



Prequalification Team Vector Control Decision Document

Fludora Fusion

Prequalification Team–Vector Control Group (PQT-VC)

Access to Medicines, Vaccines and Pharmaceuticals (MVP)

World Health Organization

Prequalification Team Vector Control Decision Document

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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, respectively.

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 Fludora Fusion which provide the basis for the prequalification listing decision.

2 Product Identification

Fludora Fusion is a wettable powder formulation packaged in water soluble bags (WP-SB), containing a combination of Clothianidin (CAS No. 210880-92-5; 500g/kg; 50%) and Deltamethrin (CAS No. 52918-63-5; 6.25 g/kg; 6.25%). Clothianidin, (*E*)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine, is a neonicotinoid insecticide already commercialized in crop protection and professional pest control in a variety of formulations. Deltamethrin, (*S*)- α -cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylate, is a broad-spectrum pyrethroid insecticide also commercialized in a variety of formulations for a variety of use patterns.

The product is intended to be used for malaria vector control as an Indoor Residual Spray (IRS). This WP product is contained in sealed water soluble bags and will be applied exclusively on the inner walls of dwellings at a rate of one 100 g sachet per 10 L sprayer or one 80 g sachet per 8 L sprayer. The target dose rate of the product is 200 mg/m²clothianidin and 25 mg/m² deltamethrin. Approximately 20 structures can be sprayed with 1 kg (10 sachets) of Fludora Fusion - assuming two structures are sprayed per 10 L sprayer).

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

- Clothianidin, declared minimum content 975 g/kg
- Deltamethrin, declared minimum content 985 g/kg

The applicant, Bayer S.A.S., 16 rue Jean-Marie Leclair CP-106-69266, Lyon Cedex 09, France, submitted a dossier containing supporting data to PQT-VC on May 17th, 2018 and requested a PQ listing for the product. The product is registered in CILSS Countries of West Africa, Benin, Ivory Coast, Ghana, Tanzania, Mozambique, Zambia and Zimbabwe. Registration is pending in a range of other countries.

3 Assessment of Quality

3.1 Chemical and Physical Properties

Data on the chemical and physical properties of the active ingredients and the product Fludora Fusion were provided and are summarized in Tables 1 and 2. These data were obtained from studies conducted according to Good Laboratory Practices (GLP) and are complete.

Table 1: Chemical and Physical Properties of Fludora Fusion.			
Title	Study Number	Test method ID	Result
pH (1% aqueous dilution)	Mo5190	MT 75.3, CIPAC Handbook J, p. 131, 2000	Measured pH=3.6 pH range should be: 3 to 7
Wettability	Mo5190	MT 53.3.1, CIPAC Handbook F, p.165, 1995	Wettability: 36-39 sec The formulation should be completely wetted in 1 min without swirling.
Wet sieve test	Mo5190	MT 185, CIPAC Handbook K, p.149, 2003	Residue: 0.00% Maximum: 1% retained on a 75 µm test sieve.
Suspensibility	Mo5190	MT 184, CIPAC Handbook K, p.142, 2003	Suspensibility: 94% (clothianidin), 92% (deltamethrin) A minimum of 70% should be in suspension after 30 minutes in CIPAC Standard Water D at 30 ± 2°C.
Persistent foam	Mo5190	MT 47.3, CIPAC Handbook O, p.177, 2017	Persistent foam: 2 ml Maximum: 50 ml after 12 min.
Dissolution of the bag	Mo5190	MT 176, CIPAC Handbook F, p. 440, 1995	Flow time of the suspension 9 sec. No fragments in the funnel observed. Flow time of the suspension: maximum 30 sec.
Stability at elevated temperature	Mo5190	MT 46.3, CIPAC Handbook J, p.128, 2000	All results were in accordance with WHO/FAO specifications limit. The determined average active ingredients content must not be lower than 95% relative to the determined average content found before storage.

3.2 Manufacturing, Composition and Formulant Information

Data on the manufacturing process and product composition have been provided and are adequate. A summary is presented in Table 3. 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 Fludora Fusion.		
Data Requirement	Study Number	Details
Description of Starting Material	Fludora Fusion Quality Dossier	Clothianidin 99.5-99.9 % purity, minimum clothianidin content 975 g/kg. Manufacturer: Bayer Cropscience AG Deltamethrin 98.6-99.5 % purity, minimum deltamethrin content 985 g/kg. Manufacturer: Bayer Cropscience AG Inert ingredients
Production / Formulation Process	Confidential Business Information Manufacturing procedure	Included in the Confidential Business Information. Appendix A (Internal use only).
Discussion of Impurities	Fludora Fusion Quality Dossier	There are no known impurities of toxicological concern in the technical material and inert ingredients of the product.
Control Product Specification Form / Confidential Statement of Formula	Fludora Fusion Quality Dossier	Included in the Confidential Business Information. Appendix A (Internal use only).
Certification of Limits	Certificate of Composition M-610764-02-1	clothianidin: 500 g/kg, acceptable limits 475 to 525 g/kg deltamethrin: 62.5 g/kg, acceptable limits 56.3 to 68.7 g/kg
Preliminary Analysis	Fludora Fusion Quality Dossier	HPLC determination for deltamethrin: 333/TC/M2/3, CIPAC Handbook L, p.46, 2006 and 333/TC/M2/4, CIPAC Handbook O, p.39, 2017 for clothianidin: 738/TC/M/3, CIPAC Handbook N, p.15, 2012
Enforcement Analytical Method	Fludora Fusion Quality Dossier	HPLC determination for deltamethrin: 333/TC/M2/3, CIPAC Handbook L, p.46, 2006 and 333/TC/M2/4, CIPAC Handbook O, p.39, 2017 for clothianidin: 738/TC/M/3, CIPAC Handbook N, p.15, 2012

3.3 Enforcement Analytical Method

The analytical method is a fully validated HPLC method, appropriate for the analysis of the active ingredients in the Fludora Fusion product and is summarized in Table 3.

Table 3. Details of the analytical method used to determine deltamethrin and clothianidin in Fludora Fusion.	
Method ID	MV 115 an HPLC method for analysis of deltamethrin and clothianidin content in Fludora Fusion
Sample preparation	Weigh to the nearest 0.1mg, 100 mg of sample into a 250 ml volumetric flask. Add approx. 150ml solvent mix (acetonitrile/water 80/20 v/v), and place in an ultrasonic bath for 15 min. After cooling fill it to the mark.
Instrument	HPLC system: pump, auto sampler, UV detector, column oven, degasser.
Detector	UV detector
Column	LiChroSpher RP 18 250x4mm, 5µm
Mobile phase (for LC)	acetonitrile/water 80/20 v/v
Column temperature	40 °C
Flow rate	1.2 ml/min
Injection volume	5µL
Wave length	220 nm
Retention time	~ 2 min for clothianidin, ~ 4.9 min for deltamethrin
Total run time	12 min

The validation data are shown in Table 4.

Table 4: Method validation for clothianidin and deltamethrin in Fludora Fusion.					
Active Ingredient	Method ID	Method type	Linearity	Recovery (%)	RSD (%)
Clothianidin	MV 115	HPLC	1.00	99.8	0.92
Deltamethrin	MV 115	HPLC	1.00	100.9	0.88

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 Fludora Fusion.

4.1 Product Specific Toxicity Data-Acute Toxicity

Acute toxicity studies have been conducted on Fludora Fusion and a summary of these studies and references are provided.

Bayer S.A.S, France, submitted acute toxicity studies conducted with the formulated product. All acute studies were conducted at CiToxLAB Hungary Ltd., Hungary, following OECD guidelines in accordance with GLP. The results are summarized below in Table 5:

- Fludora Fusion (clothianidin+ deltamethrin, 56.25%), is practically non-toxic via the oral, dermal and inhalation routes of exposure.
- Under GHS classification, Fludora Fusion has low acute oral, dermal and inhalation toxicity (Category 4), is not an eye or skin irritant, and is not a skin sensitizer.

Table 5. Acute Toxicity of Fludora Fusion.				
Route of Exposure	Species	Toxicity	GHS ^a Category	Reference
Oral	Rat	LD50 = 2000 mg/kg (males) and >2000 mg/kg (females)	4	Matyas, A., 2015
Dermal	Rat	LD50 = >2000 mg/kg	5	Matyas, A., 2015
Inhalation	Rat	LC50 = > 5.7 mg/L	Unclassified	Balazs, T., 2015
Dermal irritation	Rabbit	Non-irritant	None	Torok Batho M., 2015
Eye irritation	Rabbit	Non-irritant	None	Zelenak V., 2015
Dermal sensitization	Mouse	Non-sensitizer	Not applicable	Valiczko, E., 2015

GHS^a (Globally Harmonized System).

