WHO Prequalification Programme / Vector Control Product Assessment

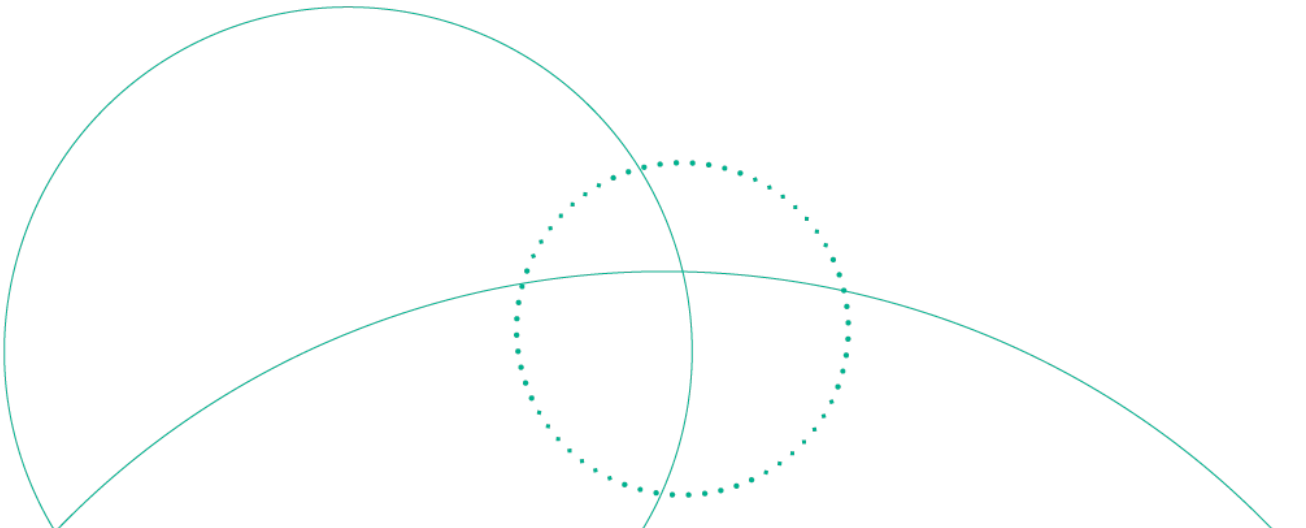
WHO Public Assessment Report: WHOPAR Part 4

OPTICA ULV

(Clarke International)

P-11637

Safety Assessment



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1 Risk Assessment Summary

1.1 Introduction

The applicant, Clarke International (Illinois USA), submitted a product dossier to the World Health Organization (WHO) Pre-Qualification Team, Vector Control Products Assessment Team (PQT-VCP) containing supporting data for the proposed product Optica ULV for use as an Indoor and Outdoor Space Spray. OPTICA ULV is a formulated liquid containing 1% (w/w) of the active ingredient Broflanilide (10.8 g a.i/L). It is intended to be used as an ultra-low volume (ULV) non-thermal cold aerosol mist space spraying insecticide to control of adult *Aedes aegypti* and adult *Aedes albopictus* mosquitoes.

1.2 Product identification

Applicant:	Clarke International, St. Charles, IL USA
Product name:	Optica ULV
Other names:	CMP 132-022 ULV
Active ingredient (AI):	Broflanilide
CAS no.:	1207727-04-5
Product type:	Indoor and Outdoor Space Spraying
Formulation type:	Formulated liquid containing 1% a.i.(w/w)(10.8 mg a.i./mL)
Description of packaging:	1 liter bottle and 10-liter plastic container for indoor and outdoor space spraying and steel drums (208 L) for outdoor application (vehicle mounted)
Target application rate:	Indoor: 0.059 g to 0.118 g Broflanilide/1000 m^2 Outdoor: 0.59 g to 1.18 g Broflanilide/1000 m^2
Spray concentration:	10.8 mg AI/mL
Volume applied:	Indoor handheld sprayer: 5.48 mL to 11.0 mL Optica ULV/1000 m^2 Outdoor handheld sprayer: 54.8 mL to 110 ml Optica ULV ULV/1000 m^2 Vehicle mounted: 183 mL OPTICA ULV/min at speed 10 km/hour Vehicle mounted: 275 mL OPTICA ULV/min at speed of 15 km/hour

1.3 Active ingredient statement

Broflanilide (CAS No. 1207727-04-5) is a meta-diamides insecticide. Broflanilide produces an insecticidal effect by binding to the gamma aminobutyric acid (GABA) receptor, thereby inhibiting the neurotransmission in insects.

1.4 Summary of Findings

For indoor uses, OPTICA ULV is intended to be sprayed using handheld, electric or gas powered ULV cold aerosol application equipment. For outdoor uses, OPTICA ULV is intended to be sprayed using standard ultra-low volume cold aerosol equipment. In this human health risk assessment, the estimated risk ratios for OPTICA ULV are based on the highest spray concentration of Broflanilide (10.8 mg a.i./mL).

The application rate of 11 mL OPTICA ULV/1000 m^2 (equivalent to 0.118 g a.i./1000 m^2) represents the worst-case scenario of **indoor** spraying and this rate is selected to assess risk to operators and residents in this human health risk assessment.

The application rate of 110 mL OPTICA ULV/ha (equivalent to 1.18 g a.i./ha) represents the worst-case scenario of **outdoor** applications (vehicle-mounted) and this rate is selected to assess risk to operators, residents and bystanders in this human health risk assessment

The assessment supports the following conclusions:

- The existing toxicology database for OPTICA ULV and Broflanilide is adequate for risk assessment and supports the proposed labelled uses of OPTICA ULV up to a concentration of 0.59 g to 1.18 g Broflanilide/1000 m^2 [100 mg broflanilide/m^2].
- All risk ratios are less than 1, hence, do not exceed the level of concern.
- The use of OPTICA ULV, a liquid formulation containing Broflanilide at 1% w/w when used as an insecticide for indoor and outdoor space spraying in the course of vector control, does not present any unacceptable risk for operators, residents, residents working as operators, or to children, toddlers, infants, or newborns exposed through breast milk.

2 Human health risk assessment

This human health risk assessment for Broflanilide is conducted according to the "*A Generic Risk Assessment Model for Indoor and Outdoor Spraying of Insecticides, 2nd edition*" (GRAM) (WHO, 2018). Risk assessment involves three steps: Hazard assessment, Exposure assessment and Risk characterization.

- **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 are used as starting points for the risk assessment of insecticides. Examples of authoritative evaluations are: Joint Meeting on Pesticide Residues (JMPR), International Programme on Chemical Safety (IPCS), International Agency for Research and Cancer (IARC), United States Environmental Protection Agency (USEPA), European Food Safety Authority (EFSA).
- **Exposure assessment** 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. Conservative high-end point estimates of the default distributions are used as defaults. No account is taken of intended misuse. All relevant routes of exposure are covered.
- In **risk characterization,** estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situations.

2.1 Hazard assessment

2.1.1 OPTICA ULV

Clarke Mosquito Control Products, LLC (St. Charles, IL) submitted six acute toxicity studies with OPTICA ULV conducted at Product Safety Labs (PSL, New Jersey) following OECD guidelines and GLP regulations. Under the GHS classification (2017), OPTICA ULV is non-toxic via the oral, dermal and inhalation routes of exposure (GHS Cat. 5). It is not a skin and eye irritant in rabbits (GHS Cat. Not Classified) and is not a dermal sensitizer in guinea pigs (GHS Cat. Not Classified).

Table 1. Acute toxicity of Optica ULV

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	LD50 > 5000 mg/kg bw	5	PSL. 2021a
Acute dermal toxicity	Rat	LD50 > 5000 mg/kg bw	5	PSL, 2021b
Acute inhalation toxicity	Rat	LC50 > 5.27 mg/L/4 hours	5	PSL. 2021c
Primary dermal irritation	Rabbit	Not irritant	Not classified	PSL. 2021d
Primary eye irritation	Rabbit	Slightly irritant/Reversible	Not classified	PSL. 2021e
Skin sensitization, Local Lymph Node	Guinea Pig	Non-sensitizer	Not classified	PSL. 2021f

2.1.2 Active ingredient – Broflanilide

The product OPTICA ULV is composed of the active ingredient, Broflanilide. This risk assessment relies heavily on toxicity studies conducted on the active ingredient (AI) itself as the AI is the biologically active

substance that produces a targeted pesticidal effect but can also have the potential to produce toxic biological effects.

