as starting points for the risk assessment of insecticides for space spraying. Examples of authoritative evaluations include: Joint Meeting on Pesticide Residues (JMPR) – monographs and Evaluations; International Programme on Chemical Safety (IPCS): Concise International Chemical Assessment Documents, Environmental Health Criteria Documents; International Agency for Research and Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans: United States Environmental Protection Agency (USEPA) – Pesticide Evaluations; European Food Safety Authority (EFSA) – Pesticide Risk Assessments; European Chemicals Agency – Information on Chemicals. JMPR assessments, if available, will be used by PQT-VC for risk assessment unless a more recent authoritative evaluation exists.

2. **Exposure assessment** may concern insecticide operators, applicators, residents of treated dwellings and users of other treated buildings, bystanders, domestic animals, wildlife and the environment. Exposure is assessed in a "guideline scenario" which assumes that the insecticide is used according to the instructions given on the product label and in WHO guideline information. A "lax standard scenario" accounts for the reality that these instructions are not necessarily followed completely.

3. In **risk characterization** estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situations.
   The purpose of risk characterization is to examine the probability of adverse effects occurring during the use of the insecticide under defined exposure conditions. Risk characterization consists of comparing the estimate of total exposure (i.e., estimated systemic dose) with the Tolerable Systemic

Dose (TSD) established in hazard assessment. The TSD is same as the ADI or the chronic RfD established for the active ingredients (WHO, 2011).
When the ratios are less than 1, the health risk is acceptable. Ratios are greater than 1 may indicated possible health risks in which case steps may be taken to reduce the risk such as changing the recommended operational conditions or the amount of active ingredient in the technical product. A risk-benefit analysis in which the risks of potential toxicity are compared with potential health benefits (disease prevention), may be needed in some cases (WHO, 2011). The risk assessment is by active ingredient based on the proposed use of the product Cielo ULV as a space spray.

4.3.1 Hazard Assessment

a) Prallethrin

According to the risk assessment model, authoritative sources may be used as starting points for the risk assessment of insecticides for space spraying. The United States Environmental Protection Agency (USEPA) is identified as such a source and is used for the risk assessment of Prallethrin. A JMPR assessment was not available for Prallethrin.

For oral exposures (acute dietary and incidental oral) the endpoint and POD were selected from a chronic dog study in which neurotoxicity was observed within 4 weeks of dosing and was considered to have potentially resulted from a single dose, based on a weight of evidence. Neurotoxic effects seen in the dog study after 4 weeks are still appropriate for setting the acute reference dose (aRfD; EPA 2014).

- The aRfD (acute reference dose) was established at 0.025 mg/kg bw based on a NOAEL of 2.5 mg/kg bw/day based on neurotoxicity at the LOAEL of 5 mg/kg/day obtained from a chronic dog study (capsule) and an uncertainty factor of 100 to account for intraspecies and interspecies differences (WHO 2004; USEPA 2014, 2016).
- The incidental oral exposure (short-term) was established at 0.025 mg/kg bw based on a NOAEL of 2.5 mg/kg bw/day based on neurotoxicity at the LOAEL of 5 mg/kg/day obtained from a chronic dog study (capsule) and an uncertainty factor of 100 to account for intraspecies and interspecies differences (WHO 2004; USEPA 2016).

The dermal exposure (short term) was established at 0.3 mg/kg bw based on a NOAEL of 30 mg/kg/day obtained from a 21-day dermal toxicity study in rats, in which clinical signs of trembling, abnormal gait, sensitivity to stimuli, twitching and body weight changes were noted at 150 mg/kg/day (LOAEL; USEPA 2016).

The incidental inhalation exposure (short-term) was established from a NOAEL of 0.001 mg/L obtained from a 28-day inhalation study. The variability factor of 10X interspecies factor was reduced to 3X in accordance with the reference concentration (RfC) guidance. The intraspecies variability factor of 10X is combined with an interspecies extrapolation factor of 3X, based on a human equivalent dose for inhalation risk assessment. Therefore, the uncertainty factor for inhalation is 30X (USEPA 2014).

For chronic exposure (cRfD), the toxicology profile of pyrethroids including Prallethrin is rapid in onset and associated with acute, peak exposures. In most repeat-dose toxicology studies, neurotoxicity was observed within a few days of dosing. As such, the totality of the information suggests that only single day risk assessments need to be conducted for Prallethrin. A short-term exposure assessment is

protective of exposures with longer durations (EPA 2014). Further, the toxicological kinetic data for Prallethrin demonstrate that it is not appropriate to assess chronic dietary risk for Prallethrin due to a lack of increased toxicity with increased duration of exposure (EPA 2014).

b) Imidacloprid

According to the risk assessment model, authoritative sources may be used as starting points for the risk assessment of insecticides for space spraying. The United States Environmental Protection Agency (USEPA) is identified as such a source and is used for the risk assessment of imidacloprid (USEPA, 2017). A JMPR assessment is available for imidacloprid (JMPR 2001).

Imidacloprid is a chloronicotinyl (also known as neonicotinoid) insecticide. Its pesticidal mode of action involves disruption of the nervous system by acting as an inhibitor at nicotinic acetylcholine receptors at the post synaptic membrane.

The acute endpoint for all populations (including females of childbearing age) is based on a NOAEL of 8 mg/kg/day obtained from the 90-day dog study. An increased incidence of tremors/trembling was observed at the LOAEL of 22.1/24.8 mg/kg/day. These effects occurred within hours of exposure, which is consistent with neonicotinoids regarding time to peak effect.

The acute RfD (acute reference dose) was established at 0.08 mg/kg bw based on a NOAEL of 8 mg/kg bw/day based on neurotoxicity at the LOAEL of 22.1/24.8 mg/kg/day obtained from a 90-day dog study (capsule) and an uncertainty factor of 100 to account for intraspecies and interspecies differences (USEPA 2017). FAO/WHO JMPR (2001) established the aRfD at 0.4 mg/kg/day based on a NOAEL of 42 mg/kg bw obtained from an acute neurotoxicity study in rats and an uncertainty factor of 100 to account for interspecies and intraspecies differences. Since the EPA aRfD is lower (0.08 mg/kg/day vs. 0.4 mg/kg/day), it will be used in this risk assessment.