4.2 Summary of Available Toxicity Data on Active Ingredients: Clothianidin and Deltamethrin

There is sufficient information on the toxicity of the two active ingredients, clothianidin and deltamethrin. For clothianidin, the primary effects as indicated by the toxicity database are on the liver, hematopoietic system and kidneys. Liver effects, body weight changes, thyroid effects, and neurotoxicity are all commonly observed in mammalian toxicity studies of neonicotinoids. Pyrethroids, which include deltamethrin, have historically 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. Deltamethrin is a Type II pyrethroid. Neurotoxicity was observed throughout the database and clinical signs characteristic of Type II 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, neuro-, or immunotoxic potential.

Points of Departures (PODs) based on the most sensitive endpoints in the toxicity database are available for both clothianidin and deltamethrin. 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-, developmental, reproductive, and immunotoxicity for all populations including infants and children.

The existing toxicology database is adequate to support the proposed labelled uses of Fludora Fusion.

4.2.1 Mammalian Toxicity

a) Clothianidin

- **Acute Toxicity**

Table 6. Acute Toxicity of Clothianidin Technical.				
Route of Exposure	Species	Toxicity	GHS Category	Reference
Oral	Rat	LD50 = >425 mg/kg	4	USEPA, 2017a
Dermal	Rat	LD50 = >2000 mg/kg	5	USEPA, 2017a

Inhalation	Rat	LC50 = > 5.538 mg/L	5	USEPA, 2017a
Dermal irritation	Rabbit	Non-irritant	5	USEPA, 2017a
Eye irritation	Rabbit	Non-irritant	5	USEPA, 2017a
Dermal sensitization	Mouse	Non-sensitizer	Not applicable	USEPA, 2017a

- **Subchronic Toxicity**

In a 90-day feeding study with male and female Sprague-Dawley rats, the NOAEL was 27.9 mg/kg/day in males and 34.0 mg/kg/day in females, and the LOAEL was 202 mg/kg/day in males and 254.2 mg/kg/day in females based on decreases in body weight and body weight gain (JMPR, 2010; USEPA, 2017a).

In a 90-day feeding study with male and female Beagle dogs, the NOAEL was 19.3 mg/kg/day in males and 42.1 mg/kg/day in females, and the LOAEL was 40.9 mg/kg/day in males and 61.8 mg/kg/day in females based on anemia, decreased body weight, decreased body weight gain in males and decreased white blood cells, albumin, and total protein levels in females (USEPA, 2017a).

In a 90-day dermal toxicity study with male and female Sprague-Dawley rats, no dermal or systemic toxicity was seen; the NOAEL was 1000 mg/kg/day (JMPR, 2010; USEPA, 2017a).

In a 90-day inhalation toxicity study with male and female Sprague-Dawley rats, the NOAEL was 22.6 mg/kg/day in males and 24.8 mg/kg/day in females, and the LOAEL was 69.3 mg/kg/day in males and 74.9 mg/kg/day in females based on partially closed eyes and decreased activity (USEPA, 2017a).

- **Chronic Toxicity / Carcinogenicity**

In a chronic toxicity study with Beagle dogs, in males, the NOAEL was 46.4 mg/kg/day; the highest dose tested. A LOAEL was not established. In females, the NOAEL was 40.1 mg/kg/day and the LOAEL was 52.9 mg/kg/day based on clinical evidence of anemia (USEPA, 2017a).

In a combined chronic toxicity/carcinogenicity study with male and female Sprague-Dawley rats, for chronic toxicity (1-year), the NOAEL was 9.7 mg/kg/day and the LOAEL was 32.5 mg/kg/day based on decreases in body weight and food consumption. For carcinogenicity (2-years), the NOAEL was 82.0 mg/kg/day in males and 32.5 mg/kg/day in females, and the LOAEL was 156.5 mg/kg/day in males and 97.8 mg/kg/day in females based on decreased body weight and food consumption and altered hepatocellular eosinophilic focus of the liver in both sexes; ovary interstitial gland hyperplasia and increased lympho-histiocytic infiltrate in females; and slightly increased incidences of pelvic mineralization and transitional cell hyperplasia in the kidney, mottled livers of males. There was no evidence of carcinogenicity in either sex (JMPR, 2010; USEPA, 2017a).

In a carcinogenicity study with male and female Crl: CD mice, the NOAEL was 171.4 mg/kg/day in males and 65.1 mg/kg/day in females, and the LOAEL was 254.1 mg/kg/day in males and 215.9 mg/kg/day in females based on decreases in body weight, body weight gain, food consumption and food efficiency. There was no evidence of carcinogenicity in either sex (USEPA, 2017a).

- **Developmental Toxicity**

In a developmental toxicity study with pregnant Sprague-Dawley rats, no maternal or developmental toxicity was observed at the highest dose tested. For maternal and developmental toxicity, the NOAEL was 125 mg/kg/day; a LOAEL was not established (USEPA, 2017a).

In a developmental toxicity study with pregnant New Zealand white rabbits, for maternal toxicity, the NOAEL was 25 mg/kg/day and the LOAEL was 75 mg/kg/day based on increased incidences of clinical signs, mortalities, decreased food consumption, early delivery, abortion, and decreased body weight gain. For developmental toxicity, the NOAEL was 25 mg/kg/day based on premature deliveries, decreased gravid uterine weights, an increased litter incidence of a missing lobe of the lung and decreased litter average for ossified sternal centra per fetus (USEPA, 2017a).

- **Reproductive Toxicity**

In a 2-generation reproduction study with male and female Sprague-Dawley rats, for parental/systemic toxicity, the NOAEL was 31.2 mg/kg/day in males and 36.8 mg/kg/day in females and the LOAEL was 163.4 mg/kg/day in males and 188.8 mg/kg/day in females based on decreased body weight, body weight gain and absolute and relative thymus weights. For reproductive toxicity, the NOAEL was 31.2 mg/kg/day in males and the LOAEL was 163.4 mg/kg/day based on decreased sperm motility and increased number of sperm with detached heads in both generations in males. For females, the NOAEL was 188.8 mg/kg/day; the highest dose tested. A LOAEL was not established. For offspring toxicity, the NOAEL was 9.8 mg/kg/day in males and 11.5 mg/kg/day in females, and the LOAEL was 31.2 mg/kg/day in males and 36.8 mg/kg/day in females based on decreased body weight gains and delayed sexual maturation of males; and an increase in stillbirths in both generations (USEPA, 2017a).

- **Neurotoxicity**

In a special acute oral (gavage) neurotoxicity study with CD-1 mice, the NOAEL was 25 mg/kg/day and the LOAEL was 50 mg/kg based on transient signs of decreased spontaneous motor activity, tremors, and deep respirations (USEPA, 2017a).

In an acute oral (gavage) neurotoxicity study with Fischer 344 rats, the NOAEL was 60 mg/kg/day and the LOAEL was 100 mg/kg/day based on changes in Field Observational Battery, decreased arousal and decreased motor and locomotor activity was seen in males (JMPR, 2010; USEPA, 2017a).

In a dietary subchronic neurotoxicity study with Sprague-Dawley rats, there was no evidence of neurotoxicity; the NOAEL was 200 mg/kg/day, highest dose tested; a LOAEL was not established (USEPA, 2017a).

- **Developmental Neurotoxicity**

In a developmental neurotoxicity study with Sprague-Dawley rats, for maternal toxicity, the NOAEL was 142 mg/kg/day, the highest dose tested; a LOAEL was not established. For offspring toxicity, the NOAEL

was 12.9 mg/kg/day and the LOAEL was 42.9 mg/kg/day based on decreased body weight and body weight gain. There was no evidence of developmental neurotoxicity.

- **Genotoxicity**

Clothianidin exhibited no evidence of genotoxicity when investigated in both *in vitro* and *in vivo* assays using bacterial and mammalian system (USEPA, 2017a).

- **Immunotoxicity**

In an immunotoxicity study with Sprague-Dawley rats, there was no evidence of immunotoxicity at the highest dose tested; NOAEL was 253 mg/kg/day and a LOAEL was not established (USEPA, 2017).

- **Developmental Immunotoxicity**

In a developmental immunotoxicity study with Sprague-Dawley rats, there was no evidence of developmental immunotoxicity at the highest dose tested 250 mg/kg/day (USEPA, 2017a).

- **Absorption, Distribution, Metabolism and Excretion (ADME)**

The ADME of clothianidin was examined in single-dose studies in rats (2.5 and 250 mg/kg) and mice (5 mg/kg) and a 14-day repeated-dose study in rats (25 mg/kg/day) using radiolabeled chemical. The rate and route of excretion and nature of metabolism were similar across species and gender for both species. Following an oral low dose, greater than 90% and greater than 4% of the administered dose (AD) was excreted in the urine and feces, respectively, within the first 24 hours for both rats and mice. At 250 mg/kg/day, there was a lag in urinary clearance time, taking up to 48 hours to excrete 90% of the AD in rats. The lag indicates saturation of the absorption mechanism at this high dose. The remaining 5-6% of the AD is eliminated via the feces. There were gender-related differences in plasma kinetics in rats, for females absorbed slightly greater amounts of the AD; 90% for males and 95% for females in the 2.5 mg/kg group. However, female rats also had a slightly greater clearance rate, so there was not a greater net accumulation in the females. Female rats were only tested at the 2.5-mg/kg dose. The times-to peak plasma concentrations in the rat (T_{max}) were 1.5 for the low dose rats and 2.7 hours for the rats in the repeated dose group. Maximum plasma concentrations (C_{max}) were approximately 10times greater and proportional in the repeat-dose group compared to the low dose group (USEPA, 2017a).