Broflanilide is a new active ingredient and toxicology studies have been evaluated by the US EPA (2020a) and JMPR (2022). The US EPA has generated a human health hazard assessment for Broflanilide (USEPA, 2020a) and a summary report is available from JMPR (2022). The toxicity profile of Broflanilide is presented in Appendix A.

The intent of the hazard assessment of the active ingredient Broflanilide is to consolidate the relevant toxicological information and authoritative evaluations from national and/or international organizations and characterize the chemical as it relates to uses of VCPs. For the active ingredient, PQT/VCP relies on these authoritative evaluations and focuses on the studies and endpoints applicable to the risk assessment of the proposed use patterns of VCPs. As such, the hazard assessment is not exhaustive in its summary of publicly available information characterizing the hazard of the AI. The toxicity database of Broflanilide has adequate studies for hazard characterization.

2.1.3 Broflanilide Profile Statement

Technical grade Broflanilide is a meta-diamides insecticide. It was registered in 2021 for uses on corn, seeds, grains, agricultural crops and for control of a broad range of soil-dwelling insects (USEPA, 2020). Administration of Broflanilide to rats and mice by the oral route resulted in increases in organ weight and histopathological findings. The principal target organ in all studies and in all species was the adrenal gland, with the rat being the most sensitive species. In the rat, after chronic administration there were treatment-related increases in Leydig cell adenomas noted in males at all doses tested; in luteomas and granuloma cell tumors in the ovaries; uterine adenocarcinomas, and adrenal cortex carcinomas in females. No oncogenic potential was found in mice. Exposure to Broflanilide did not result in developmental toxicity in rats and rabbits and reproductive toxicity in rats. There is no evidence to suggest that Broflanilide is mutagenic or clastogenic. No neurotoxic or immunotoxic effects were found in studies with Broflanilide (USEPA, 2020a).

2.1.3.1 Acute studies

Broflanilide is of low toxicity following acute exposure. The acute oral and dermal LD_{50} were greater than 5000 mg/kg (GHS Cat 5). Acute inhalation exposure was conducted for 4-hours nose-only in male and female rats. The combined LC_{50} value was above 2.20 mg/L, the highest attainable concentration in the study. Broflanilide was not a skin or eye irritant (GHS Not Classified) and was not a skin sensitizer in either the murine local lymph node assay in mice or the Magnusson and Kligman Maximization assay in guinea pigs (USEPA, 2020a). Acute studies were conducted following OECD guidelines and GLP regulations.

Table 2 Acute toxicity of broflanilide technical

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	LD_{50} > 5000 mg/kg	5	USEPA, 2020a
Acute dermal toxicity	Rat	LD_{50} > 5000 mg/kg	5	USEPA, 2020a
Acute Inhalation	Rat	LC_{50} > 2.20 mg/L	Not classified	USEPA, 2020a
Dermal irritation	Rabbit	Non-irritant	Not classified	USEPA, 2020a

Eye irritation	Rabbit	Non-irritant	Not classified	USEPA, 2020a
Skin sensitization, LLNA	Mouse	Non-sensitizer	Not classified	USEPA, 2020a

2.1.3.2 Absorption, distribution, metabolism, and excretion

Absorption, distribution, metabolism and elimination (ADME) studies on the AI are considered and integrated into the hazard assessment. Further details on ADME for Broflanilide are available in Appendix B.

Oral absorption: Absorption via the oral route is assumed to be 100% (default value).

Dermal absorption: In an *in-vivo* dermal penetration study in male rats, the results indicated that 5.0% (low dose 1.25 µg/cm^2), 5.1% (mid-dose, 2.5 µg/cm^2) or 2.35% (high dose, 1000 µg/cm^2) of the applied radioactivity was absorbed after 120 hours. A dermal absorption of 5% was selected by the USEPA (2020b) for risk assessment.

Inhalation absorption: Absorption via the inhalation route is assumed to be 100% that via the oral route. Due to the lack of a long-term inhalation study, the oral equivalent is used for the inhalation risk assessment.

2.1.4 Points of departure (POD) and reference doses (RfD)

Points of departure (PODs) (No Observed Adverse Effect Level [NOAEL]; Benchmark Dose [BMD]) are determined from the toxicological database based on the most sensitive endpoints. Once PODs are developed, safety factors (SF) and uncertainty factors (UF) are used in conjunction with the PODs to derive a safe exposure level, generally referred to as reference dose (RfD) or acceptable daily intake (ADI).

2.1.4.1 Reference doses

A reference dose (RfD) is an estimate of daily oral exposure (acute, aRfD) for a duration of 24 hours or less or chronic oral exposure (cRfD) for a duration of several months to a lifetime that is likely to be without an appreciable risk of deleterious effects during a lifetime. Both an aRfD and a cRfD can be derived from a NOAEL, LOAEL, or a benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used.

2.1.4.1.1 Acute reference dose (aRfD)

For Broflanilide, an acute RfD has not been established by regulatory agencies (USEPA, 2020a; JMPR, 2022) since toxicological effects attributable to a single exposure were not identified in the toxicity data base including developmental toxicity studies in rats and rabbits. Therefore, PQT/VCP did not establish an aRfD for Broflanilide and no risk ratio is calculated for acute exposure.

aRfD: not established

2.1.4.1.2 Chronic reference dose (cRfD)

The USEPA (2020a) selected the 2-generation reproductive toxicity study in rats with a NOAEL of 3 mg/kg bw/day and a LOAEL of 8 mg/kg bw/day based on increased adrenal weights with corroborative histopathological findings (increase vacuolation and diffuse hypertrophy in the adrenal gland cortex) in both sexes and both generations. This study is appropriate for the route of duration of exposure and for the population of concern. An uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation) is applied to establish the cRfD.

cRfD = 3 mg/kg bw/day: 100 = 0.03 mg/kg bw/day

2.1.4.1.3 Acceptable daily intake (ADI)

JMPR (2022) established an ADI of 0.02 mg/kg bw, based on the LOAEL of 5.9 mg/kg bw/day in the two-year toxicity and carcinogenicity study in rats, and using an uncertainty factor of 300X (10X for intraspecies variation, 10X for interspecies extrapolation and an additional safety factor of 3 for using a LOAEL as the POD). This ADI is supported by the 90-day rat study NOAEL of 2.0 mg/kg bw/day, and the two-generation reproductive study with the parental NOAEL of 2.3 mg/kg bw/day (JMPR, 2022).

ADI = 5.9 mg/kg bw/day: 300 = 0.02 mg/kg bw/day

2.1.4.2 Selection of the tolerable systemic dose (TSD)

The PQT/VCP did not select a TSD for acute exposure (TSD_{AC}) since an aRfD for broflanilide has not been established. No risk ratio is calculated for acute exposure.

The PQT/VCP selected the cRfD of 0.03 mg/kg bw/day established by the USEPA in 2020(a) as the TSD for long term risk characterization.

TSD = 0.03 mg/kg bw/day = 30 µg/kg bw/day

2.1.4.3 Cancer Classification

The US EPA (2020) classified Broflanilide as “Likely to be Carcinogenic in Humans” based on Leydig cell tumors and all ovarian tumors combined (granuloma cell benign and malignant, luteomas, thecomas and sex cord stromal tumors). The linear slope factor (Q_1*) was calculated as 2.48×10^{-3} $(mg/kg\ bw/day)^{-1}$ based upon male rat testicular Leydig cell tumors.

JMPR (2022) concluded that Broflanilide is not carcinogenic in mice but is carcinogenic in rats based on increased incidence of ovarian tumors of sex cord stromal origin and uterus adenocarcinomas and an increase in the incidence of Leydig cell adenomas at 953 mg/kg bw/day. The Meeting also concluded that the upper bound of the ADI (0.02 mg/kg bw/day provides a margin of at least 4750 relative to the LOAEL (95 mg/kg bw/day) for the ovarian tumors observed in female rats.

To address and consider the potential for carcinogenicity based on its classification, PQT/VCP relies upon the available guidance in the GRAM to assess the risk of carcinogenicity. The complete assessment is available in Appendix D.

2.2 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 various parameters into consideration, 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.