The incidental oral short term (1-30 days), intermediate term (1-6 months) and long term (> 6 months) endpoints are based on the NOAEL of 8 mg/kg/day obtained from the 90-day dog study, in which an increased incidence of tremors/trembling was observed at the LOAEL of 22.1/24.8 mg/kg/day. These effects occurred within hours of exposure, which is consistent with neonicotinoids regarding time to peak effect (USEPA 2017).

The incidental dermal [short (1-30 days), intermediate (1-6 months) and long (> 6 months)] term endpoints are based on the NOAEL of 8 mg/kg/day obtained from the 90-day dog study, in which an increased incidence of tremors/trembling was observed at the LOAEL of 22.1/24.8 mg/kg/day. These effects occurred within hours of exposure, which is consistent with neonicotinoids regarding time to peak effect (USEPA 2017). A dermal absorption factor (DAF) of 7.2% is used to extrapolate oral doses to dermal equivalent doses. Consequently, the dermal NOAEL is 114 mg/kg/day (USEPA 2017).

The incidental inhalation short term (1-30 days), intermediate term (1-6 months) and long term (> 6 months) endpoints are based on the NOAEL of 8 mg/kg/day obtained from the 90-day dog study, in which an increased incidence of tremors/trembling was observed at the LOAEL of 22.1/24.8 mg/kg/day. These effects occurred within hours of exposure, which is consistent with neonicotinoids regarding time to peak effect (USEPA 2017). Toxicity via the inhalation route is assumed to be equivalent to the oral route and inhalation absorption is assumed to equal oral absorption. Consequently, the inhalation NOAEL is 8 mg/kg/day (USEPA 2017).

The chronic dietary endpoint for all populations (including females of childbearing age) is based on the NOAEL of 8 mg/kg/day obtained from the 90-day dog study, in which an increased incidence of tremors/trembling was observed at the LOAEL of 22.1/24.8 mg/kg/day. These effects occurred within hours of exposure, which is consistent with neonicotinoids regarding time to peak effect (USEPA 2017). Therefore, the chronic RfD (Reference Dose) was established at 0.08 mg/kg bw based on a NOAEL of 8 mg/kg bw/day and an uncertainty factor of 100 to account for intraspecies and interspecies differences (USEPA 2017). The FAO/WHO JMPR (2001) set the ADI (Allowable Daily Intake) at 0.06 mg/kg bw/day based on the NOAEL of 5.7 mg/kg bw/day derived from a 2-year chronic rat study and an uncertainty factor of 100 to account for interspecies and intraspecies differences. The EPA cRfD is 0.08 mg/kg/day based on a subchronic oral dog NOAEL of 8 mg/kg/day. Although the EPA cRfD is slightly higher than the ADI set by FAO/WHO (0.08 mg/kg/day vs. 0.06 mg/kg/day), the EPA cRfD is used in this risk assessment since it is based on imidacloprid neurotoxic endpoint.

The second step in performing a risk assessment is to estimate exposure to the insecticide in the various groups of people potentially at risk. Exposure must take account of various parameters, including the route of exposure, the actual amounts of material involved, the duration of exposure in terms of both daily and annual exposure and seasonality, and whether this exposure is intermittent or continuous.

4.3.2 Exposure Assessment

The second step in performing a risk assessment is to estimate exposure to the insecticide in the various groups of people potentially at risk. Exposure must take account of various parameters, including the route of exposure, the actual amounts of material involved, the duration of exposure in terms of both daily and annual exposure and seasonality, and whether this exposure is intermittent or continuous
Exposure is assessed in a "**guideline scenario**", which assumes that the insecticide is used according to the instructions given on the product label and in WHO guideline information. A "**lax standard scenario**", however, takes into account the reality that these instructions are not necessarily followed completely. Conservative, high end-point estimates of the default distributions are used as defaults. No account is taken of intentional misuse. All relevant routes of exposure are covered. The exposure assessment based on the "lax standard scenario" is presented in Appendix A for information and to show the reduction of risk from the use of protective equipment.

a) Prallethrin

The exposure assessment for prallethrin is based on the following assumptions:

- ✓ For the 1L containers, the dermal exposure in mixing and loading is 0.01 mL/operation.
- ✓ For the 200L drum used in vehicle-mounted spraying, the dermal exposure in mixing and loading is 0.5 mL/operation.
- ✓ The number of operations per day = 1.
- ✓ Dermal absorption based on the default value of 10%.
- ✓ Translodgeability from hard surfaces of prallethrin to the skin is 11%.
- ✓ Tolerable Systemic Dose (TSD), chronic exposure = cRfD = 0.025 mg/kg bw/day.
- ✓ Tolerable Systemic Dose, acute exposure (TSD acute) = aRfD = 0.025 mg/kg bw/day.

The following groups of people may be exposed to insecticide through space spraying:

- Spray operators

- Residents and bystanders (adults, children, including breastfed children).

b) Imidacloprid

Assessment of exposure for imidacloprid is based on the following assumptions:

- ✓ The 1L containers, the dermal exposure in mixing and loading is 0.01 mL/operation.
- ✓ For the 200L drum used in vehicle-mounted spraying, the dermal exposure in mixing and loading is 0.5 mL/operation.
- ✓ The number of operations per day = 1.
- ✓ Translodgeability from hard surfaces of imidacloprid to the skin is 11%
- ✓ Tolerable Systemic Dose (TSD) = cRfD = 0.08 mg/kg bw/day.
- ✓ Acute Tolerable Dose (TSD acute) = aRfD = 0.08 mg/kg bw/day.
- ✓ Dermal absorption based on a default value of 8%.

The following groups of people may be exposed to insecticide through space spraying:

- Spray operators.
- Residents and bystanders (adults, children, including breastfed children).

Table 6. Prallethrin: Exposure Estimates and Ratios for Operators (Mixing/Loading/Applying) Using the Guideline Scenario.