Following absorption, clothianidin is distributed throughout the body. Although the organs associated with the absorption and elimination systems (i.e., bladder, kidney, liver, and nasal mucosa) initially demonstrate elevated levels, none of the tissues examined contained residue levels >1% of the AD 24 hours after dosing in the rat. Therefore, bioaccumulation is not a concern (USEPA, 2017a).

Parent was the most abundant residue identified in the urine, at 30% AD in the mouse and 55-74% in the rat. Three metabolites were identified as major (>10% AD), with several additional metabolites identified at <10% AD. The major metabolites were the result of demethylation of the parent or cleavage products of the nitrogen-carbon bond between the nitroimino and thiazolyl moieties (USEPA, 2017a).

- **Dermal Absorption**

A dermal penetration study was conducted in rhesus monkeys using the undiluted FS 600 formulation of clothianidin (10% AI). The exposure duration was 8 hours, and the subjects were monitored for 120 hours. Dermal absorption was estimated based on the sum of the AD measured in fecal and urinary excretions. Dermal penetration was low at 0.24% of the AD. A value of 1% dermal absorption has been recommended as appropriate for use in risk assessment (USEPA, 2017a).

b) Deltamethrin

Table 7. Acute Toxicity of Deltamethrin Technical				
Route of Exposure	Species	Toxicity	GHS Category	Reference
Oral	Rat	LD50 = > 5000 mg/kg (1% aqueous methyl cellulose) LD50 = 66.7 mg/kg (M), 86 mg/kg (F) (polyethylene glycol) LD50 = 128.5 mg/kg (M), 138.7 mg/kg (F) (sesame oil)	3/4	JMPR, 2000; USEPA, 2017b
Dermal	Rat	LD50 = >2000 mg/kg	5	USEPA, 2017b
Inhalation	Rat	LC50 = > 2.2 mg/L	4	USEPA, 2017b
Dermal irritation	Rabbit	Non-irritant	5	USEPA, 2017b
Eye irritation	Rabbit	Mild/moderate irritant	2B	USEPA, 2017b
Dermal sensitization	Mouse	Non-sensitizer	Not applicable	USEPA, 2017b

The Points of Departure (PODs) are from a published study (Wolansky, 2006). In this acute toxicity study, groups of 55 to 57-day old Long Evans male rats were given a single oral gavage dose of deltamethrin in 1 ml/kg corn oil at doses ranging from 0.015-900 mg/kg. Locomotor activity was measured at 1-4 hours after dosing utilizing a figure eight maze with motion photodetectors. The total locomotor activity was plotted versus administered pyrethroid amount. At study termination, the animals were euthanized but not pathologically examined (i.e. no necropsy or histology performed). A bench mark dose (BMD) was conducted and a benchmark response (BMR) was selected. As a general approach, it is preferable to use a combination of biological and statistical factors in the BMR selection. In the case of motor activity data, the scientific community has not established a specific level of change that would be adverse. Therefore, one standard deviation (1SD) from the control group, as suggested, for continuous endpoints in the agency’s BMD guidance (USEPA 2012) as the BMR. The BMD_{1SD} and the BMDL_{1SD} for deltamethrin are 2.48 mg/kg and 1.49 mg/kg, respectively. As a matter of science policy, EPA uses the BMD_L, not the BMD, for deriving PODs. Therefore, the BMDL_{1SD} of 1.49 mg/kg was used as the dose for risk assessment (USEPA, 2017b).

- **Subchronic Toxicity**

In a 90-day dietary study with male and female rats, the NOAEL was 2.5 mg/kg/day and the LOAEL was 10 mg/kg/day based on increased hypersensitivity to sound in both sexes (USEPA, 2017b).

In a 90-day dietary study with male and female dogs, the NOAEL was 1 mg/kg/day and the LOAEL was 2.5 mg/kg/day based on pupil dilation, depressed patellar reflex, and an increased incidence of diarrhea and vomiting (USEPA, 2017b).

In a 21-day dermal toxicity study with male and female rats, for systemic toxicity, the NOAEL was 1000 mg/kg/day, the highest dose tested. For dermal toxicity, a NOAEL was not established since signs of local irritation (paresthesia) was seen at all dose levels tested (USEPA, 2017b).

In a 21-day inhalation toxicity study with male and female rats, the NOAEL was 0.003 mg/L (equivalent to approximately 0.783 mg/kg/day) and the LOAEL was 0.0096 mg/m³ (approximately 2.5 mg/kg) based on excessive salivation, hunched posture, peripheral vasodilation, aggressive behavior, hypersensitivity to noise, and scarring of the ears (USEPA, 2017b).

- **Chronic Toxicity/Carcinogenicity**

In a chronic oral (capsule) toxicity with male and female dogs, the NOAEL was 1 mg/kg/day, and the LOAEL was 10 mg/kg/day based on based on chewing and scratching of extremities, abnormal gait with body tremors, and liquid feces (JMPR, 2000; USEPA, 2017b).

In chronic toxicity/carcinogenicity study with rats, the NOAEL was 22.2 mg/kg/day in males and 29.5 mg/kg/day in females and the LOAEL was 35.9 mg/kg/day in males and 47.1 mg/kg/day in females based on unsteady gait and splayed hindlimbs observed in the first few weeks of the study in male rats. There was no evidence of carcinogenicity in either sex (USEPA, 2017b).

Deltamethrin was not carcinogenic in long-term studies conducted with three strains of rats [CD, BDV1 and CrI: CD(SD)]. There was a non-dose-dependent increase in thyroid tumors in one of the studies and no increase in tumors were seen in the other two studies (JMPR, 2000).

In a carcinogenicity study with mice, the NOAEL was 314.8 mg/kg/day in males and 395.1 mg/kg/day in females, and the LOAEL was 603.4 mg/kg/day in males and 738.8 mg/kg/day in females based on decreased body weight. There was no evidence of carcinogenicity in either sex (USEPA, 2017b).

Deltamethrin was not carcinogenic in CD-1 or C57BL/6 mice in two different studies. The NOAEL was 16 mg/kg/day and the LOAEL was 160 mg/kg/day based on skin ulcerations secondary to scratching and irritation due to the pharmacological effects of the teste material (JMPR, 2000).

- **Developmental Toxicity**

In a developmental toxicity study with mice, for maternal toxicity, the NOAEL 3 mg/kg/day based on convulsions and decreased body weight at 6 mg/kg/day (LOAEL). No developmental toxicity was seen at the highest dose tested. For developmental toxicity, the NOAEL was 12 mg/kg/day and a developmental LOAEL was not established. (JMPR, 2000)

In a developmental toxicity study with rats, for maternal toxicity, the NOAEL was 3.3 mg/kg/day and the LOAEL was 7 mg/kg/day based on increased salivation in 11/25 animals and convulsions in one animal (9 animals had convulsions at the next highest dose) (USEPA, 2017b). No developmental toxicity was seen at the highest dose tested. For developmental toxicity, the NOAEL was 11 mg/kg/day and a developmental LOAEL was not established (JMPR, 200; USEPA, 2017b).

In a developmental toxicity study with pregnant New Zealand white rabbits, no maternal or developmental toxicity was seen at the highest dose tested. For maternal and developmental toxicity, the NOAEL was 32 mg/kg/day; a LOAEL was not established (JMPR, 2000; USEPA, 2017b).

- **Reproductive Toxicity**

In a 2-generation reproduction study with rats, for parental/systemic toxicity, the NOAEL was 5.4 mg/kg/day in males and 6.1 mg/kg/day in females and the LOAEL was 21.2 mg/kg/day in males and 23.5 mg/kg/day in females based on clinical signs, decreased body weights, and gross pathological lesions. For reproductive toxicity, the NOAEL was greater than 25 mg/kg/day in both sexes; a reproductive LOAEL was not established. For offspring toxicity, the NOAEL was 5.8 mg/kg/day in males and 6.7 mg/kg/day in females, and the LOAEL was 24.9 mg/kg/day in males and 27.2 mg/kg/day in females based on clinical sign, decreased body weight and gross pathological findings (USEPA, 2017b).

- **Neurotoxicity**

In an acute oral (gavage) neurotoxicity study with rats, the NOAEL was 15 mg/kg/day and the LOAEL was 50 mg/kg/day based on clinical signs during handling, open field, and sensory observations including, convulsions and tremors, increased salivation, soiled fur, impaired mobility, low arousal, decreased rearing, decreased fore- and hind-limb grip strength, and decreased body temperature. (JMPR, 2010; USEPA, 2017b). For this study, the JMPR established a NOAEL of 5 mg/kg/day and a LOAEL of 15 mg/kg/day based on effects in a battery of tests for function and locomotor activity at 15 mg/kg/day (JMPR, 2000).