Conservative, high-end point estimates of the default distributions are used as defaults in the exposure assessment. The default values may be modified by users of the models on a case-by-case basis and replaced with appropriate measured or otherwise improved point estimates or distributions, when applicable. Similarly, the application of anthropometric and physiological datasets derived from the true target population, when available, is likely to yield more accurate exposure predictions. The exposure assessment (i.e., exposure calculations) is assessed according to the *Generic Risk Assessment Model for Indoor and Outdoor Space Spraying of Insecticide (GRAM),* 2nd Edition (WHO, 2018) and chemical-specific data.

The exposure assessment includes operator exposure. OPTICA ULV is to be applied by professional applicators only. Since OPTICA ULV is a ready-to-use insecticide for indoor and outdoor uses, there are no mixing and loading activities and operators may be exposed to OPTICA ULV only via the dermal and inhalation route during spray application. Inhalation may occur but is considered negligible considering the low vapor pressure of the active ingredient Broflanilide (6.7×10^{-11} mmHg).

In the total exposure assessments, all relevant routes and different scenarios are summed to derive the total systemic dose. In a **"**guideline scenario", the insecticide is assumed to be used according to the instructions provided on the product label and in WHO guideline information. Operators are expected to use appropriate personal protective equipment (PPEs) such as gloves, other clothing and respirators according to WHO manual. Residents are instructed to "not enter the house during or right after spraying", therefore, residential exposure is only through particles that settle on the floor, shelves, and surfaces. Exposure is also assessed in a "lax standard scenario", which increases the anticipated exposure based on the removal of a safety factor associated with the use of personal protective equipment. This is presented for informational purposes based on its inclusion in the GRAM. WHO does not recommend the application of spray insecticide without PPE.

The target dose of the product is 0.1188 mg Broflanilide per m^2 for both indoor and outdoor. The volume applied per m^2 is 0.011 ml. The concentration of Broflanilide in the spray solution is 10.8 mg a.i/mL spray.

Abbreviations and default values used throughout the exposure assessment of OPTICA ULV			
Abbreviation	**Definition**	**Value**	**Data derived or Default Value**
Abs-D	Dermal absorption	5%	Data derived (USEPA, 2020b)
Abs-P	Respiratory absorption	100%	Default (GRAM)
Abs-O	Oral absorption	100%	Default (GRAM)
AT	Average time	356 days	Default (GRAM)
BV	Breathing volume	1.25 m^3/hour for adults 1.32 m^3/hour for children 1.26 m^3/hour for toddlers 0.84 m^3/hour for infants	Default (GRAM)
BW	Body weight	60 kg/adult 23.9 kg/children 10 kg/toddlers 8 kg for infants	Default (GRAM)
CF	Concentration of AI in formulation	Broflanilide 1% w/w = 10.8 g a.i./L = 10.8 mg a.i./mL OPTICA ULV	Data derived (Applicant)
C_{SUR}	Concentration on surface	2.5 x concentration in air mg/m^3) = 2.5 x 0.06 mg a.i./m^3 = 0.15 mg a.i./m^2	Data derived (Applicant)
C_{spray}	Concentration of the AI in the spray	10.8 mg a.i./mL	Data derived (Applicant)
$Dose_{Mbw}$	Daily dose to the mother (mg kg_{bw}^{-1})	0.001	Default (GRAM)
ED	Exposure duration	Operators = 6 hours/day Bystanders and Residents: 0.25 hours/day	Default (GRAM)
EF	Exposure frequency	Operators: 6 days per week, for 26 weeks = 156 days/year Bystanders and Residents: 15 days	Default (GRAM)
ESA	Exposed skin areas	0.308m^2 for adults 0.153m^2 for children 0.133m^2 for toddlers 0.394m^2 for infants	Default (GRAM)
FEXS	Fraction extracted in saliva	0.57	Default (GRAM)
FHM	Fraction of hand area mouthed	0.164 – 75th percentile	Default (GRAM)
IR	Ingestion rate of milk	0.54 kg/day for newborns 0.68 kg/day for infants	Default (GRAM)
Lax	Lax standard scenario	1 (no protection)	Default (GRAM)
NOD	Number of mixing operations per day	N/A applied undiluted – Default = 1	Default (GRAM)
PPE	Personal protective equipment	0.1 (90% protection represents guideline scenario)	Default (GRAM)
RPE	Respiratory protection	0.1 (guideline scenario) and 1.0 (lax scenario)	Default (GRAM)
SAF	Surface area of food in contact with the shelf. Half of food items are in contact with contaminated surfaces.	0.0169, 0.0126, 0.0124 and 0.0105 m^2 for adults, children, toddlers, and infants, respectively	Default (GRAM)
Sol C	Solubility constant	0.361 for lipid-soluble	Default (GRAM)
$SysD_{TWA}$	TWA systemic dose	Calculated value	
$SysD_{MAX}$	Maximal systemic dose	Calculated value	
TAR	TAR Target Application Rate (Outdoor)	0.1 x rate in grams a.i/ha = 0.1 x 1.188 g a.i/ha = 0.012 mg a.i/m2	Data derived (Applicant)
HSC	Height of spray cloud	3 m	Default (GRAM)
$T_{1/2}$	First-order kinetics' half-time in the body of the insecticide	2 days	Data derived (Applicant)

TC_{AIR}	Conc of active ingredient in air - INDOOR	1.1 mL (volume of spray applied per house) = 0.0055 ml spray/m^3 = 200 m^3 (volume of house) 0.0055 ml spray/m^3 x 10.8 mg a.i/ml spray = 0.06 mg a.i/m^3	Data derived (Applicant)
Transl	Fraction translodged onto skin	8% of the amount on the surface	Default (GRAM)
UE_{LIQ}	Unit exposure for handling	0.01 mL/operation	Default (GRAM)
VLH	Volume of spray on hands	Since OPTICA ULV is applied undiluted and the container is attached to a spray nozzle, there is no mixing/loading and washing of tanks and the application rate is only 11 mL/1000 m^2, it is expected that the volume of spray on hands would be less than the default of 8.2 mL/day (GRAM, 2018). Conservatively, a VLH of 8.2 mL x 20% = 1.64 mL/day would be more appropriate for OPTICA ULV.	Data derived (Applicant)

Table 3. Assumptions and parameters used throughout the exposure assessment of Optica ULV

Description	Assumption	Data Derived or Default
Application Rate – INDOOR	11 mL OPTICA ULV per 1000 m^2 = 118.8 mg a.i./1000 m^2 = 0.118 mg a.i./m^2 (maximum application rate)	Data derived (Applicant)
Application Rate = OUTDOOR (vehicle mounted)	110 mL OPTICA ULV per ha = 1,188 mg a.i./ha = 1,188 mg a.i./10,000 m^2 = 0.118 mg a.i./m^2 (maximum application rate)	Data derived (Applicant)
Application volume - INDOOR	11 mL OPTICA ULV/1000 m^2 = 0.011 mL OPTICA ULV/m^2	Data derived (Applicant)
Application volume – OUTDOOR	110 mL OPTICA ULV/ha = 110 mL : 10,000 m^2 = 0.011 mL OPTICA ULV/m^2	Data derived (Applicant)
Dilution factor for spray solution	N/A – OPTICA ULV applied undiluted	
Dimensions of a typical house	10m x 10m x 2m Floor area = 100m^2, Volume of house = 200 m^3	Default (GRAM)
Frequency of spraying	Total 15 sprays/year	Default (GRAM)
HANDHELD SPRAY – Daily exposure - INDOOR	200 m^3/house x 60 houses = 12,000 m^3 0.06 mg a.i./m^3 x 12,000 m^3 = 720 mg a.i./day Volume required daily = 720 mg a.i. / 10.8 mg a.i./mL = 66.6 mL/day	Data derived (Applicant)
Mixing-loading frequency HANDHELD - OUTDOOR	N/A applied undiluted Area to cover = 200 ha/day (GRAM, 2018) 110 mL/ha x 200 = 22 Liters	Data derived (Applicant)
Number of houses treated per day (standard)	60	Default (GRAM)
Tank Size	N/A – OPTICA ULV applied undiluted	
Volume of spray solution applied per house	INDOOR = 0.011 mL OPTICA ULV/m^2 Volume spray per house = 0.011 mL/m^2 x 100 m^2 = 1.1 mL spray/house Concentration of a.i. sprayed per house = 1.1 mL x 10.8 mg a.i./mL spray = 11.88 mg a.i./house	Data derived (Applicant)

2.2.1 Occupational exposure

Exposure to operators occurs during indoor and outdoor spraying of the insecticide. Exposure via the dermal route may occur during washing and maintenance of equipment and via the inhalation route during application. Operators are assumed to follow WHO guidance for spray procedures and wear appropriate PPE (respirator, protective gloves, long sleeved protective clothes) providing a reduction coefficient of 0.1 (i.e., 10%) referred to as "guideline scenario". (WHO, 2018)

The estimated long-term [time-weighted average (TWA)] estimated systemic doses for operators are presented in the following tables.