Exposure Guideline Scenario: Prallethrin	**Estimated Systemic dose (µg/kg bw/day)**	**ratio**
Indoor spraying		
Total Operator (mixing loading + dermal + inhalation)		
TWA	9.32	0.37
Maximal Daily Systemic Dose	22.50	0.90
Residents of Sprayed Dwelling		
Adult Resident	0.01	0.004
Adult resident operator	23.61	0.94
Child	0.01	0.004
Toddler	0.03	0.001
Newborns exposed via mother's milk	< 0.001	< 0.001
Outdoor spraying		
Total Operator (mixing loading + dermal + inhalation)		
TWA	0.49	0.036
Maximal Daily Systemic Dose	1.15	0.06
Residents of Sprayed Dwellings (Adults; Adult resident operator; Child; Toddler)	Negligible, See Note	
Re-use of empty packages for storing drinking water		
Maximum daily systemic dose: adults	22.91	0.92
Maximum daily systemic dose: children	22.19	0.89
Maximum daily systemic dose: toddlers	50.73	2.01

Ratio = Systemic dose/TSD (0.025 mg/kg/day for both acute and chronic RfD)
Note: The model for outdoor spraying using hand held equipment is lower than that in indoor space spraying and that exposure in vehicle-mounted spraying is low. Since the risk ratios are <1 for indoor spraying, i.e., ratio < 1, then the risk ratio for outdoor spraying should also not be >1.

Table 7. Imidacloprid: Exposure Estimates and Ratios for Operators (Mixing/Loading/Applying) Using the Guideline Scenario.			
Exposure Guideline Scenario: Imidacloprid	Systemic dose µg/kg bw /day	Ratio: Chronic	Ratio: Acute
Indoor spraying			
Total Operator			
(Mixing and loading + dermal + inhalation)			
TWA	31.1	0.39	
Maximal Daily Systemic Dose	72.9	0.91	
Residents of Sprayed Dwellings			
Adult residents	0.037		
Adult Resident Operator	76.48		
Child	0.05		
Toddler	0.11		
Newborns exposed via mother's milk	< 0.001	< 0.001	< 0.001
Outdoor spraying			
Total Operator (Mixing loading + dermal +inhalation)			
TWA	No data	See Note	See Note
Maximal Daily Systemic Dose	No data	See Note	See Note
Residents of Sprayed Dwellings (Adult; Adult resident operator; Child; Toddler)	Negligible See Note	See Note	See Note
Re-use of empty packages for storing drinking water			
Maximum daily systemic dose: adults	91.6		1.14
Maximum daily systemic dose: children	88.8		1.10
Maximum daily systemic dose: toddlers	202.9		2.54
Ratio Chronic = Systemic Dose/cRfD (0.08 mg/kg/day); Ratio Acute = Systemic Dose/aRfD (0.08 mg/kg/day) Note: The model for outdoor spraying using hand held equipment is lower than that in indoor space spraying and that exposure in vehicle-mounted spraying is low. Since the risk ratios are <1 for indoor spraying, then the risk ratio for outdoor spraying should also not be > 1.			

4.3.3 Risk Characterization

The aim of risk characterization is to evaluate the level of risk of adverse effects occurring under defined exposure conditions. In its simplest form, risk characterization consists of the comparison of estimates of exposure with systemic doses defined in the hazard assessment in all relevant exposure situations. The risk assessment is by active ingredient based on the proposed use of the product Cielo ULV as a space spray.

a) Prallethrin

Under the "guideline scenario" of the generic risk assessment model, based on the time-weighted average (TWA) daily systemic dose and maximum daily systemic dose for operator from the indoor space spraying of Cielo ULV, the risk ratios are less than 1 and therefore there is no potential health risk. Re-using of empty packages for storing water should be avoided for toddlers since the ratio is >1 for this population (WHO, 2018).

The “Lax standard scenario” is presented in Appendix A for informational purposes only to point out the importance of protective equipment in reducing exposure and risk.

b) Imidacloprid

Under the “guideline scenario” of the generic risk assessment model, based on the TWA daily systemic dose and maximum daily systemic dose for operator from the indoor space spraying of Cielo ULV, the risk ratios are <1 and therefore there is no potential health risk (WHO 2018).
Re-using of empty packages for storing water should be avoided since all ratios are >1 for all populations (adults, children and toddler, WHO 2018).

The “Lax standard scenario” is presented in Appendix A for informational purposes only to point out the importance of protective equipment in reducing exposure and risk.

4.4 Environmental Safety Assessment

According to the WHO generic risk assessment model for the indoor and outdoor space spraying of insecticides, ecological risks need to be considered. Information on the ecotoxicity of Cielo ULV has been provided in the dossier.

4.4.1 Product Specific Toxicity Data

Cielo ULV is proposed for use and non-target species could be exposed. The following ecotoxicological studies were submitted to assess the risk to non-target species form exposure to Cielo ULV Adulticide Space Spray and are summarized in Table 8.

Table 8: Ecotoxicity Data for Cielo ULV Adulticide Space Spray

Study	Result	GHS Classification	Study Reference
Acute Toxicity to Rainbow trout	LC50 = 17.25 ug a.i./L (96 hours) - NOEC = 6.25 ug a.i./L	GHS Classification: Acute I	Stillmeadow Lab. #19959-16, September 2016
Acute Toxicity to Daphnia magna	LC50 = 3.9 ug a.i./L (48 hours) - NOEC = 2.5 ug a.i./L	Acute I	Stillmeadow Lab. #19951-16, September 2016
Acute Oral Toxicity – Bobwhite Quail	LD50 > 2000 mg/kg	Not Applicable	Stillmeadow Lab.#19936-16, September 2016.
Bee Contact Toxicity	LD50 at 48 hrs = 0.1 ug/bee LD50 at 72 hrs = 0.01 ug/bee	Not Applicable	Stillmeadow Lab.#20045-16 October 2016

4.4.2 Ecotoxicity Data on the Active Ingredients

a) Prallethrin

- Acute toxicity to Aquatic Organisms: Highly toxic to both vertebrate and invertebrate aquatic organisms (GHS Category Acute I) as reflected from results in rainbow trout (96-h LC50 = 12 ug

a.i./L), bluegill (96-h LC50 = 22 ug a.i./L), sheepshead minnow (96-h LC50 = 26 ug a.i./L), daphnia magna (48-h LC50 = 6.2 ug a.i./L) and mysid shrimp (96-h LC50 = 0.007 ug a.i./L).