In a dietary subchronic neurotoxicity study with rats, the NOAEL was 14 mg/kg/day in males and 16 mg/kg/day in females and the LOAEL was 54 mg/kg/day and 58 mg/kg/day in females based on clinical signs, FOB findings, and decreased body weights, body weight gains, and food consumption (JMPR, 2000; USEPA, 2017b).

- **Developmental Neurotoxicity**

In a developmental neurotoxicity study with rats, for maternal toxicity, the NOAEL was 6.8 mg/kg/day and the LOAEL was 16.1 mg/kg/day based on decreased body weight on gestation days 13 and 20. For offspring toxicity, the NOAEL was 6.8 mg/kg/day and the LOAEL was 16.1 mg/kg/day based on increased incidence of vocalizations during FOB and decreased pre-and-post-weaning body weight and body weight gain. There was no evidence of developmental neurotoxicity (USEPA, 2017b).

- **Genotoxicity**

There was no evidence of genotoxic/mutagenic potential of deltamethrin when investigated in both *in vitro* and *in vivo* assays using bacterial and mammalian system (USEPA, 2017a).

- **Immunotoxicity**

In an immunotoxicity study with rats, there was no evidence of immunotoxicity at the highest dose tested; NOAEL was 48.3 mg/kg/day and a LOAEL was not established (USEPA, 2017).

- **Absorption, Distribution, Metabolism and Excretion (ADME)**

Deltamethrin is hydroxylated at the 2', 4' and 5 positions of the alcohol moiety and the methyl group trans to the carboxylate linkage; extensive ester cleavage of deltamethrin yields a series of alcohols and carboxylic acids and their glucuronide, glycine, and sulfate conjugates. Metabolism of 14C-Deltamethrin was studied in male and female rats dosed orally with 14C-Deltamethrin labeled in two positions (14C-benzyl at 59.2 mCi/mmol or 14C-dimethyl deltamethrin at 60 mCi/mmol) (Bosch, 1990). Groups of 5 Crl:CD(SD)BR rats per sex were given 0.55 mg/kg (single oral dose), 0.55 mg/kg (14 non-radiolabeled doses followed by a radiolabeled dose on day 15) or 5.50 mg/kg (single oral dose). It was shown that most of the radioactivity was excreted in the urine and feces within 24 hours of dosing and that tissue and carcass residues were less than 2% of the dose at 7 days. Most residual radioactivity was stored in the fat; for the low dose groups, radioactivity concentrations ranged from 0.047 to 0.093 ppm. For the high doses, these values ranged from 0.504 to 0.840 ppm. Rats dosed with 14C-benzyl deltamethrin had 30 to 49% excreted in the urine as the sulfate conjugate 4'SO₄-mPBAcid and 2% to 4% as unconjugated mPBAcid. In the feces, 17 to 46% was excreted as deltamethrin (the higher dosage rats excreted a higher percentage in the feces as deltamethrin and a lower percentage in the urine as 4'SO₄- Deltamethrin Risk Characterization June 13, 2000 15 mPBAcid). For rats dosed with 14C-Dimethyl deltamethrin, 22 to 38% of the dose was excreted in the urine as the glucuronide conjugate Br2CA-glucuronide and 4 to 10% as the unconjugated Br2CA; in the feces, 21 to 35% was excreted as deltamethrin. The metabolism of deltamethrin by the rat has been extensively studied by Cole, et al. (1982).

4.3 Development of the Risk Assessment

A risk assessment for Fludora Fusion 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 indoor residual spraying. Examples of authoritative evaluations are: 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 pesticide 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.

- In **risk characterization** estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situation.

The risk assessment is by active ingredient based on the proposed use of the product Fludora Fusion for indoor residual spraying.

4.3.1 Hazard Assessment

a) Clothianidin

The Points of Departure and toxicological endpoints of concern used for acute and chronic dietary as well as non-dietary (incidental oral (hand-to-mouth activity), dermal, and inhalation exposure) risk assessments are presented below.

- Acute Reference Dose (ARfD).

Table 8: Acute Reference Dose established by JMPR and U.S. EPA						
Population of Concern	POD= NOAEL (mg/kg/day)	Uncertainty Factor	Acute RfD (mg/kg)	Toxicological Endpoint of Concern	Study Selected	Reference
General Population	60	100	0.6	Reduced motor activity at 100 mg/kg (LOAEL)	Acute Neurotoxicity-Rat	JMPR, 2010
Females 13-49 years of age	25	100	0.25	Missing lobe of the lung at 75 mg/kg/day (LOAEL)	Developmental Toxicity-Rabbit	USEPA, 2017a
General Population	25	100	0.25	Transient signs of decreased spontaneous motor activity, tremors and deep respirations at 50 mg/kg/day (LOAEL)	Special neurotoxicity/ pharmacology study - Mouse	USEPA, 2017a

- Acceptable Daily Intake (ADI)- JMPR.

Table 9. Acceptable Daily Intake - JMPR					
NOAEL (mg/kg/day)	Uncertainty Factor	ADI (mg/kg/day)	Toxicological Endpoint of Concern	Study Selected	Reference
9.7	100	0.1	Decreased body weight gain and food consumption	Chronic Toxicity- Rat	JMPR, 2010

- Chronic Reference Dose (CRfD)-USEPA.

Table 10. Chronic Reference Dose - USEPA					
NOAEL (mg/kg/day)	Uncertainty Factor	Chronic RfD (mg/kg/day)	Toxicological Endpoint of Concern	Study Selected	Reference

9.8	100	0.098	Decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations at 31.2 mg/kg/day (LOAEL)	Chronic Toxicity-Rat	USEPA, 2017a
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- Incidental Oral Exposure (Short-term; 1-7 days).

Table 11. Incidental Oral Exposure				
POD= Oral NOAEL (mg/kg/day)	Uncertainty Factor	Toxicological Endpoint of Concern	Study Selected	Reference
9.8	100	Decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations at 31.2 mg/kg/day (LOAEL)	Two-generation Reproduction - Rat	USEPA, 2017a

- Dermal Exposure (All Durations).

Table 12. Dermal Exposure				
POD= Oral NOAEL (mg/kg/day)	Uncertainty Factor	Toxicological Endpoint of Concern	Study Selected	Reference
9.8	100	Decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations at 31.2 mg/kg/day (LOAEL)	Two-generation Reproduction - Rat	USEPA, 2017a

The two-generation reproduction study in the rat was selected since the adverse effects in the offspring were seen in the absence of parental toxicity. The route-specific dermal toxicity was not selected since that study did not evaluate developmental/reproductive parameters. Since an oral POD was used, 1% dermal absorption factor will be applied to convert oral doses to dermal equivalent doses to assess risks from dermal exposures (USEPA, 2017a).

- Inhalation Exposure (All Durations)

Table 13. Inhalation Exposure				
POD= Oral NOAEL (mg/kg/day)	Uncertainty Factor	Toxicological Endpoint of Concern	Study Selected	Reference
9.8	100	Decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations at 31.2 mg/kg/day (LOAEL)	Two-generation Reproduction - Rat	USEPA, 2017a

The two-generation reproduction study in the rat was selected since the adverse effects in the offspring were seen in the absence of parental toxicity. The route-specific inhalation toxicity was not selected

since that study did not evaluate developmental/reproductive parameters. Toxicity via the inhalation route is assumed to be equivalent to toxicity via the oral route (USEPA, 2017a).

b) Deltamethrin

- Acute Reference Dose (ARfD).

Table 14. Acute Reference Dose						
Population of Concern	POD= NOAEL (mg/kg/day)	Uncertainty Factor	Acute RfD (mg/kg)	Toxicological Endpoint of Concern	Study Selected	Reference
General Population	5	100	0.05	FOB changes and locomotor activity at 15 mg/kg (LOAEL)	Acute Neurotoxicity-Rat	JMPR, 2010
Acute Dietary- (>= 6 years old)	BMDL1SD = 1.49 mg/kg	100	0.015	Decreased motor activity. BMD1SD value= 2.48 mg/kg	Wolansky et al., 2006	USEPA, 2017b
Acute Dietary- (< 6 years old)	BMDL1SD = 1.49 mg/kg	300	0.005	Decreased motor activity. BMD1SD = 2.48 mg/kg	Wolansky et al., 2006	USEPA, 2017b

Acute RfDs were established for age-related sensitivity for children less than and greater than 6 years of age. An uncertainty factor of 100 is adequate for all adult populations and children ≥6 years of age based on the absence of pre-natal sensitivity observed in the toxicology database. However, an uncertainty factor of 300 is required to protect for exposures of children <6 years of age based on the increased quantitative susceptibility seen in studies on pyrethroid PKs and the increased quantitative juvenile susceptibility observed in high dose studies in the literature (USEPA, 2017b).