2.2.1.1 Operator dermal exposure during mixing and loading

OPTICA ULV is applied undiluted and the container is attached to a spray nozzle. Therefore, there is no dermal exposure during mixing and loading.

2.2.1.2 Operator inhalation exposure during application – Indoor Space Spray

The estimated time weighted average (TWA) systemic dose from Broflanilide to operators due to potential inhalation exposure from application is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{TC_{AIR} \times RPE \times BV \times ED \times ABS_P) \times EF \times 1000}{BW \times AT}$$

Table 4. Estimated Long Term Systemic Dose (TWA) to Operator from Inhalation Exposure During Application

TC_{AIR} (mg/m³)	RPE	BV (m³/hr)	ED (hr)	ABS_P (%)	EF (days)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario								
0.06	0.1	1.25	6	100	156	60	365	0.320

2.2.1.3 Operator dermal exposure during application, washing, and maintenance – Indoor Space Spray

The estimated time weighed average (TWA) systemic dose to operators due to potential dermal exposure from application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{VLH \times C_{spray} \times PPE \times EF \times Abs_D \times 1000}{(BW \times AT)}$$

Table 5. Estimated Long Term Systemic Dose (TWA) to Operator from Dermal Exposure during application, washing and maintenance

VLH (mL/day)	C_{SPRAY} (mg AI/mL)	PPE	EF (days)	Abs_D (%)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario							
1.64	10.8	0.1	156	5	60	365	0.63

2.2.1.4 Operator dermal exposure during mixing and loading – Outdoor Space Spray

OPTICA ULV is applied undiluted and the container is attached to a spray nozzle. Therefore, there is no dermal exposure during outdoor mixing and loading.

2.2.1.5 Operator inhalation exposure during application with hand-held sprayer – Outdoor Space Spray

The estimated time weighted average (TWA) systemic dose from Broflanilide to operators due to potential inhalation exposure from outdoor application (hand-held sprayer) is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{TAR \times RPE \times BV \times ED \times EF \times ABS_P \times 1000}{(HSC \times BW \times AT)}$$

Table 6. Estimated Long-Term (TWA) Systemic Dose to Operator from Inhalation Exposure during Outdoor Application

TAR (mg AI/m²)	RPE	BV (m³/hr)	ED (hours)	Abs-P (%)	EF (days)	HSC (m)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario									
0.012	0.1	1.25	0.5	100	156	3	60	365	0.001

2.2.1.6 Operator dermal exposure during application, washing and maintenance – Outdoor Space Spray

The estimated time weighted average (TWA) systemic dose from Broflanilide to operators due to potential dermal exposure from outdoor application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{VLH \times C_{Spray} \times PPE \times EF \times ABS_D}{(BW \times AT)}$$

Table 7. Estimated Long Term Systemic Dose (TWA) to Operator from Dermal Exposure during outdoor application, washing and maintenance

VLH (mL/day)	C_{SPRAY} (mg AI/mL)	PPE	EF (days)	Abs_D (%)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario							
1.64	10.8	0.1	156	5	60	365	0.630

2.2.1.7 Operator dermal exposure during mixing and loading – Vehicle Mounted

OPTICA ULV is applied undiluted and the container is attached to a spray nozzle. Therefore, there is no dermal exposure during vehicle-mounted mixing and loading.

2.2.1.8 Operator dermal exposure during application, washing and maintenance – Vehicle Mounted

The estimated time weighted average (TWA) systemic dose from Broflanilide to operators due to potential dermal exposure during vehicle mounted application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{VLH \times C_{Spray} \times PPE \times EF \times ABS_D \times 1000}{(BW \times AT)}$$

Table 8. Estimated Long Term Systemic Dose (TWA) to Operator from Dermal Exposure during outdoor application, washing and maintenance

VLH (mL/day)	C_{SPRAY} (mg AI/mL)	PPE	EF (days)	Abs_D (%)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario							
1.64	10.8	0.1	156	5	60	365	0.630

2.2.2 Bystanders or Residential Exposure

2.2.2.1 Inhalation Exposure – Outdoor Space Spray

The estimated time weighted average (TWA) systemic dose from Broflanilide to bystanders or residents due to potential inhalation exposure is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{TAR \times BV \times ED \times EF \times ABS_P \times 1000}{(HSC \times BW \times AT)}$$

Table 9. Estimated Long Term Systemic Dose (TWA) to Bystanders/Residents from Inhalation Exposure during application

Population	TAR (mg AI/m³)	BV (m³/hr)	ED (hr)	EF (days)	ABS_P (%)	HSC (m)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
TWA scenario									
Adults	0.012	1.25	0.25	15	100	3	60	365	0.0008
Children	0.012	1.32	0.25	15	100	3	23.8	365	0.002
Toddlers	0.012	1.26	0.25	15	100	3	10	365	0.005
Infants	0.012	0.84	0.25	15	100	3	8	365	0.004

2.2.2.2 Dermal Exposure from Touching Contaminated Surfaces

The estimated time weighted average (TWA) systemic dose from Broflanilide to bystanders or residents due to potential dermal exposure from touching of contaminated surfaces is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{C_{sur} \times Trans \times ESA \times EF \times ABS_D \times 1000}{BW \times AT}$$

Table 10. Estimated Long Term Systemic Dose (TWA) to Bystanders/Residents from Dermal Exposure (touching contaminated surfaces – walls, floors, furnitures, etc.)								
Population	**C_{SUR} (mg/m³)**	**Transl (%)**	**ESA (m²)**	**EF (days)**	**Abs_D (%)**	**BW (kg)**	**AT (days)**	**Systemic dose (µg/kg/day)**
TWA scenario								
Adults	0.15	8	0.308	15	5	60	365	0.0001
Children	0.15	8	0.153	15	5	23.9	365	0.0002
Toddlers	0.15	8	0.133	15	5	10	365	0.0003
Infants	0.15	8	0.394	15	5	8	365	0.0012

2.2.2.3 Oral Exposure from Consuming Contaminated Foodstuff

The estimated time weighted average (TWA) systemic dose from Broflanilide to bystanders or residents due to potential oral exposure from ingestion of contaminated foodstuff is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{0.5 \times C_{sur} \times \text{Transl} \times \text{SAF} \times Abs_O \times \text{EF}}{(\text{BW} \times \text{AT})}$$

Table 11. Estimated Long Term Systemic Dose (TWA) to Bystanders/Residents from Oral Exposure (Ingestion of contaminated foodstuff)								
Population	**C_{SUR} (mg/m³)**	**Transl (%)**	**SAF (m²)**	**EF (days)**	**Abs_O (%)**	**BW (kg)**	**AT (days)**	**Systemic dose (µg/kg/day)**
TWA scenario								
Adults	0.15	8	0.0169	15	100	60	365	0.00007
Children	0.15	8	0.0126	15	100	23.9	365	0.00013
Toddlers	0.15	8	0.0124	15	100	10	365	0.00031
Infants	0.15	8	0.0105	15	100	8	365	0.00032

2.2.2.4 Oral Exposure – Toddler Exposure from Hand-to-Mouth Activities

The estimated time weighted average (TWA) systemic dose from Broflanilide to toddler residents due to potential oral exposure from hand to mouth activities is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{C_{sur} \times \text{Transl} \times \text{ESA} \times F_{HM} \times F_{EXS} \times Abs_O \times \text{EF}}{(\text{BW} \times \text{AT})}$$

Table 12. Estimated Long Term Systemic Dose (TWA) to Toddler Residents Oral Exposure from Hand to Mouth Activities									
C_{SUR} (mg AI/m²)	**Transl (%)**	**ESA mg/m²**	**F_{HM}**	**F_{EXS}**	**Abs_O**	**EF (days)**	**BW (kg)**	**AT (days)**	**Systemic dose (µg/kg/day)**
Guideline scenario									
0.15	8	0.023	0.164	0.57	100	15	10	365	0.01