- Fish Early Life Stage: In an early life stage with rainbow trout, the 90-day NOEC was > 3.0 ug a.i./L since no effects were noted at this highest tested concentration.
- Honey Bees: Prallethrin is very toxic to honey bees (48-h LD50 = 0.028 ug/bee).
- Avian: Prallethrin is mildly toxic to Bobwhite quail as reflected by an oral LD50 of 1171 mg/kg and non-toxic to Mallard duck (LD50 > 2000 mg/kg).
- The WHO/PCS hazard classification of Prallethrin is "Moderately Hazardous Class II".

b) Imidacloprid

- Acutely, imidacloprid is not toxic to both vertebrate and invertebrate aquatic organisms as reflected in values noted in rainbow trout (96h LC50 = 211 mg a.i./L), golden orfe (96h LC50 = 237 mg a.i./L) and daphnia magna (48h LC50 = 85 mg a.i./L).
- The acute oral toxicity LD50 in Bobwhite quail was 152 mg/kg bw and the LD50 in Mallard duck was 283 mg/kg/kg bw. In 20-week reproduction studies, the NOECs in the diet were 126 ppm and 128 ppm for Bobwhite quail and Mallard duck, respectively.
- The acute oral toxicity LD50s to honey bee were greater than 21 ng/bee at 48 h (purity = 98.6%), 40.9 ng/bee at 48h (purity = 99.4%) and 3.7 ng/bee at 48 h (purity = 99.8%)
- The acute contact toxicity LD50 to honey bee was 81 ng/bee at 48h (99.8% purity).

4.4.3 Environmental and Ecotoxicity Risk Assessment

Environmental exposure and ecological effects of prallethrin and imidacloprid have been assessed at higher application rates than the proposed rates of Cielo ULV, hence the existing data can be used for Cielo ULV.

a) Prallethrin

The USEPA 2014 assessment of prallethrin used as a mosquito adulticide and insecticide included an evaluation of the risks to the environment from the use of prallethrin as a component of an insecticide used for cold fogging at a target rate of 0.00072 lb a.i./A (single application rate) which is equivalent to .807 g/ha. This rate was used to inform potential risks based on the outdoor space spraying rate for Cielo ULV (maximum 1.25 g/ha) for public health purposes. The US EPA documents were used to assess the environmental risks associated with the use of Cielo ULV.

The half-life photodegradation is 0.57 day and is the major route of dissipation from aqueous environments. The microbial degradation half-time is 3 days in aerobic soil.

- The predicted concentrations of prallethrin remained below the acute and chronic level of concern (LOC) for terrestrial mammals and birds and terrestrial plants, based on a model with a water depth of 10 cm.
- The predicted concentrations of prallethrin exceeded the acute LOC for fresh water and estuary/marine invertebrates, based on a model with a water depth of 10 cm (agricultural model).
- The predicted concentrations of prallethrin exceeded the acute LOC for freshwater fish, based on a model with a water depth of 10 cm (agricultural model). The predicted concentrations of Prallethrin are not likely to exceed the acute LOC on a model with a water depth of 50 cm (non-agriculture model).

- Prallethrin is very toxic to honey bees.
- The WHO/PCS hazard classification of prallethrin is “Moderately Hazardous Class II”.
- For non-agricultural uses and with a water depth of 50 cm, the proposed applications of prallethrin are not likely to exceed the LOC for environment, aquatic vertebrate and invertebrate, mammals, and plants.

b) Imidacloprid

The European Food Safety Authority (EFSA) assessed the environmental risks of imidacloprid for agricultural uses at an application rate of 100 g/ha. The labelled application rate of imidacloprid in space spraying using Cielo ULV is 5 g/ha (1/20 of values assessed by EFSA).

- Imidacloprid is very persistent in the soil, half-life is approximately 280-1330 days. For non-agricultural uses and with a water depth of 50 cm, the proposed applications of imidacloprid are not expected to exceed the LOC for environment, aquatic vertebrate and invertebrate, mammals, and plants.
- EFSA indicated that the toxicity-exposure-ration (TER) for birds was 5.5-9.8 for acute and short-term exposure.
- EFSA indicated that the toxicity-exposure-ration (TER) for birds was 3.0-3.1 for long term exposure.
- For earthworm, the sublethal time scale TER was 1.2 – 2.1
- Imidacloprid has little effects on the growth and survival of the 12 plant species tested.
- Imidacloprid has little effects on the growth and survival of aquatic vertebrate (fish) and invertebrate (daphnia) species.
- Arthropods are very sensitive to Imidacloprid.
- Imidacloprid is very toxic to honey bees.

4.5 Safety conclusions

Space spraying with Cielo ULV following the labelled instructions (Guideline scenario) is not expected to pose a health risk as the risk ratios are <1 for both prallethrin and imidacloprid. Hence, there are no anticipated risks of concern to operators, residents, residents working as operators, children, newborns, and bystanders.

5 Assessment of Efficacy

The primary intention for the use of a pesticide is for the control of a pest or vector, whether resistant or susceptible, rather than for resistance management. Tools which provide effective management of pests or vectors can be used as part of a resistance management plan. For public health pesticides, this is a component of Integrated Vector Management (IVM) which relies on a suite of diverse interventions and implementation of best practices to manage the vector and chemical/behavioral resistance.

Cielo ULV combines two active ingredients with different modes of actions (IRAC Group 4A and 3A). The premise of a combination of two different modes of action is that the likelihood of simultaneous occurrence of resistance to two unrelated modes of action is less. The product does not include any claims of synergistic or additive effects associated with the combination of the active ingredients.

A series of studies were provided in the submitted dossier including laboratory, indoor (houses) and outdoor (field) scale. These studies were conducted in several locations. All studies were evaluated individually and a summary of the results are provided in the next section.

The studies were conducted in accordance with prequalification requirements.