- Acceptable Daily Intake (ADI)- JMPR

Table 15. Acceptable Daily Intake (ADI) - JMPR					
NOAEL (mg/kg/day)	Uncertainty Factor	ADI (mg/kg/day)	Toxicological Endpoint of Concern	Study Selected	Reference
1.0	100	0.01	Decreased body weight gain and food consumption	Chronic Toxicity- Rat	JMPR, 2010

- Chronic Reference Dose (CRfD) – USEPA

Deltamethrin is rapidly absorbed following an oral dose, and effects are typically observed within two to five hours after dosing. Like other pyrethroids, the no observed adverse effect levels (NOAELs) for the acute and chronic studies are similar, and the acute endpoint is protective of the endpoints from repeat dosing studies. Thus, for purposes of endpoint selection and exposure assessment, only single-day exposures need to be considered in the risk assessment.

Therefore, the USEPA did not establish a chronic RfD since there is no apparent increase in hazard from repeated/chronic exposures to deltamethrin. The acute dietary exposure assessment is protective of chronic dietary exposures.

- Incidental Oral (Short Term).

Table 16. Incidental Oral					
Population of Concern	POD= NOAEL (mg/kg/day)	Uncertainty Factor	Toxicological Endpoint of Concern	Study Selected	Reference
Children 1-2 years old	BMDL1SD = 1.49 mg/kg	300	Decreased motor activity. BMD1SD = 2.48 mg/kg	Wolansky et al., 2006	USEPA, 2017b
Children > 6 years	BMDL1SD = 1.49 mg/kg	100	Decreased motor activity. BMD1SD = 2.48 mg/kg	Wolansky et al., 2006	USEPA, 2017b

An uncertainty factor of 300 is required to protect for exposures of children <6 years of age based on the increased quantitative susceptibility seen in studies on pyrethroid PKs and the increased quantitative juvenile susceptibility observed in high dose studies in the literature. An uncertainty factor of 100 is adequate for children ≥6 years of age based on the absence of pre-natal sensitivity observed in the toxicology database. (USEPA, 2017b).

- Dermal Exposure.

A POD was not selected for dermal risk assessment since there is no toxicological endpoint of concern. No treatment-related dermal or systemic toxicity were observed following repeated dermal applications of deltamethrin at 1000 mg/kg/day, 5 days/week for 21 days to rats. There was also no toxicity observed following acute dermal exposure to deltamethrin up to a dose of 2000 mg/kg. Therefore, quantification of dermal risk is not required (USEPA, 2017b).

- Inhalation Exposure (All Durations).

An oral POD is used due to the lack of a repeated exposure inhalation toxicity study. Toxicity via the inhalation route is assumed to be equivalent to toxicity via the oral route.

Table 17. Inhalation Exposure				
POD= NOAEL (mg/kg/day)	Uncertainty Factor	Toxicological Endpoint of Concern	Study Selected	Reference
BMDL1SD = 1.49 mg/kg	100	Decreased motor activity. BMD1SD value of 2.48 mg/kg	Wolansky et al., 2006	USEPA, 2017b

c) Potential additive effects of Clothianidin and Deltamethrin

Acute toxicity studies have been conducted on Fludora Fusion and a summary of these studies and references are provided. Under GHS classification, Fludora Fusion has low acute oral, dermal and inhalation toxicity (Category 5), is not an eye or skin irritant, and is not a skin sensitizer. The acute toxicity package generated with Fludora Fusion demonstrated that the combination of both insecticides: clothianidin and deltamethrin did not potentiate the toxicological profile of 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.

To assess the potential additive effects or other interactions between the two active ingredients, acute toxicity studies were conducted with each of the active ingredients (clothianidin and deltamethrin) and the formulated product (Fludora Fusion). The results are tabulated below.

Table 18: Comparison of Acute Toxicity of Fludora Fusion, Clothianidin and Deltamethrin.				
Study Type	Fludora Fusion (50% clothianidin+6.25% deltamethrin)	Clothianidin (51.28% w/w)	Deltamethrin (6.35% w/w)	
Acute Oral - Rat	LD50 =2000 mg/kg (M)	LD50 = >1216 mg/kg (M)	LD50 = > 2000 mg/kg (M)	
	LD50 =>2000 mg/kg (F)	LD50 = >523-1216 mg/kg(F)	LD50 = >2000 mg/kg (F)	
Reference	Matyas, 2015	Sheets, 2000	Schungel, 2005	
Acute Dermal - Rat	LD50 = >2000 mg/kg	LD50 = >2000 mg/kg	LD50 = > 2000 mg/kg	
Reference	Matyas, 2015	Nishikata, 2997	Eiben, 2005	
Acute Inhalation - Rat	LC50 = > 5.17 mg/l air	LC50 = > 5.54 mg/l air	LC50 = 0.6 mg/l air	
Reference	Balazs, 2015	Shepherd, 1998	Coombs, 1978	
Skin irritation - Rabbit	Non-irritant	Non-irritant	Non-irritant	
Reference	Toeroek-Batho, 2015	Gardner, 1997	Schungel, 2005	
Eye Irritation - Rabbit	Non-irritant	Non-irritant	Non-irritant	
Reference	Zelenak, 2015	Gardner, 1997	Schungel, 2005	
Skin Sensitization	Non-sensitizer	Non-sensitizer	Non-sensitizer	
Reference	Valiezko, 2015	Denton, 1997; Leidenfrost, 2012	Vohr, 2005	

- Acute Oral Toxicity

The oral LD₅₀ of the product (Fludora Fusion) is comparable to the LD₅₀ value of deltamethrin and slightly higher than that of clothianidin. An oral dose of 2000 mg/kg of Fludora Fusion caused mortality in 3 of 7 (43%) rats compared to 7 of 10 rats (70%) treated with 1216 mg/kg of clothianidin alone. Major clinical signs seen with the formulated product were decreased activity, tremor and locomotor incoordination.

These signs were also seen at a similar incidence with clothianidin. The combination of both insecticides did not induce the major clinical signs seen with deltamethrin such as impaired grip strength, salivation or convulsions. Results shows that the combination of both insecticides does not cause any potentiation of the acute oral toxicity (Lasserre-Bigot, 2015).

- Acute Dermal Toxicity

The use of Fludora Fusion (clothianidin + deltamethrin 6.25 WP-SB) for mosquito control as Indoor Residual Spraying does not present any unacceptable risk for operators Fludora Fusion is not acutely toxic through the dermal route as clothianidin and deltamethrin with the LD50 values of > 2000 mg/kg body weight (Lasserre-Bigot, 2015).

- Acute Inhalation Toxicity

The LC50 of Fludora Fusion is in the same range as the LC50 of clothianidin and much higher than the LC50 of deltamethrin. The only clinical signs observed with the formulated product were restricted to labored respiration and noisy respiration on day 1. In contrast, more severe clinical signs such as closed eyes, hunched back, poor motor coordination, cold to touch and piloerection were seen with clothianidin alone, and ptyalism, hunched back, hypersensitivity to touch and poor motor coordination were seen with deltamethrin alone.

Therefore, the combination of both insecticides does not cause any potentiation of the acute toxicity through the inhalation route (Lasserre-Bigot, 2015).

- Skin and Eye Irritation

Fludora Fusion is not a skin or an eye irritant and it is not a skin sensitizer

4.3.2 Exposure and Risk Characterization

The second step in conducting a risk assessment is to estimate exposure to the insecticide in the various populations potentially at risk. Exposure must take into account 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 provided on the product label and in WHO guideline information. A “**lax standard scenario**” (appendix B), 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.

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 the same as the ADI or the chronic RfD established for the active ingredients (GRAM, 2010).

When the ratios are <1, the health risk is acceptable. Ratios >1 may indicate possible health risks in which case, steps may be taken to reduce the risk.

For trained applicators (including mixing/loading/applying activities), the risk ratios are all <1 for both clothianidin and deltamethrin. For adult resident scenario (dermal + dietary), the risk ratios are <1 for both clothianidin and deltamethrin. For the possible resident work as spray operators, the risk ratios are all <1 for both clothianidin and deltamethrin in the lax standard and guideline scenarios (Table 19).

For the potential exposure via the dermal and/or oral ingestion (food stuff+ hand-to-mouth) routes by children and toddlers as well as via breast milk to new born, the risk ratios are below 1 for both clothianidin and deltamethrin (Table 20). Ratios for the use of Fludora Fusion (clothianidin (50%) +deltamethrin (6.25%) are presented in tables 19 through 26.