2.2.3 Exposure Via Breastmilk

There is no data on excretion of Broflanilide in milk, therefore, the defaults and algorithms presented in the GRAM (2018) guidance are used. Newborns might be exposed to Broflanilide through breast milk of lactating mother. The estimated systemic dose to the newborn is calculated based on the estimated systemic dose to the mother through residential exposure under the guideline scenario. The scenario of nursing/lactating mothers working as resident-operator is not recommended or recognized by WHO.

$$\text{Sys-D}_{TWA} = \frac{\text{Sol C} \times \text{Dose}_{Mbw} \times T½ \times \text{IR} \times \text{Abs}_o}{\text{BW}}$$

Table 13. Estimated systemic dose from exposure to breast milk (residential exposure)

Population	SolC	DoseMbw (µg/kg bw)	$T_{1/2}$ (days)	IR (kg/day)	Abs-O (%)	BW (kg)	Systemic dose (µg/kg/day)
TWA							
Newborns	0.361	0.001	2	0.53	100	4.2	0.091
Infants	0.361	0.001	2	0.68	100	8	0.061

2.2.4 Total Exposure Assessment

2.2.4.1 Total Operator Exposure

Exposure to operators occurs during indoor and outdoor spraying of the insecticide. Exposure via the dermal route may occur during washing and maintenance of equipment and via the inhalation route during application. Operators are assumed to follow WHO guidance for spray procedures and to wear PPE and a respirator, providing a reduction factor of 0.1 (i.e., 10%) referred to as "guideline scenario"

The estimated long-term [time-weighted average (TWA)] estimated systemic doses for operators are presented in the following tables.

2.2.4.1.1 Indoor – Total Operator Exposure – Handheld Sprayer

Table 14. INDOOR - OPERATOR – HANDHELD - Estimated LONG TERM (TWA) Systemic Dose.

Scenario	Dermal exposure		Inhalation exposure	Estimated systemic dose (µg/kg/day)
	Mixing/Loading (µg/kg/day)	Application/Washing/ Maintenance (µg/kg/day)	Application (µg/kg/day)	
Estimated TWA				
Guideline	N/A	0.630	0.320	0.950

OPTICA ULV is applied undiluted – no mixing and loading activities

2.2.4.1.2 *Outdoor – Total Operator Exposure – Handheld Sprayer*

Table 15. OUTDOOR - OPERATOR – HANDHELD - Estimated LONG TERM (TWA) Systemic Dose.				
Scenario	**Dermal exposure**		**Inhalation exposure**	**Estimated systemic dose (µg/kg/day)**
	Mixing/Loading (µg/kg/day)	**Application/Washing/ Maintenance (µg/kg/day)**	**Application (µg/kg/day)**	
Estimated TWA				
Guideline	N/A	0.630	0.001	0.631

OPTICA ULV is applied undiluted – no mixing and loading activities

2.2.4.1.3 *Outdoor – Total Operator Exposure – Vehicle Mounted*

Table 16. OUTDOOR - OPERATOR – Vehicle Mounted - Estimated LONG TERM (TWA) Systemic Dose.				
Scenario	**Dermal exposure**		**Inhalation exposure**	**Estimated systemic dose (µg/kg/day)**
	Mixing/Loading (µg/kg/day)	**Washing/Maintenance (µg/kg/day)**	**Application/Spraying (µg/kg/day)**	
Estimated TWA				
Guideline	N/A	0.630	N/A	0.630

OPTICA ULV is applied undiluted – no mixing and loading activities, Operator in closed cabin

2.2.4.2 Total Residential Exposure

Residents may be exposed to OPTICA ULV via dermal, inhalation and oral routes.

Dermal exposure may result from contact with directly sprayed walls and sometimes from furniture, shelves and floors sprayed inadvertently. Dermal exposure is also assumed to result from dermal exposure to spray residues dislodging from furniture, shelves and floors on which they were deposited (having settled following spraying – surfaces are not intentionally sprayed).

Oral exposure to toddlers can occur from ingestion of contaminated foodstuff and house dust (insecticides loosen from walls) as well as from hand-to-mouth activity (put objects in their mouth). The sprayed insecticide may be translodged to food items, and also be lost from walls, ending up in house dust and leading to ingestion by toddlers. Mother's milk may be a source of exposure to infants and newborns.

Residents are instructed not to enter houses during or immediately after spraying; it is therefore assumed that they are not exposed via inhalation to space spraying indoors and that residential exposure via inhalation is limited to outdoor applications (bystander).

The estimated long-term TWA estimated systemic doses from residential and bystander exposure are presented in the following table.

Table 17. Estimated total residential systemic dose from dermal, oral, hand-to-mouth, and breast milk exposure						
Population	**Dermal exposure (Contaminated Surfaces) (µg/kg/day)**	**Oral exposure from ingestion of contaminated food stuff (µg/kg/day)**	**Inhalation exposure: Bystanders or Residents (µg/kg/day)**	**Oral Exposure from Hand to mouth (µg/kg/day)**	**Breast Milk Exposure (µg/kg/day)**	**Estimated systemic dose (ug/kg bw/day)**
TWA scenario						
Adults	0.0001	0.00007	0.0008	N/A	N/A	0.001
Children	0.0002	0.00013	0.002	N/A	N/A	0.0023
Toddlers	0.0003	0.00031	0.005	0.0001	N/A	0.0057
Infants	0.0012	0.00032	0.004	N/A	0.061	0.0665
Newborn	N/A	N/A	N/A	N/A	0.091	0.091

N/A = Lack of exposure to the concerned population

2.2.4.3 Combined Resident-Operator Total Exposure

This represents the worst-case scenario for a resident who also works as a spray operator.

Combined Exposure = Total Operator Exposure + Total Residential exposure

Table 18. Combined exposure for resident operator			
Application Type	**Total operator exposure (µg/kg/day)**	**Total residential exposure (adult) (µg/kg/day)**	**Total combined exposure (µg/kg/day)**
TWA exposure – guideline			
Indoor Handheld	0.950	0.001	0.951
Outdoor Handheld	0.631	0.001	0.632
Outdoor Vehicle Mounted	0.630	0.001	0.631

2.3 Risk characterization

The purpose of risk characterization is to examine the probability of adverse effects occurring from 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 TSD established in the hazard assessment. The TSD is the same as the ADI or the cRfD established for the active ingredients (WHO, 2018).

$$\text{Ratio} = \frac{\text{Estimated Long Term (TWA(systemic dose (µg/kg bw/day)}}{\text{TSD (µg/kg bw/day)}}$$

When the ratios are less than 1, the health risk is deemed acceptable. Ratios greater than 1 may indicate 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, 2018). The Tolerable Estimated Systemic Doses (TSD) for Broflanilide is:

TSD = 0.03 mg/kg bw/day = 30 µg/kg bw/day

The long-term (TWA) exposure estimates are compared to the steady state/chronic TSD and are presented in the following tables.

2.3.1 Risk Estimates for Operator and Operator/Resident (Adult) – Guideline Scenario

Table 19. Risk characterization for Operators and Aggregate Operator-Resident (adult) Exposure

Activities	Operator exposure (dermal, oral, inhalation) (µg/kg bw/day)	TSD (µg/kg bw/day)	Risk ratio
Total operator exposure – TWA scenario			
Indoor Hand-Held Spray	0.950	30	0.031
Outdoor Hand-Held Spray	0.631	30	0.021
Vehicle Mounted Sprayer	0.630	30	0.021
Total operator/residential exposure – TWA scenario			
Indoor Hand-Held Spray	0.951	30	0.031
Outdoor Hand-Held Spray	0.632	30	0.021
Vehicle Mounted Sprayer	0.631	30	0.021

2.3.2 Risk Estimates for Residents/Bystanders

Table 20. Risk characterization for all Resident/Bystander Exposure

Population	Resident/Bystander exposure (dermal, oral, inhalation) (µg/kg bw/day)	TSD (µg/kg bw/day)	Risk ratio
Total exposure – TWA scenario			
Adult	0.001	30	0.00003
Children	0.0023	30	0.00007
Toddler	0.0057	30	0.00019
Infant	0.0665	30	0.00221
Newborns	0.091*	30	0.00303

**breast milk exposure only*

For operators' exposure activities (indoor, outdoor, and vehicle mounted), under the guideline scenario where workers wear appropriate personal protective equipment (PPE) the risk ratios are all below 1.

For residential exposure scenario (dermal exposure through touching contaminated surfaces, oral exposure through ingestion of contaminated food stuff and toddler hand-to-mouth, and inhalation exposure), the risk ratios are below 1 for all populations of concern.