<table>
<tr><th colspan="2">Efficacy studies for Cielo ULV Adulticide Space Spray- Laboratory, Indoor (houses) & Outdoor (field) studies.</th></tr>
<tr><td colspan="2">Laboratory studies were conducted to investigate the following:
1. dose–response line(s) and determination of the lethal dosage (LD) of the insecticide for 50% and 90% mortality (LD50 and LD90);
2. the intrinsic activity of the insecticide against adult females of susceptible mosquito strains;
3. the lethal concentration (LC) of the insecticide (technical material and formulations) for 50% contact with insecticide spray;
4. the diagnostic concentration for monitoring resistance to the insecticide in the field;
5. cross-resistance with commonly used insecticides.</td></tr>
<tr><td>CF1 & CF2</td><td>Statement on Clarke formulation codes for Ultra-Low Volume Cold Aerosol Misting CMP123-003 and CMP123-004 (Imidacloprid 3.00% + Prallethrin 0.75%) and CF2: Confidential Certificate of Composition for Cielo ULV (cmp 123-004). 2018</td></tr>
<tr><td></td><td>Some of the internal studies were conducted on a version of CIELO ULV (CMP123-003) which was slightly different to the current commercial product (CMP123-004).
The study presented information to demonstrate that the two Cielo ULV formulations, CMP123-003 and CMP123-004, are similar regarding their potential bio-efficacy and present minor differences in the purity of the solvents used.
The minor differences in the solvent purity rates of both formulations are unlikely to influence bio-efficacy against target organisms.</td></tr>
<tr><td>N/A</td><td>Rossignol et al. (2018). WHOPES phase I efficacy testing of active ingredients (prallethrin, imidacloprid) of product CMP123-004 UL from Clarke, USA for space spray applications, IRD, France</td></tr>
<tr><td></td><td>This study presented information on intrinsic toxicity, the lethal and KD effects through tarsal contact of prallethrin, imidacloprid and combination of these active ingredients. A susceptible strain and two resistant strains of Aedes aegypti were tested:
- Susceptible Bora strain
- Resistant strain LHP originated from Vietnam. This strain was made homozygous for the kdr mutation Leucine/Tryptophan2 (L982W) in domain II of sodium channel
- Resistant South American strain, Guiana, originating from French Guiana - multi resistant with several kdr mutations (1011, 1016, 1534) and metabolic mechanisms (P450 and carboxylesterases)
Results:
The study was conducted in accordance with the requirements for prequalification.
Intrinsic Toxicity – Topical application
• Prallethrin (in acetone)
o LD50 24h values of 0.71(0.65-0.76), 1.96 (1.74-1.23), and 4.14 (3.65-4.68) ng/mg mosquito for Bora, LHP, and Guiana strains respectively
o Prallethrin more toxic for the susceptible strain Bora than for LHP (RR50 24h of 2.77). The Guiana strain was the more resistant to prallethrin. (RR50 24h of 5.83)</td></tr>
</table>

	○ No significant change in LD50 values between 24 and 72 hrs for any of the strains • **Imidacloprid (in acetone)** ○ LD50 24h values of 3.64(3.13-4.22), 0.83 (0.71-0.96), and 14.27 (9.69-21.02) ng/mg mosquito for Bora, LHP, and Guiana strains respectively. ○ The LD50 and LD95 of imidacloprid for all three strains tended to increase between 24 h and 72 h suggesting that toxicity of imidacloprid decreased during the holding period. ○ The results demonstrated differences of susceptibility between the three strains. Bora being the reference susceptible strain, the LHP strain was about 4-5 times more susceptible than Bora. The pyrethroid resistant Guiana field strain was more resistant to imidacloprid with resistance ratios ranging 2.4 to 3.9 times • **Mixture 1:4 Prallethrin: Imidacloprid (in acetone)** ○ LD50 24h values of 0.19 (0.16-0.22), 0.25 (10.10-0.63), and 1.43 (1.18-1.78) ng/mg mosquito for Bora, LHP, and Guiana strains respectively. ○ The LD50 and LD95 for prallethrin within the mixture shows that they were significantly lowered for the three strains even if significant resistance levels were maintained for LHP and Guiana strains compared to Bora. ○ For the susceptible strain Bora, the LD50 of prallethrin when combined with imidacloprid was 3-4 times lower than the LD50 of prallethrin alone and the LD50 of imidacloprid in the combination was 5-9 times lower than imidacloprid alone. ○ For the resistant strain LHP, the LD50 for the combination was 6 to 8 lower than prallethrin alone and similar to imidacloprid alone, owing to the greater susceptibility of LHP strain to imidacloprid. For the resistant Guiana strain the LD50 for the combination was 2 to 3 times lower than both insecticides individually. Tarsal Toxicity -Filter paper tests • Good efficacy of prallethrin on impregnated papers with diagnostic concentration estimated between 0.1 and 1%. • As has been observed with other neonicotinoids it was not possible to establish a diagnostic concentration for imidacloprid using the impregnated paper method. Tarsal Toxicity – bottle tests • A mortality rate of 100% was systematically obtained with the susceptible Bora strain (3 replicates) exposed to 20 µg of prallethrin. The same dose gave only 72-75% mortality for the LHP and 46-50% for Guiana strain, confirming that exposure to 20 µg of prallethrin for one hour was suitable for resistance detection according to WHO criteria • Four doses of imidacloprid (1 000, 2 000, 4 000 and 10 000 µg) were selected and tested using Bora strain to determine the LD100 for susceptible mosquitoes. However even with the highest dose of 10 000 µg/bottle it was not possible to obtain systematically 100% mortality rates and they were not significantly increased compared to exposure at 4000 µg/bottle.