Table 19: Exposure Estimates and Ratios for Operators (Mixing/Loading/Applying) Using the Guideline Scenario						
Exposure Scenario	Active Ingredient	Estimated Systemic Dose (mg/kg bw/day)	Estimated Systemic Dose (mg/kg bw/day)	TSD Mg/kg bw/day ADI/RfD	Ratio*	Ratio*
		40 mL/m2	20 mL/m2		40 mL/m2	20 mL/m2
Operator	Clothianidin	0.00167	0.00315	0.1	0.017	0.032
Operator	Deltamethrin	0.0000279	0.000032	0.0075	0.004	0.004
Operator + Resident (Adult)	Clothianidin	0.00236	0.00384	0.1	0.024	0.038
Operator + Resident (Adult)	Deltamethrin	0.0000389	0.000043	0.0075	0.005	0.006

*Ratio= Estimated Systemic Dose/TSD

Table 20: Exposure Estimates and Ratios for Resident (Adults) and Children, Toddlers and Newborns Using the Guideline Scenario.				
Exposure Scenario	Active Ingredient	Estimated Systemic Dose (mg/kg bw/day)	TSD mg/kg bw/day ADI/RfD	Ratio*
Resident (Adult) Exposure: Dermal+ Dietary	Clothianidin	0.000695	0.1	0.007
Resident (Adult) Exposure: Dermal + Dietary	Deltamethrin	0.000011	0.0075	0.001
Dermal+ Ingestion + Breast Milk: Child	Clothianidin	0.00129	0.1	0.01
Dermal+ Ingestion +Breast Milk: Toddler	Clothianidin	0.00503	0.1	0.05
Dermal+ Ingestion+ Breast Milk: Newborn	Clothianidin	0.00154	0.1	0.02
Dermal+ Ingestion+ Breast Milk: Child	Deltamethrin	0.000021	0.0075	0.003
Dermal+ Ingestion+ Breast Milk: Toddler	Deltamethrin	0.000060	0.0075	0.008
Dermal+ Ingestion+ Breast Milk: Newborn	Deltamethrin	0.0000023	0.0075	0.0003

*Ratio= Estimated Systemic Dose/TSD

4.4 Environmental Safety Assessment

Environmental safety was not assessed as Fludora Fusion is proposed for use as an indoor residual spray.

4.5 Safety conclusions

The use of Fludora Fusion for mosquito control as an Indoor Residual Spraying does not present any unacceptable risk for operators, residents, residents working as operators, or to new born, children and toddlers. The risk ratios for all exposure scenarios (dermal, inhalation, oral ingestion) are <1 . It is highly recommended that label instructions are strictly followed, and personal protective equipment is worn accordingly.

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

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.

Fludora Fusion 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 active ingredients.

A series of studies were provided in the submitted dossier including laboratory, experimental hut, and operational 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.

5.1 Summary of Efficacy Study Results

Study Number:	Results
BES 664-15-05 (MU 150904)	Nentwig, G. (December 2015). Intrinsic Insecticidal Efficacy of Clothianidin Determined with Topical Application of Clothianidin A.I. Technical Grade on <i>Anopheles gambiae</i> KISUMU.
	<p>Laboratory Study: The study presented information on the efficacy and activity of Clothianidin (CLD) technical grade on the target mosquito (<i>Anopheles gambiae</i> KISUMU: Clothianidin susceptible strain).</p> <p>Results: The study was conducted in accordance with the requirements for prequalification. The concentration of CLD in acetone 0.001% and 0.01% (3.125 and 32.25 CLD nanograms per mg body wt) was applied to the test strain and yielded 100% mortality after 24h. Similarly, CLD concentrate in acetone 0.0001% showed 100% mortality after 24h during the first two trials and later 90-93%.</p> <p>The resulting LC50, LC90 and LC99 were reported as follows: LC 50: 0.022531 nanogram/mg body weight (0.00000721 % Clothianidin) LC90: 0.399187 nanogram/mg body weight (0.00012774 % Clothianidin). LC 99: 4.159593 nanogram/mg body weight (0.00133107% Clothianidin).</p>
BES 664-10-01	Nentwig, G et al. (2015). Application rates series of Clothianidin: Efficacy on glazed tile against Malaria mosquitoes (<i>Anopheles gambiae</i> , strain RSP-H and Kisumu).
	<p>Laboratory Study: The study presented information on the evaluation of a series of application rates of Clothianidin 600 FS (600 g/L CLD). Performance was tested on glazed tile using the</p>

	<p>test strains <i>Anopheles gambiae</i>, strain Kisumu and strain RSP-H. Concentrations ranging from 25 to 800 mg AI/m² were tested.</p> <p>Results: The study was conducted in accordance with the requirements for prequalification. Strain Kisumu: There were no marked differences between the application rates (mortality between 90% and 95%). Strain RSP-H: The application rates ≥100 mg a.i./m² revealed 95% to 100% mortality. 50 and 25 mg a.i./m² revealed mortality of 70% and 55%, respectively.</p>
<p>BES 664-14-02 (Mo ES 06237)</p>	<p>Horstmann, S. (2015). Efficacy and residual activity of Clothianidin (CLD) + Deltamethrin (DLT) WG 56.25 and WG 62.5 at two application rates compared to Deltamethrin single active ingredient and Clothianidin single active ingredient at the same respective application rates on various surfaces stored at room temperature and in climatic chamber.</p>
	<p>Laboratory Study: The study presented information on the evaluation of residual activity of two formulations of Clothianidin in combination with Deltamethrin. These two formulations were developed for IRS and are described here:</p> <ul style="list-style-type: none"> • WG 56.25 (50% CLD + 6.25% DLT) applied at 200 mg/m² and 25 mg/m² respectively • WG 62.5 (50% CLD + 12.5% DLT) applied at 100 mg/m² and 25 mg/m² respectively <p>These formulations were tested in comparison to the following single AI formulations:</p> <ul style="list-style-type: none"> • Deltamethrin WG 25 applied at 25 mg/m² • Clothianidin WG 70 applied at 200 mg/m² • Clothianidin WG 70 applied at 100 mg/m² <p>The following strains were reported on:</p> <ul style="list-style-type: none"> • <i>Anopheles gambiae</i>, strain RSP-H Malaria mosquito, Deltamethrin resistant laboratory strain (east African <i>kdr</i> resistance) • <i>Anopheles funestus</i>, strain FUMOZ-R Malaria mosquito, Deltamethrin resistant laboratory strain (increased P450 metabolic resistance) • <i>Aedes aegypti</i>, strain Monheim Yellow-fever mosquito, susceptible laboratory strain <p>Results: The study was conducted in accordance with the requirements for prequalification.</p> <ul style="list-style-type: none"> • The residual activity of the two formulations WG 56.25 and WG 62.5 on tile, wood, concrete, mud (Ethiopia) and mud (Benin) was reported as ≥9 months for all tested strains. The only exception was for the scenario in which strain FUMOZ-R was tested on concrete which was stored at elevated temperatures (27°C). In this case, the residual activity was reported as 6 months. • The residual activity of the two formulations WG 56.25 and WG 62.5 was longer than the residual activity of the single AI formulations in nearly all scenarios.

<p>BES 664-15-04 (MU 150225)</p>	<p>Nentwig, G. (2015). Bridging trial between formulations Clothianidin+ Deltamethrin WP 56.25-SB and a prototype formulation CTD+DLT WG 56.25 at final application rate on tile, wood, and concrete.</p>
	<p>Laboratory Study: The study presented information for the purposes of bridging efficacy data on a WG formulation to the submitted formulation which is a WP in water soluble bags. The following strains were tested on tile, wood and concrete surfaces:</p> <ul style="list-style-type: none"> • Anopheles gambiae, strain RSP-H Malaria mosquito, Deltamethrin resistant laboratory strain (KDR resistance) • Anopheles funestus, strain FUMOZ-R Malaria mosquito, Deltamethrin resistant laboratory strain (Metabolic resistance) • Aedes aegypti, strain Monheim Yellow fever mosquito, susceptible laboratory strain <p>Results: The study was conducted in accordance with the requirements for prequalification.</p> <ul style="list-style-type: none"> • The residual activity of the WP and WG formulations against the three strains was reported ≥80% on all three surfaces for at least 28 weeks. • The WP formulation was slightly weaker than the WG when the strain FUMOZ-R was tested on wood.
<p>BES 664-14-01</p>	<p>Efficacy and residual activity of Clothianidin + Deltamethrin WG 56.25 against mosquito strains on glazed tile using Petri dish method. Tested at Liverpool Insect Testing Establishment, LITE, Liverpool, UK. Bayer. 2015.</p>
	<p>Laboratory Study: The study presented information on the evaluation of residual activity of a formulation of Clothianidin in combination with Deltamethrin. The formulation was developed for IRS and is described here:</p> <ul style="list-style-type: none"> • WG 56.25 (50% CLD + 6.25% DLT) applied at 200 mg/m² and 25 mg/m² respectively <p>The formulation was tested in comparison to the following single AI formulations:</p> <ul style="list-style-type: none"> • Deltamethrin WG 25 applied at 25 mg/m² • Clothianidin WG 70 applied at 200 mg/m² <p>The following strains were reported on:</p> <ul style="list-style-type: none"> • Anopheles gambiae, strain Tiassalé 13, Malaria mosquito, Carbamate resistant laboratory strain (CYP6 P450 enzymes and ACE-1 duplication) • Anopheles gambiae, strain Akron, Malaria mosquito, Carbamate resistant laboratory strain (ACE-1 mutation) • Aedes aegypti, strain Cayman, Yellow fever mosquito, Deltamethrin resistant laboratory strain (KDR mutation elevated P450s and esterases) <p>Results: The study was conducted in accordance with the requirements for prequalification. Bioassays indicated the following residual activity of the formulation based on mortality ≥80%:</p>