For resident operators, the risk ratios are all below 1.

For the potential exposure via breast milk of mother as resident, the risk ratio is below 1.

2.4 Environmental Safety Assessment

Environmental risk assessment is complex and multifaceted. Regional and national guidelines should be considered in assessing environmental risk as there is no globally established system for environmental risk assessment.

Applicators are instructed to follow manufacturer's label directions for Optica ULV to mitigate impacts to non-target species and environmental exposure including:

- Avoiding application to blooming harvest at flower or when bees are visiting as the product is highly toxic to bees exposed to direct treatment
- Ensuring appropriate storage and disposal or spray mixture or rinse water
- Considering mosquito activity patterns and weather conditions when applying outdoors
- Appropriately adjusting equipment flow rate according to vehicle speed and wind

Please refer to the GRAM (2018) which includes environmental risk assessment models intended for first-tier risk assessment using case-specific values relevant to the geographical area of intended application area.

2.5 Conclusions

The use of OPTICA ULV formulated as liquid containing 1% (w/w) broflanilide to be used as an ultra-low volume non-thermal cold aerosol mist as an indoor and outdoor space spray in the course of vector control does not present any unacceptable risk for operators, residents, residents working as operators, or to children, toddlers, infants, or newborns exposed through breastmilk. Therefore, it can be concluded that Optica ULV can be used safely for its intended purpose. Assessment of the submitted information supports the prequalification of this product.

3 References

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4 Appendices

4.1 Appendix A. Toxicity profile: Broflanilide technical

Table A1 Acute toxicity of broflanilide technical

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	LD_{50} > 5000 mg/kg	5	USEPA, 2020
Acute dermal toxicity	Rat	LD_{50} > 5000 mg/kg	5	USEPA, 2020
Acute Inhalation	Rat	LC_{50} > 2.20 mg/L	Not classified	USEPA, 2020
Dermal irritation	Rabbit	Non-irritant	Not classified	USEPA, 2020
Eye irritation	Rabbit	Non-irritant	Not classified	USEPA, 2020
Skin sensitization, LLNA	Mouse	Non-sensitizer	Not classified	USEPA, 2020

Table A2. Summary of Subchronic, Chronic, and Carcinogenicity Studies with Broflanilide

Study dose levels	Results (mg/kg bw/day)	Reference
28-day dermal study, Wistar rats. Doses: 0, 100, 300, or 1000 mg/kg bw/day, 6 hours/day, 5 days/week for 4 weeks	Dermal and Systemic NOAEL = 1000 (HDT) No dermal or systemic toxicity	USEPA, 2020
4-week inhalation (nose only) study, Wistar rats Nominal conc: 30 mg/m^3, 200 mg/m^3 and 1000 mg/m^3 Actual conc: 0, 31, 193, and 940 mg/m^3	NOAEC = 31 mg/m^3 LOAEC = 193 mg/m^3 based on increased adrenal weight, increased incidence of ovary vacuolation, and increased incidence of adrenal vacuolation in both sexes	USEPA, 2020
90-day feeding study, mice. Doses: 0, 200, 1500 or 7000 ppm equivalent to 0, 26.3, 199.4, and 955.3 mg/kg bw/day for males and 0, 32.3, 229.8 and 1147.6mg/kg bw/day for females, respectively.	A NOAEL and LOAEL were not established since clinical chemistry was not performed	USEPA, 2020
90-day dietary oral toxicity, Wistar rats Doses: 0 ppm, 500 ppm, 1500 ppm, 5000 ppm and 15,000 ppm (equivalent to 0, 35, 104, 345, and 1109 mg/kg bw/day males and 0, 41, 126, 418, and 1239 mg/kg bw/day)	NOAEL not established. LOAEL = 500 ppm, corresponding to 35 mg/kg bw/day in males and 41 mg/kg bw/day in females based on increased absolute and relative adrenal weights, increased incidence of adrenal cortex vacuolation in both sexes, and increased adrenal cortex hypertrophy and vacuolation of ovarian interstitial cells noted in all treated female animals	USEPA, 2020
90-day dietary oral toxicity study, Wistar rats Single dose of 30 ppm in the diet, corresponding to 2.0 mg/kg bw/day in males and 2.2 mg/kg bw/day in females. This was a follow up study to the previous	NOAEL = 2.0 mg/kg bw/day (males) and 2.2 mg/kg bw/day (females)	USEPA, 2020

Table A2. Summary of Subchronic, Chronic, and Carcinogenicity Studies with Broflanilide		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
90-day study with the LOAEL established at the lowest concentration tested at 500 ppm		
90-day oral (capsule) study, Beagle dogs Doses: 0, 100, 300 and 1000 mg/kg bw/day	NOAEL = 1000 mg/kg bw/day LOAEL= not established	USEPA, 2020
Combined Chronic Toxicity Carcinogenicity Dietary Study in Wistar Rats 24 Months Doses: 0, 30, 100, 300, 1500 or 15000 ppm corresponding to: After one year: 0, 1.7, 5.7, 16, 84 and 822 mg/kg/day (M) 0, 2.1, 7.2, 20, 104, and 1128 mg/kg/day (F) After two years: 0, 4.5, 14, 70, or 709 mg/kg bw/day (males) 0, 5.9, 19, 95 or 953 mg/kg bw/day (females)	Male Systemic NOAEL = 4.5 mg/kg bw/day Male Systemic LOAEL = 14 mg/kg bw/day (increased adrenal weight; increased adrenal vacuolation) Female Systemic NOAEL = 2.1 mg/kg bw/day Female Systemic LOAEL = 7.2 mg/kg bw/day (increased incidence of ovarian interstitial gland vacuolation) There was treatment related increased incidence of Leydig cell adenomas in males, and luteomas and granulosa cell tumors in ovaries, and findings of uterine adenocarcinoma, adrenal cortex carcinomas, etc.	USEPA, 2020
78 Week Dietary Combined Chronic Carcinogenicity Study in CD-1 Mouse Doses: 0, 200, 1500 or 7000 ppm equivalent to 0, 21, 157 or 745 mg/kg bw/day (males) and 0, 22, 172 or 820 mg/kg bw/day (females)	Male systemic NOAEL = 745 mg/kg bw/day Male systemic LOAEL = not established Female systemic NOAEL = 172 mg/kg bw/day Female systemic LOAEL = 820 mg/kg bw/day (increased ovary and adrenal weight; etc.) No evidence of carcinogenic effect in both male and female mice	USEPA, 2020
1-year oral (capsule) study in Beagle dogs Doses: 0, 100, 300 and 1000 mg/kg bw/day	Systemic NOAEL = not established Systemic LOAEL = 100 mg/kg bw/day (increased adrenal weight; increased incidence of hypertrophy and vacuolation in the zona fasciculata)	USEPA, 2020

Table A3. Summary of Developmental Toxicity and Reproduction Studies with Broflanilide		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
Developmental Toxicity Study in Wistar Rats Oral Administration (Gavage). 0, 100, 300 and 1000 mg/kg/day	Maternal tox NOAEL = 1000 mg/kg bw/day (HDT) Developmental tox NOAEL = 1000 mg/kg bw/day Maternal tox LOAEL = not established Develop. tox LOAEL = not established	USEPA, 2020
Developmental Toxicity Study in New Zealand White Rabbits Oral Administration (Gavage). 0, 100, 300 and 1000 mg/kg/day	Maternal tox NOAEL = 1000 mg/kg bw/day (HDT) Developmental tox NOAEL = 1000 mg/kg bw/day Maternal tox LOAEL = not established Develop. tox LOAEL = not established	USEPA, 2020

Two Generation Reproduction Toxicity Study in Wistar Rats. Diet at 0, 30, 100, 300, 1 500 and 15 000 ppm corresponding to 0, 3, 8, 26, 127 or 1288 mg/kg bw/day	Parental systemic NOAEL = 3 mg/kg bw/day Parental systemic LOAEL = 8 mg/kg bw/day (increased adrenal weights with histopathologic findings) Reproductive NOAEL = 8 mg/kg bw/day Reproductive LOAEL = 26 mg/kg bw/day (increased ovary weight; increased incidence of vacuolation in interstitial gland of ovary) Offspring NOAEL = 26 mg/kg bw/day Offspring LOAEL = 127 mg/kg bw/day (decreased pup weights in F1 and F2 generations).	USEPA, 2020
Combined Reproduction and Developmental Toxicity Study, rats. (OECD 422)	The NOAEL was 15,000 ppm (983 mg/kg/day for males, and 1067 mg/kg/day for females). A LOAEL was not established. There were no treatment-related effects on gestational length, number of implantation sites, pup numbers, pup survival, body weight gain to Day 21 *post-partum*, physical development or functional tests. No treatment-related findings were seen in the weanling offspring at necropsy. There were no adverse effects of treatment on functional or behavioral development, nor any adverse effects of treatment on motor activity data.	JMPR,2022