	• These results as well as the low mortality obtained using impregnated papers at high concentration (10%) suggested that tarsal contact is probably not appropriate to evaluate mosquito susceptibility to imidacloprid. Irritability • Prallethrin had an irritant effect at a level similar to permethrin • Imidacloprid had no significant irritancy effect to mosquitoes.
BE8	Adanan Che Rus et al. (2018), Laboratory Study the effectiveness of lethal concentrations of the active ingredient used in Aerosol/space spray formulation against Aedes sp, using Wind Tunnel Test Method, VCRU, Universiti Sains Malaysia, WHOPES 019/2016
	This study presented information on the lethal concentrations of the active ingredients (Imidacloprid and Prallethrin) used in space spray formulation and final formulation (CMP 123-004) as determined by contact with insecticide spray using two susceptible strains of *Aedes Aegypti (*Bora-Bora (B-B) and VCRU strain (Penang)) through the wind tunnel test. **Results:** • Mosquito bioassays using prallethrin in solvent showed that LC_{50} 24h values for *Aedes aegypti* ranged from 628 mg/L (B-B strain) to 701 mg/L (VCRU strain) • Mosquito bioassays using imidacloprid in solvent showed that LC_{50} 24h values for *Aedes aegypti* ranged from 6919 mg/L (B-B strain) to 7907 mg/L (VCRU strain) • Mosquito bioassays using CMP123-004 in solvent showed that LC_{50} 24h values for *Aedes aegypti* was 329 mg/L (based on Prallethrin content) for both B-B and VCRU strains. • Mosquito bioassays using CMP123-004 in solvent showed that LC_{50} 24h values for *Aedes aegypti* ranged from 1286mg/L (B-B strain) to 1947 mg/L (VCRU strain), based on imidacloprid content.
Indoor:	
A total of 3 field trials (3 indoor) have been carried out in Malaysia, Brazil, and Mexico. These studies evaluated the efficacy of CIELO ULV (CMP123-004) against *Aedes aegypti* following application using Ultra low volume cold fogging equipment.	
BE4	Rus et al. (2017). Ground Ultra-low volume application (outdoor and indoor) field trials using CMP123-004 as a mosquito adulticide for the control of *Aedes aegypti* and *Aedes albopictus*, Malaysia, August 2017.
	The study presented information on the efficacy of CMP 123-004 and the determination of the effective application rates required to achieve an average of ≥90% mortality in indoor settings. Susceptible strains *Aedes aegypti* (VCRU strain) and *Aedes albopictus* (VCRU Strain) were used as the test reference (both strains originated from Penang Island, Malaysia). Applications were made with undiluted and diluted (10% in PEG 400) product. ***Results:*** The study was conducted in accordance with the requirements for prequalification. ≥90% mortality of both strains was observed at application rates of 0.30 g imidacloprid per 1000m^2 (0.075 g/1000m2 of Prallethrin) at 24h and 48h in indoor applications with a portable ULV Nebulizer.
BE 5	Maria de Lourdes Graca Macoris et al. (2017). Field testing and evaluation of CMP12-004 for outdoor and indoor ULV space spraying for control of *Aedes aegypti* in Marilia, SP Brazil.

	The study presented information on the efficacy of CMP 123-004 and the determination of the effective application rates required to achieve an average of ≥90% mortality in indoor settings. A susceptible strain of *Aedes aegypti* (local field collected eggs) was tested. Applications were made with diluted (10% in PEG 400) product in order to properly calibrate the spray to the room volume. ***Results:*** The study was conducted in accordance with the requirements for prequalification. Mortality just below 90% was observed at application rates of 0.50 g imidacloprid per 1000m^2 (0.125 g/1000m2 of Prallethrin) at 24h and 48h in indoor applications with a portable ULV Nebulizer. ≥97% mortality was observed at application rates of 0.70 g imidacloprid per 1000m^2 (0.175 g/1000m2 of Prallethrin) at 24h and 48h in indoor applications with a portable ULV Nebulizer. A calculated application rate of 0.5 g imidacloprid per 1000m^2 (0.125 g/1000m2 of Prallethrin) is expected to result in ≥90% mortality of the *Aedes aegypti* population at 48 hours in indoor applications with a portable ULV Nebulizer.
BE6	Said et al. (2017). Evaluation of Cielo ULV as a mosquito adulticide for the control *Aedes aegypti* in space outdoor and indoor, Mexico.
	The study presented information on the efficacy of CMP 123-004 and the determination of the effective application rates required to achieve an average of ≥90% mortality in indoor settings. A susceptible strain of *Aedes aegypti* (Cienega de Flores, Nuevo Leon CF) was tested. Applications were made with undiluted product. ***Results:*** The study was conducted in accordance with the requirements for prequalification. ≥90% mortality was observed in most rooms in the houses at application rates of 0.33 g imidacloprid per 1000m^2 (0.0825 g/1000m2 of Prallethrin) at 24h and 48h in indoor applications with a portable ULV Nebulizer. A calculated application rate of 0.355 g imidacloprid per 1000m^2 (0.088 g/1000m2 of Prallethrin) is expected to result in ≥90% mortality of the *Aedes aegypti* population at 48 hours in indoor applications with a portable ULV Nebulizer.
Outdoor	
Outdoor applications of CIELO ULV were conducted in Mexico, USA, Malaysia, and Brazil. Both Clarke sponsored and WHO supervised studies were submitted. These studies presented information on the efficacy of CIELO ULV as an adulticide applied as a space spray for control of native strains of *Aedes aegypti* and *Aedes albopictus.*	
BE2	Mexico- Open field efficacy trial of CMP123-003 Adulticide against *Aedes aegyptii* with Truck Mounted ULV Cold Aerosol Sprayer- field study
	Results: The results demonstrate the performance of CMP123-003 when applied by vehicle mounted cold fogging undiluted at a rate of 125ml/min and a speed of 15 KPH with a ULV spray characterized at 24.92 µm VMD for adult *Aedes aegypti* mosquito control. The rate of 125 mls/min and a speed of 15 km per hour is equivalent to a rate of 2g/ha Imidacloprid + 0.5g/ha Prallethrin. The study was conducted in accordance with the requirements for prequalification. **1.** 1h knockdown mortality was 84% for the susceptible strain and 85.4% for the field strain.