	<ul style="list-style-type: none"> The residual activity of the tested formulation WG 56.25 on glazed tile was reported as 47 weeks for the Tiassalé 13 and Cayman strains. The residual activity was reported as 33 weeks for the Akron strain.
BES-EH-Mo 06231	Rossignol, M et al. (2017). WHOPES Phase I testing and evaluation of Fludora Fusion 562.5 WP-SB, an insecticide mixture product of clothianidin and deltamethrin from Bayer, France for indoor residual spraying (IRS).
	<p>Laboratory Study:</p> <p>The study presented information on the performance and residual activity of Fludora Fusion 562.5 WP-SB on cement, mud, and wood. The following three strains of <i>An. gambiae</i> were reported on:</p> <ul style="list-style-type: none"> Susceptible strain (Kisumu) Pyrethroid resistant strain (Kdr-Kis) obtained by introgression of kdr mutation into the genome of Kisumu strain through successive backcrosses Organophosphate/carbamate resistant stain (Acer-Kis) obtained by introgression of insensitive acetylcholinesterase (ace-1R, G119S) into the genome of Kisumu strain <p>Studies were also conducted with the individual AIs to be used as comparators on the same surfaces and with the same strains.</p> <p>Results:</p> <p>The study was conducted in accordance with the requirements for prequalification. Fludora Fusion WP-SB CLD WG @200 mg/m² +DLT 25 mg/m²:</p> <ul style="list-style-type: none"> On cement mortality rates ≥ 80% at 24h post-exposure were reported as up to 6 months for all strains. The overall results presented in the study for 72h post-exposure reported the mortality rates above 80% as follows: <ul style="list-style-type: none"> up to 10 months for Kisumu up to 8 months for Kdr-Kis up to 6 months for Acer-Kis On mud the mortality rates ≥ 80% at 24h post-exposure were reported as up to 7 months for Kisumu, 1 month for Kdr-Kis and 6 months for Acer-Kis. The overall results presented in the study for 72h post-exposure reported the mortality rates above 80% as follows: <ul style="list-style-type: none"> up to 10 months for Kisumu up to 6 months for Kdr-Kis and Acer-Kis On wood the mortality rates ≥ 80% at 24h post-exposure were reported as up to 10 months for Kisumu and Acer-Kis strains and 0 months for Kdr-Kis. The overall results presented in the study for 72h post-exposure reported the mortality rates ≥ 80% as follows: <ul style="list-style-type: none"> up to 10 months for Kisumu and Acer-Kis up to 1 month for Kdr-Kis
BES Mo-ES- 06227	Coetzee, M. Evaluation of efficacy and residual activity of Clothianidin and Deltamethrin WG 56.25 against laboratory colonies of resistant <i>Anopheles arabiensis</i> Senn DDT and <i>Anopheles funestus</i> FUMOZR, as well as susceptible <i>Anopheles gambiae</i> SUA.

	<p>Laboratory Study:</p> <p>The study presented information on the evaluation of residual activity of two formulations of Clothianidin in combination with Deltamethrin on wood, cement and tile. These two formulations were developed for IRS and are described here:</p> <ul style="list-style-type: none"> • WG 56.25 (50% CLD + 6.25% DLT) applied at 200 mg/m² and 25 mg/m² respectively • WG 62.5 (50% CLD + 12.5% DLT) applied at 100 mg/m² and 25 mg/m² respectively <p>These formulations were tested in comparison to the following single AI formulations:</p> <ul style="list-style-type: none"> • Deltamethrin WG 25 applied at 25 mg/m² • Clothianidin WG 70 applied at 200 mg/m² • Clothianidin WG 70 applied at 100 mg/m² <p>The following strains were reported on:</p> <ul style="list-style-type: none"> • Resistant <i>Anopheles arabiensis</i> Senn (DDT) • Resistant <i>Anopheles funestus</i>, strain FUMOZR • Susceptible <i>Anopheles gambiae</i> SUA <p>Results:</p> <p>The study was conducted in accordance with the requirements for prequalification.</p> <ul style="list-style-type: none"> • Clothianidin + Deltamethrin WG 56.25 and WG 62.5 remained fully effective with efficacy ranging between 90 % and 100% over 12 months against susceptible <i>An.g.</i> SUA as well as against DDT resistant <i>An.ar.</i> Senn DDT on all surfaces. • Against <i>An.fun.</i> FUMOZR, the efficacy of Clothianidin + Deltamethrin WG 56.25 and WG 62.5 remained above 80% level for 10 months on tile, 7-8 months on cement, and 8 months on wood. • In all cases, Clothianidin in combination with Deltamethrin WG 56.25 and WG 62.5 performed better than single DLT or single CLD applied at the respective dosages.
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Experimental hut and operation field studies submitted by the applicant are summarized below. Fludora Fusion was originally submitted to the WHO Pesticide Evaluation Scheme (WHOPES). In accordance with the procedures for transition from WHOPES to PQT-VC, the responsibility for evaluation of this product was transferred to PQT-VC. As such, the supporting studies were either overseen by WHO or sponsored by the applicant. The following studies were overseen by WHO:

- BES 664-18-05
- BES 664-17-11
- BES 664-17-04

The following studies were sponsored by the applicant:

- BES-664-17-10
- BES 664-17-09
- BES 664-17-12

BES 664-18-05	Ahoua et al. (2017). Phase II study of the residual efficacy of a new insecticide formulation for indoor residual spraying from Bayer against free-flying <i>Anopheles gambiae</i> and other mosquitoes in experimental huts, IRD/LIN Cote d'Ivoire.
	<p>Experimental Hut Study:</p> <p>The study presented information on the efficacy and residual activity of Fludora Fusion (applied at 200 mg CLD/m² and 25 mg DLT/m²) against lab and wild free-flying <i>An. gambiae s.l</i> mosquitoes in an area with strong pyrethroid resistance in Cote d'Ivoire. The tests were conducted in experimental huts with cemented walls. The following single AI formulations were included as comparators:</p> <ul style="list-style-type: none"> • Clothianidin WG 700 applied at 200mg AI/ m² • Deltamethrin WG 250 (K-Othrine) applied at 25mg AI/ m² • Bendiocarb 80 WP-SB (Ficam VC) applied at 400mg AI/m². <p>Results:</p> <p>The study was conducted in accordance with the requirements for prequalification.</p> <ul style="list-style-type: none"> • The quality of spray determined by the analysis of filter papers has not been reported. Therefore, results of efficacy and residual activity cannot be presented. • However, results on the resistance status have been presented for the wild mosquitoes strain <i>An. gambiae</i> M'be <ul style="list-style-type: none"> ○ Highly resistant to deltamethrin (RR=1786) ○ Exhibited resistance to clothianidin (RR=130). • Potential antagonist effects between clothianidin and deltamethrin identified in the study are not supported by the review due to the lack of spray quality analysis and the differences in formulation type.
BES 664-17-11	Raghavendra et al. (2018). Phase II evaluation of the efficacy and residual activity of Fludora Fusion 562.5 WP-SB (Clothianidin 50% + deltamethrin 6.25%) for indoor residual spraying for malaria vector control in Gujarat State, India. September 2016-October 2017.
BES 664-17-04	Raghavendra, K. Evaluation of the efficacy and residual activity of Fludora Fusion 562.5 WP-SB (Clothianidin 50% + deltamethrin 6.25%) for indoor residual spraying for malaria vector control in Gujarat State, India. Phase III. May 2017-February 2018.
	<p>Operational Field Studies (Small Scale and Village Scale)</p> <p>The studies presented information on the efficacy and residual activity of Fludora Fusion (applied at 200 mg CLD/m² and 25 mg DLT/m²) against lab reared <i>An. culicifacies</i> mosquitoes (deltamethrin resistant, bendiocarb susceptible) in Gujarat State, India. The tests were conducted in households with mud and cement walls. The following comparators were used in the studies:</p> <ul style="list-style-type: none"> • Clothianidin WG 700 applied at 200mg AI/ m² • Deltamethrin WG 250 (K-Othrin) applied at 25mg AI/ m² • Bendiocarb 80 WP-SB (Ficam VC) applied at 400mg AI/m²* <p>* Bendiocarb 80 WP-SB (Ficam VC) was the only comparator for the village scale study</p> <p>Results:</p> <p>The study was conducted in accordance with the requirements for prequalification.</p>