Table A4. Summary of Genotoxicity Studies with Broflanilide

Study dose levels	Results	Reference
Bacterial reverse mutation assay, Ames Dose range: 33 to 10,000 ug/plate with and without metabolic activation	Negative in S. typhimurium and E. Coli	USEPA, 2020
In-vitro mammalian cell gene forward mutation in CHO cells Dose range: 39.1 to 5000 ug/ml with and without metabolic activation	Did not induce gene mutation at the HPRT locus in CHO cells	USEPA, 2020
In-vitro chromosomal aberration assay with Chinese hamster lung fibroblasts Dose range: 72 – 5000 ug/ml (-S9 mix); 72 to 1080 ug/ml (+S9 mix)	Negative in chromosomal aberration assay in presence and absence of metabolic activation	USEPA, 2020
In-vivo micronucleus assay – Bone marrow cells in mice Dose range: 0 – 2000 mg/kg/day	Negative in producing micronuclei in mice bone marrow – Not a clastogen	USEPA, 2020

Table A5. Summary of Neurotoxicity Studies with Broflanilide

Study dose levels	Results (mg/kg bw/day)	Reference

Acute neurotoxicity study Rat (Wistar,Crl:WI(Han)), 0, 200, 600 or 2000 mg/kg bw	No neurotoxic effects noted at 2000 mg/kg bw/day (HDT)	USEPA, 2020
Subchronic (90-day) neuro-toxicity study Rat (Wistar, Crl:WI(Han)), 0, 1 500, 5 000 and 15 000 ppm	NOAEL = 1041 mg/kg bw/day (males) NOAEL = 1137 mg/kg bw/day (females)	USEPA, 2020

Table A6. Summary of ADME Studies with Broflanilide

Study dose levels	Results (mg/kg bw/day)	Reference
Dermal penetration Rat (Wistar Crl) Applied as a dilution of a liquid formulation Achieved average dose (mg/kg b.w.) Group I: 0.18; Group II: 1.96; Group III: 19.38 Purity: 95.49%	Dermal absorption 10-hours after administration of test material was 55.4% of the applied dose in animals dosed w/49.2 ug/10.8 sq. cm (4.6 ug/sq. cm)	USEPA, 2020
Absorption study, Rats (male and female) Doses: from 2 to 500 mg/kg bw	In absorption study in rats, from 68 to 87% was eliminated in the first 48 hours. The total absorption was 14-19% dose at the 5 mg/kg dose level and 2% dose at the 500 mg/kg dose level. Following daily oral doses, unchanged Broflanilide was identified as the major component in fecal extracts, accounting for 52.9-75.0% of dose during the first 24 hours. The half-life is in the range of 2-3 days.	USEPA, 2020

4.2 Appendix B. Hazard assessment Broflanilide (CAS No. 2061933-85-3)

1 Introduction to Broflanilide

The use of vector control products (VCPs) is critical in the protection of global human health by combatting and preventing the transmission of major vector-borne diseases. Through the procedures of Prequalification Unit Vector Control Product Assessment Team (PQT/VCP), VCPs and public health pesticide active ingredients are assessed to determine that they can be used safely and effectively and are manufactured to a high-quality standard. The intent of the hazard assessment of each active ingredient (AI) is to consolidate the relevant toxicological information and authoritative evaluations from national and/or international organizations and characterize the chemical as it relates to uses of VCPs. PQT/VCP relies these authoritative evaluations, focusing on the studies and endpoints applicable to the safety assessment of the use patterns of VCPs. As such, this hazard assessment is not exhaustive in its summary or assessment of publicly available information characterizing the hazard of the AI.

Chemically, Broflanilide (CAS No. 1207727-04-5) is a meta-diamides insecticide developed by Mitsui Chemicals Crop & Life Solutions, Inc., Japan under co-development with BASF Corporation, Germany. Broflanilide produces an insecticidal effect by binding to the gamma aminobutyric acid (GABA) receptor, thereby inhibiting the neurotransmission in insects. It is registered with the United States Environmental Protection Agency (USEPA) for uses on corn, seeds, grains, agricultural crops and for control of a broad range of soil-dwelling insects (USEPA, 2020).

There is sufficient information on the toxicity of the active ingredient, Broflanilide technical, to conduct a human health hazard assessment. Administration of Broflanilide to rats and mice by the oral route resulted in increases in organ weight and histopathological findings. The principal target organ in all studies and in all species was the adrenal gland, with the rat being the most sensitive species. In the rat, after chronic administration there were treatment-related increases in Leydig cell adenomas noted in males at all doses tested; in luteomas and granuloma cell tumors in the ovaries; uterine adenocarcinomas, and adrenal cortex carcinomas in females. No oncogenic potential was found in mice. Exposure to Broflanilide did not result in developmental toxicity in rats and rabbits and reproductive toxicity in rats. There is no evidence to suggest that Broflanilide is mutagenic or clastogenic. No neurotoxic or immunotoxic effects were found in studies with Broflanilide.

Based on the existing toxicity database, Points of Departure (PODs) based on the most sensitive endpoints can be established for Broflanilide. The PODs and toxicological endpoints of concern selected for risk assessment are considered protective of any potential adverse effects, including chronic toxicity, neurotoxicity, developmental, reproductive, and immunotoxicity for all populations including infants and children.

2 Hazard Characterization

Only studies relevant to the hazard evaluation are discussed, for a full description of all toxicology studies related to the active ingredient, the reader is referred to the references cited. There is sufficient

information on the toxicity of the active ingredient, broflanilide technical, to conduct a human health hazard assessment.

2.1 Acute Toxicity

All acute toxicity studies with Broflanilide were conducted following OECD or EPA guidelines and GLP (Good Laboratory Practice) regulations. Broflanilide is of low toxicity following acute exposure. The acute oral and dermal LD_{50} were greater than 5000 mg/kg bw when tested in female or male and female rat, respectively, under the experimental conditions employed (GHS Category V). Acute inhalation exposure was conducted for 4-hours nose-only in male and female rats. The combined LC_{50} value was above 2.20 mg/L, the highest attainable concentration in the study (GHS Category: Not Classified). Broflanilide was not a skin or eye irritant (GHS Category: Not Classified). Broflanilide was not a skin sensitizer in either the murine local lymph node assay in mice or the Magnusson and Kligman Maximization assay in guinea pigs.

2.2 Subchronic Toxicity

Dermal application of Broflanilide in 1% carboxy methyl cellulose to male and female Wistar rats at dose levels of 0, 100, 300, or 1000 mg/kg, bw/day for 6 hours/day, 5 days/week for 28-days did not result in any treatment-related findings on the skin or systemic effects up to the limit dose of 1000 mg/kg. The dermal and systemic NOAEL (No Observed Adverse Effect Level) was 1000 mg/kg bw/day (USEPA, 2020).

To evaluate the toxicity of Broflanilide via inhalation, groups of Wistar rats (10 sex/group) were exposed to Broflanilide by nose only exposure for 6 hours a day, 5 days per week for 4 weeks (20 exposures). The target concentrations were 30 mg/m³, 200 mg/m³ and 1000 mg/m³ as a dust aerosol. The actual concentrations were 0, 31, 193, and 940 mg/m^3 corresponding to 0, 0.031, 0.193 and 0.94 mg/L/6hours. A concurrent control group of ten male and ten female animals were exposed to fresh air. A concurrent control group of ten male and ten female animals were exposed to fresh air. A recovery group consisting of five males and five females in high concentration and control groups was exposed simultaneously with the main group animals and observed for an additional 4 weeks. There were no treatment-related adverse effects in animals exposed to 30 mg/m^3. Minimal regenerative hyperplasia of the bronchial epithelium and cellular debris in bronchial lumina were observed in the lungs of animals exposed to 200 and 1000 mg/m³. The NOAEC (No Observed Adverse Effect Concentration) was established at 31 mg/m³ (0.031 mg/L) and the LOAEC was 193 mg/m^3 (0.193 mg/L) based on increased adrenal weight, increased incidence of ovary vacuolation, and increased incidence of adrenal vacuolation in both sexes (USEPA, 2020).