	2. 24h and 48h mortality was ≥ 98% for caged susceptible and field *Aedes aegypti* was observed at 33, 66 and 100m
BE3	Natalia Ziemianska et al. (2016), Clarke Mosquito Control, 2016. Ground ULV Bioassay Screening against Caged Adult Female Mosquitoes Using CMP123-004 at 0.67 oz/acre and 0.99 oz/acre. Lake Wales, Florida, USA.
	The study presented information on the efficacy of CMP 123-004 in an open field caged trial against adult *Aedes aegypti*, *Culex quinquefasciatus*, and *Anopheles quadrimaculatus* mosquitoes. CMP 123-004 was applied, using the vehicle mounted Clarke Cougar™ ultralow-volume (ULV) cold aerosol spray equipment, calibrated to deliver a rate of 0.67 fl.oz/acre (120 ml/min, 2g/ha imidacloprid, 0.5 g/ha prallethrin) and a rate of 0.99 fl.oz/acre (177.4 ml/min, 3 g/ha imidacloprid, 0.75 g/ha prallethrin) of undiluted formulation. The 0.99 fl oz/acre application rate is the lowest labeled application rate. ***Results:*** The study was conducted in accordance with the requirements for prequalification. Droplet VMDs ranged from 15.0 to 17.1 microns. Applied at a rate of 0.99 fl.oz/acre (177.4 ml/min, 3 g/ha imidacloprid, 0.75 g/ha prallethrin) the following 24h mortality was observed at various distances from spraying: 1. *Aedes aegypti* – 100% (100ft), 100% (200ft), 81% (300ft) 2. *Culex quinquefasciatus* – 100% (100ft), 100% (200ft), 81% (300ft) 3. *Anopheles quadrimaculatus* – 100% (100ft), 98% (200ft), 96% (300ft) Applied at a rate of 0.67 fl.oz/acre (120 ml/min, 2g/ha imidacloprid, 0.5 g/ha prallethrin) the following 24h mortality was observed at various distances from spraying: 4. *Aedes aegypti* – 98% (100ft), 98% (200ft), 88% (300ft) 5. *Culex quinquefasciatus* – 100% (100ft), 100% (200ft), 95% (300ft) 6. *Anopheles quadrimaculatus* – Not reported
BE4	Rus et al. (2017). Ground Ultra-low volume application (outdoor and indoor) field trials using CMP123-004 as a mosquito adulticide for the control of *Aedes aegypti* and *Aedes albopictus*, Malaysia, August 2017.
	The study presented information on the efficacy of CMP 123-004 and the determination of the effective application rates required to achieve an average of ≥90% mortality in outdoor settings. A susceptible strain *Aedes aegypti* (VCRU strain) and *Aedes albopictus* (VCRU Strain) were used as the test reference (both strains originated from Penang Island, Malaysia). The target VMDs was 20 microns for the lower rates and 25 microns for the highest rate. ***Results:*** The study was conducted in accordance with the requirements for prequalification. *Aedes aegypti*:

Check Points	Knockdown (Minutes)			Adult Mortality	Adult Mortality
	15	30	60	(24h)	(48h)
3 g/ha, Treatments 13, 14, 15					
25 m	100.00±0.00	100.00±0.00	100.00±0.0	95.11±1.46	95.11±1.46
50 m	100.00±0.00	100.00±0.00	100.00±0.0	91.11±1.46	92.00±1.49
75 m	100.00±0.00	100.00±0.00	100.00±0.0	84.88±1.39	84.88±1.39
100 m	100.00±0.00	100.00±0.00	100.00±0.0	79.55±5.86	80.00±0.67
Mean±SE	100.00±0.00	100.00±0.00	100.00±0.0	87.64±3.43	88.00±3.42

4 g/ha, Treatments 2,4,6					
25 m	100.00±0.00	100.00±0.00	100.00±0.00	96.00±3.99	93.60±6.39
50 m	80.00±19.96	80.00±19.96	97.60±2.40	81.60±14.70	80.80±14.69
75 m	100.00±0.00	100.00±0.00	100.00±0.0	100.00±0.00	100.00±0.00
100 m	89.60±6.63	100.00±0.00	100.00±0.0	77.60±15.7	72.00±14.73
Mean±SE	92.40±4.81	95.00±5.00	99.40±0.60	88.80±5.44	86.60±6.29

Aedes albopictus:

Check Points	Knockdown (Minutes)			Adult Mortality	Adult Mortality
	15	30	60	(24h)	(48h)
3g/ha, Treatments 13, 14, 15					
25 m	100.00±0.00	100.00±0.00	100.00±0.00	95.56±1.41	95.56±1.41
50 m	100.00±0.00	100.00±0.00	100.00±0.00	91.55±1.64	91.55±1.64
75 m	100.00±0.00	100.00±0.00	100.00±0.00	84.89±1.11	84.89±1.11
100 m	100.00±0.00	100.00±0.00	100.00±0.00	77.78±1.51	79.55±5.86
Mean±SE	100.00±0.00	100.00±0.00	100.00±0.00	87.44±3.95	87.89±3.54
4 g/ha, Treatments 2, 4, 6					
25 m	100.00±0.00	100.00±0.00	100.00±0.00	84.00±14.99	84.00±14.99
50 m	80.00±19.96	80.00±19.96	80.00±19.96	80.00±19.96	80.00±19.96
75 m	100.00±0.00	100.00±0.00	100.00±0.00	100.00±0.00	100.00±0.00
100 m	84.80±9.31	99.20±0.80	99.20±0.80	59.20±19.58	80.00±13.48
Mean±SE	91.00±5.26	94.80±4.94	94.80±4.94	80.80±8.40	86.00±4.76

A probit analysis was conducted which calculated expected 90% mortality after 48h:

1. *Aedes aegypti* - 4.24 g/ha imidacloprid (1.06 g/ha prallethrin)
2. *Aedes albopictus* - 3.65 g/ha imidacloprid (0.91 g/ha prallethrin)

BE 5

Maria de Lourdes Graca Macoris et al. (2017). Field testing and evaluation of CMP12-004 for outdoor and indoor ULV space spraying for control of *Aedes aegypti* in Marilia, SP Brazil.

The study presented information on the efficacy of CMP 123-004 and the determination of the effective application rate required to achieve an average of ≥90% mortality in outdoor settings. A susceptible strain of *Aedes aegypti* (local field collected eggs) was tested.

Results:

The study was conducted in accordance with the requirements for prequalification.

Droplet VMDs ranged from 16 to 22 microns.