	<ul style="list-style-type: none"> • Small Scale <ul style="list-style-type: none"> ○ The quality of spray was determined by the analysis of filter papers. All applications were within the acceptable target range ○ Bioassays indicated the following residual activity of Fludora Fusion on mud and cement based on mortality ≥80%: <ul style="list-style-type: none"> ▪ 4 months based on 24h post-exposure mortality ▪ 6 months based on 72h post-exposure mortality ▪ 7 months based on 96h post-exposure mortality • Village Scale <ul style="list-style-type: none"> ○ The quality of spray was determined by the analysis of filter papers. All applications were under dosed by approximately 50%. ○ Bioassays indicated the following residual activity of Fludora Fusion on mud and cement based on mortality ≥80%: <ul style="list-style-type: none"> ▪ 6 months based on 24h post-exposure mortality ▪ 7 months based on 72h post-exposure mortality ○ The overall mortality of <i>An. culicifacies</i> in villages sprayed with Fludora Fusion was 10.81% whereas it was 4.96% for villages sprayed with bendiocarb.
BES-664-17-10	Kirby, M. Efficacy and residual activity of Clothianidin + Deltamethrin WP, a mixture formulation for IRS in Tanzania, Study code 41B001-P. 2016-2018.
	<p>Experimental Hut Study: The study presented information on the efficacy and residual activity of Fludora Fusion (applied at 200 mg CLD/m² and 25 mg DLT/m²) in Lower Moshi, Tanzania. The tests were conducted in experimental huts with cement, mud and thatch surfaces. The following single AI formulations were included as comparators:</p> <ul style="list-style-type: none"> • Clothianidin WG 700 applied at 200mg AI/ m² • Deltamethrin WG 250 (K-Othrin) applied at 25mg AI/ m² • Bendiocarb 80 WP-SB (Ficam VC) applied at 400mg AI/m². <p>The following strains were reported on:</p> <ul style="list-style-type: none"> • <i>Anopheles gambiae</i> Kisumu • <i>Anopheles gambiae</i> s.s. Muleba-Kis pyrethroid-resistant (kdr East L1014S and metabolic-based mechanisms: a 10-20-fold overexpression of CYP6P3 • Wild <i>Anopheles arabiensis</i> and <i>Culex quinquefasciatus</i> <p>Results: The study was conducted in accordance with the requirements for prequalification.</p> <ul style="list-style-type: none"> • The quality of spray was determined by the analysis of filter papers. All applications were within the acceptable target range • Bioassays indicated the following residual activity of Fludora Fusion based on mortality ≥80%: <ul style="list-style-type: none"> ○ Concrete, mud, and thatch: ≥9 months based on 72h post-exposure mortality for both <i>Anopheles gambiae</i> Kisumu and <i>Anopheles gambiae</i> s.s. Muleba-Kis

	<ul style="list-style-type: none"> Fludora Fusion and clothianidin alone outperformed the comparator formulations in terms of free flying mosquito mortality over 6 months.
BES 664-17-09	<p>Dadzie et al. Evaluation of a new IRS Combination containing Clothianidin and Deltamethrin for control of multi-resistant <i>Anopheles gambiae</i> in comparison to Deltamethrin clone, Clothianidin clone, and Bendiocarb, in Experimental Hut Trials in Ghana. July 2016-September 2017.</p>
	<p>Experimental Hut Study: The study presented information on the efficacy and residual activity of Fludora Fusion (applied at 200 mg CLD/m² and 25 mg DLT/m²) in Dondowa, Ghana. The tests were conducted in experimental huts with cement and mud surfaces. The following single AI formulations were included as comparators:</p> <ul style="list-style-type: none"> Clothianidin WG 700 applied at 200mg AI/ m² Deltamethrin WG 250 (K-Othrin) applied at 25mg AI/ m² Bendiocarb 80 WP-SB (Ficam VC) applied at 400mg AI/m². <p>The following strains were reported on:</p> <ul style="list-style-type: none"> <i>Anopheles gambiae</i> Kisumu Wild <i>Anopheles gambiae</i> s.s. <p>Results: The study was conducted in accordance with the requirements for prequalification.</p> <ul style="list-style-type: none"> The quality of spray was determined by the analysis of filter papers. All applications were within the acceptable target range. No information was provided on the spray quality of Ficam. Bioassays indicated the following residual activity of Fludora Fusion based on mortality ≥80% for <i>Anopheles gambiae</i> Kisumu: <ul style="list-style-type: none"> Concrete <ul style="list-style-type: none"> 9 months based on 24h post-exposure mortality 10 months based on 72h post-exposure mortality Mud <ul style="list-style-type: none"> 1 months based on 24h post-exposure mortality 4 months based on 72h post-exposure mortality Fludora Fusion and clothianidin alone outperformed the comparator formulations in terms of free flying mosquito mortality on cement surfaces. Fludora Fusion and bendiocarb alone outperformed the comparator formulations in terms of free flying mosquito mortality on mud surfaces.
BES 664-17-12	<p>Evaluation of a new IRS product containing a combination of clothianidin and deltamethrin for control of <i>Anopheles gambiae</i> in Senegal. December 2017.</p>
	<p>Experimental Hut and Small Scale Field Study: The study presented information on the efficacy and residual activity of Fludora Fusion (applied at 200 mg CLD/m² and 25 mg DLT/m²) in Ndioukhane, Senegal. The tests were conducted in experimental huts with cement and mud surfaces and in village dwellings with cement surfaces (one dwelling had straw surfaces). The following single AI formulations were included as comparators:</p> <ul style="list-style-type: none"> Clothianidin WG 700 applied at 200mg AI/ m² Deltamethrin WG 250 (K-Othrine) applied at 25mg AI/ m² Pirimiphos-methyl (Actellic 300 CS) applied at 1000mg AI/m².

	<p>Results for <i>Anopheles coluzzi</i> were reported on.</p> <p>Results:</p> <p>The study was conducted in accordance with the requirements for prequalification.</p> <ul style="list-style-type: none"> • The quality of spray was determined by the analysis of filter papers. Fludora Fusion and Clothianidin applications were within the acceptable target range. Deltamethrin was 2-3 times overdosed. Pirimiphos-methyl was not reported on. • Bioassays indicated the following residual activity of Fludora Fusion based on mortality $\geq 80\%$: <ul style="list-style-type: none"> ○ Concrete <ul style="list-style-type: none"> ▪ ≥ 11 months based on 24h post-exposure mortality ○ Mud <ul style="list-style-type: none"> ▪ 6 months based on 24h post-exposure mortality ▪ ≥ 11 months based on 72h post-exposure mortality
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5.2 Efficacy Conclusions

Taking into account the entirety of the submitted efficacy studies in lab, experimental hut, and field settings, there is sufficient information to demonstrate that Fludora Fusion is at least as good as, and in many cases more efficacious than alternative formulations also available for IRS. The insecticides against which this has been compared include, clothianidin alone, deltamethrin alone, and bendiocarb, all sprayed as per labelled instructions. The main advantage of the Fludora Fusion formulation is derived from the longevity of residual activity. In the majority of studies, the product achieved a greater residual effect than the other products tested. Improved performance relative to deltamethrin alone and bendiocarb alone was observed against *Anopheles* mosquitoes which exhibited resistance to pyrethroids. This benefit was not observed in one study in West Africa where the mosquitoes were found to be resistant also to Clothianidin. When used, the resistance situation should be considered, since co-located resistance to both modes of action have been identified.

Based on the available evidence, Fludora Fusion is an effective product for IRS. It is appropriate for use in settings where the insecticide resistance profile of mosquito populations has been assessed and where the product efficacy lasts sufficiently long on common indoor surfaces (e.g. cement, mud, thatch, wood, etc.). The supporting data indicate that the product may have continued efficacy for a duration of 6-8 months depending on the mosquito strain, surface type and environmental conditions. In certain circumstances, efficacy beyond 8 months was shown.

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 Fludora Fusion 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 mosquitoes. The product is allowed inclusion on the list of prequalified vector control products.

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Appendix A: Confidential Business Information

Internal Use Only

Appendix B: Exposure and Risk Assessment Using the “Lax Standard Scenario”.

Table 21: Exposure Estimates and Ratios for Operators (Mixing/Loading/Applying) Using the “Lax Standard Scenario”.					
Exposure Scenario	Active Ingredient	Estimated Systemic Dose (mg/kg bw/day)	Estimated Systemic Dose (mg/kg bw/day)	Ratio*	Ratio*
		40 mL/m2	20 mL/m2	40 mL/m2	20 mL/m2
Operator	Clothianidin	0.0167	0.0315	0.17	0.32
Operator	Deltamethrin	0.000279	0.000316	0.04	0.04
Operator + Resident (Adult)	Clothianidin	0.0174	0.0322	0.17	0.32
Operator + Resident (Adult)	Deltamethrin	0.000290	0.000327	0.04	0.04
Dermal+ Ingestion+ Breast Milk: Newborn	Clothianidin	0.0129	--	0.13	--
Dermal+ Ingestion+ Breast Milk: Newborn	Deltamethrin	0.002	--	0.002	--

*Ratio= Estimated Systemic Dose/TSD