Distance (m)	Dose*	2g/ha			3g/ha			4g/ha			5g/ha		
	Parameter	1h	24h	48h	1h	24h	48h	1h	24h	48h	1h	24h	48h
25	Average %	92	92	88	94	98	97	100	99	98	100	100	99
50	Average %	90	85	80	94	93	88	99	97	96	100	100	100

	75	Average %	96	88	85	99	92	89	97	93	90	100	99	98
	100	Average %	83	62	59	87	79	67	91	81	76	99	96	95

A probit analysis was conducted which calculated expected 90% mortality rates after 48h indicated an application rate of 3.0 g of Imidacloprid/ 0.75 g of Prallethrin per hectare.

BE6 Said et al. (2017). Evaluation of Cielo ULV as a mosquito adulticide for the control *Aedes aegypti* in space outdoor and indoor, Mexico.

The study presented information on the efficacy of CMP 123-004 and the determination of the effective application rate required to achieve an average of ≥90% mortality in outdoor settings. A susceptible strain of *Aedes aegypti* (Cienega de Flores, Nuevo Leon CF) was tested.

Results:

The study was conducted in accordance with the requirements for prequalification.
Droplet VMDs ranged from 16.0 to 22 microns.

Dose	Distance (m)	Knockdown mortality (%)	Mortality at 24h (%)	Mortality at 48h (%)
1.39 10th April	25	71	72	68
	50	56	52	53
	75	26	24	25
	100	27	27	30
3 5th April	25	95	97	96
	50	89	94	91
	75	88	92	92
	100	74	83	79
4 6th April	25	99	100	100
	50	99	100	100
	75	95	98	99
	100	95	98	99

A probit analysis was conducted which calculated expected 90% mortality rates after 48h indicated an application rate of 3.19 g of Imidacloprid/ 0.79 g of Prallethrin per hectare.

5.1 Efficacy conclusions

Taking into account the entirety of the submitted efficacy studies in lab, and indoor/outdoor settings, there is sufficient information to demonstrate that Cielo ULV, when applied according to the labelled directions, meets the efficacy requirements for prequalification. It is appropriate for use in a variety of settings against *Aedes aegypti* and *Aedes albopictus* mosquitoes.

The efficacy component of the dossier is complete. The assessment of the submitted information supports the prequalification of the product.

6 Labelling

The proposed Declaration of Labelling has been reviewed by PQT-VC and found to be consistent with the supporting information.

7 Pre-Qualification Listing Decision

The review of the dossier submitted for the product Cielo ULV Adulticide Space Spray has been completed by PQT-VC. The results of the assessments show the product is safe and effective when used according to the directions for use on the label for the control of *Aedes aegypti* and *Aedes albopictus* mosquitoes. This product is allowed inclusion in the list of prequalified vector control products.

8 References

Quality

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3. CIELO ULV Long term Stability- interim 9 month report- Jan 2018 (PC3)

Safety

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Efficacy

14. Medina-barreiro et al. April 2016. Open field efficacy trial of CMP123-003 adulticide against caged Aedes aegypti with truck mounted ultra-low volume cold aerosol sprayer.BE 2
15. Natalia Ziemianska, Clarke Mosquito Control, 2016. Ground ULV Bioassay Screening against Caged Adult Female Mosquitoes Using CMP123-004 at 0.67 oz/acre and 0.99 oz/acre. Lake Wales, Florida, USA. August 2016. BE3
16. Rus et al. Ground Ultra-low volume application (outdoor and indoor) field trials using CMP123-004 as a mosquito adulticide for the control of Aedes aegypti and Aedes albopictus, Malaysia, August 2017. BE4
17. Maria de Lourdes Graca Macoris et al. Field testing and evaluation of CMP12-004 for outdoor and indoor ULV space spraying for control of Aedes aegypti in Marilia, SP Brazil. August 2017. BE 5

18. Said et al. Evaluation of Cielo ULV as a mosquito adulticide for the control of Aedes aegypti in space spray outdoor and indoor, Mexico. July 2017. BE 6
19. Rossignol et al. (2018). WHOPES phase I efficacy testing of active ingredients (prallethrin, imidacloprid) of product CMP123-004 UL from Clarke, USA for space spray applications, IRD, France, BE7
20. Adanan Che Rus et al. (2018), Laboratory Study the effectiveness of lethal concentrations of the active ingredient used in Aerosol/space spray formulation against Aedes sp, using Wind Tunnel Test Method, VCRU, Universiti Sains Malaysia, WHOPES 019/2016, BE8
21. Statement on Clarke formulation codes for Ultra-Low Volume Cold Aerosol Misting CMP-123-003 and CMP 123-004 (Imidacloprid 3.00% + Prallethrin 0.75%) and CF2: Confidential Certificate of Composition for Cielo ULV (cmp 123-004). 2018. CF1 & CF2

Appendix A: Confidential Business Information

Internal Use Only

Appendix B: Exposure Assessment Using the "Lax Standard Scenario"

Table 11. Exposure Assessment Using the "Lax Standard Scenario"- Prallethrin		
Exposure Scenario: Prallethrin	**Systemic dose µg/kg bw**	**ratio**
OPERATOR: Indoor Spraying		
Time-weighted average daily systemic dose		
Mixing and loading		
Application/maintenance, inhalation		
Application/maintenance, dermal		
Total	95.9	3.84
Maximal daily systemic dose		
Mixing and loading	0.23	
Application/maintenance, inhalation		
Application/maintenance, dermal		
Total	224.7	8.99
Ratio = Systemic dose/TSD (0.025 mg/kg/day for both acute and chronic RfD).		

Table 11. Exposure Assessment Using the "Lax Standard Scenario"- Imidacloprid			
Exposure Scenario: Imidacloprid	Systemic dose µg/kg bw	RATIO Chronic	RATIO Acute
OPERATOR: Indoor Spraying			
Time-weighted average daily systemic dose			
Mixing and loading	0.4		
Application/maintenance, inhalation	19.7		
Application/maintenance, dermal	291.3		
Total	311	3.88	
Maximal daily systemic dose			
Mixing and loading	0.92		
Application/maintenance, inhalation	46.0		
Application/maintenance, dermal	681.8		
Total	729		9.11
Note: Ratio Chronic = Systemic Dose/cRfD (0.08 mg/kg/day); Ratio Acute = Systemic Dose/aRfD (0.08 mg/kg/day).			