In a 90-day feeding study, groups of 10 male and 10 female Crl:CD 1 (ICR) mice were fed diets containing. Broflanilide (purity, 99.51%) at 0, 200, 1500 or 7000 ppm equivalent to 0, 26.3, 199.4, and 955.3 mg/kg bw/day for males and 0, 32.3, 230, and 1148 mg/kg bw/day for females, respectively. Additionally, 4 male and 4 female mice from each group were assessed for the presence of Broflanilide and its primary metabolite (DM-8007) in plasma. A NOAEL and LOAEL were not established since clinical chemistry was not performed (USEPA, 2020).

In a 90-day oral toxicity study, Broflanilide (purity 99.58%) was administered to groups of Wistar (Crl:WI(Han) rats (10/sex/dose) in the diet at dose levels of 0 ppm, 500 ppm, 1500 ppm, 5000 ppm and 15,000 ppm (equivalent to 0, 35, 104, 345, and 1109 mg/kg bw/day males and 0, 41, 126, 418, and 1239 mg/kg bw/day females). Two additional groups of 10 rats/sex/dose were administered 0 and 15,000 ppm for 90-days and maintained for 4 additional weeks without access to Broflanilide to assess recovery.

There were no treatment related effects on clinical observation, mortality, functional observation battery, or motor activity assessment. In all treated male and female rats, there was an increase in adrenal cortex vacuolation. Interstitial gland vacuolation in the ovaries was found in all female treated groups. A NOAEL was not established, and the LOAEL was 500 ppm, corresponding to 35 mg/kg bw/day in males and 41 mg/kg bw/day in females based on increased absolute and relative adrenal weights, increased incidence of adrenal cortex vacuolation in both sexes, and increased adrenal cortex hypertrophy and vacuolation of ovarian interstitial cells noted in all treated female animals (USEPA, 2020).

In a 90-day oral toxicity study, 10 male and 10 female Wistar rats were exposed to a single dose of 30 ppm in the diet, corresponding to 2.0 mg/kg bw/day in males and 2.2 mg/kg bw/day in females. This was a follow up study to the previous 90-day study with the LOAEL established at the lowest concentration tested at 500 ppm. Under the conditions of this study, the NOAEL was established at 2.0 mg/kg bw/day and 2.2 mg/kg bw/day for male and female rats, respectively (USEPA, 2020).

Broflanilide was administered orally by capsule to groups of 5 male and 5 female beagle dogs at dose levels of 0, 100, 300 and 1000 mg/kg bw/day for 3 months. No treatment related adverse effects in clinical observations, body weight, clinical pathology and histopathology were reported at any of the treated levels. Under the conditions of the study, the NOAEL was 1000 mg/kg bw/day, and the LOAEL was not established in beagle dogs (USEPA, 2020).

2.3 Chronic Toxicity and Carcinogenicity

Broflanilide was administered orally by capsule to groups of 5 male and 5 female beagle dogs at dose levels of 0, 100, 300 and 1000 mg/kg body weight per day for 12 months. Increased adrenal weights and increased incidence of hypertrophy and vacuolation in the cortical cells of the zona fascicula were noted at 100 mg/kg bw/day. In females, there was a statistically significant decrease in body weight development and an increase in absolute neutrophil and total white blood cell counts at the 1000 mg/kg bw/day dose level. Under the conditions of the study, a NOAEL was not established, and the LOAEL was 100 mg/kg bw/day in male and female beagle dogs based on increased adrenal weight and increased incidence of hypertrophy and vacuolation in the zona fasciculata (USEPA, 2020).

In a rat combined chronic/carcinogenicity study, Broflanilide, purity 98.67%, was administered in the diet to Wistar [Crl:WI(Han)] rats (50/sex/dose) at doses of 0, 100, 300, 1500 or 15,000 ppm (equivalent 0, 4.5, 14, 70, and 709 mg/kg bw/day to males and 0, 5.9, 19, 95, and 953 mg/kg bw/day for females) for 104 weeks. An additional 10 Wistar rats/sex/dose (satellite group) were exposed in the diet at dose levels of 0, 30, 100, 300, 1500 or 15000 ppm (equivalent to 0, 1.7, 5.7, 16, 84, or 822 mg/kg bw/day in males and 0, 2.1, 7.2, 20, 104, or 1128 mg/kg bw/day in females) for a period of 1 year.

In the satellite groups (1-year duration), there were no compound related effects on mortality and clinical observations but alterations in blood chemistry were noted but not of toxicological significance. Increased in relative and absolute adrenal weights were observed in both sexes at 300 ppm and higher. Increased incidence of adrenal vacuolization was noted in both sexes at 300 ppm and higher. Increased incidence of interstitial gland vacuolation in the ovaries at 100 ppm and higher in females.

In the main groups, there were no compound related effects on mortality and clinical observations. Absolute and relative adrenal weights were increased in both males and females following Broflanilide administration at 300 ppm, and higher. Increased incidence of adrenal vacuolization was noted in both sexes at 300 ppm and higher. Increased incidence of interstitial gland vacuolation in the ovaries at 100

ppm and higher in females. Neoplastic lesions were observed in the testes of the male rats at 15,000 ppm. In the ovaries, benign granulosa cell tumors were statistically significantly increased at 1500 ppm. In the uterus, adenocarcinoma was statistically significantly increased at 15,000 ppm. The incidence of uterine glandular hyperplasia was statistically significantly increased at dietary levels of 300 ppm and 15,000 ppm, but not at 1500 ppm.

For males, the systemic NOAEL was 100 ppm (4.5 mg/kg bw/day) and the systemic LOAEL at 300 ppm (14 mg/kg bw/day) based on increased adrenal weight and increased incidence of adrenal vacuolation. For females, the systemic NOAEL was 30 ppm (2.1 mg/kg bw/day), and the systemic LOAEL was 100 ppm (7.2 mg/kg bw/day) based on increased incidence of ovarian interstitial gland vacuolation. There were treatment-related increases in Leydig cell adenomas noted in males; in luteomas and granuloma cell tumors in the ovaries; uterine adenocarcinomas, and adrenal cortex carcinomas in females. A treatment-related increase in the incidence of Leydig cell adenomas was observed at the highest dose of 15,000 ppm (equal to 953 mg/kg bw/day).

In an 18-month carcinogenicity study, groups of 51 male and 51 female Crl:CD-1 (ICR) mice were fed diets containing Broflanilide at dietary levels of 0, 200, 1500 or 7000 ppm for 78 weeks, equivalent to 0, 21, 157, and 745 mg/kg/day for males and 0, 22, 172, and 820 mg/kg/day for females, respectively. There were no treatment-related effects on mortality, clinical signs, body weight, food consumption, ophthalmology, urinalysis or hematological findings. There was no treatment related on neoplastic and non-neoplastic lesions at any dose in either sex. Under the conditions of this study, for males, the systemic NOAEL was established at 745 mg/kg bw/day; a LOAEL was not established. For females, the systemic NOAEL was established at 172 mg/kg bw/day and the LOAEL was 820 mg/kg bw/day based on increased adrenal and ovarian weights and slight increased incidence of ovarian cysts, adrenal hemopoiesis and inflammatory cell foci in the adrenal glands. . There was no evidence of carcinogenicity at any dose level in either sex.

2.4 Developmental toxicity

In a rat developmental study, Broflanilide was administered as an aqueous suspension to 25 time mated female Wistar rats per group by gavage at doses of 100, 300 and 1000 mg/kg bw/day on gestation days (GD) 6 through 19. The control group, consisting of 25 females, was dosed with the vehicle (1% aqueous carboxymethylcellulose suspension (1% CMC)) in parallel. A dose volume of 10 mL/kg body weight was used. There were no test substance-related adverse effects on dams, gestational parameters or fetal parameters including visceral and skeletal malformations and variations considered to be treatment related. The NOAELs for maternal toxicity and developmental toxicity were 1000 mg/kg bw/day. The LOAEL was not determined (USEPA, 2020).

In a rabbit developmental study, female New Zealand rabbits were artificially inseminated and treated with Broflanilide at dose levels of 0, 100, 300 or 1000 mg/kg bw/day by oral gavage from day 6 to 28 of gestation (GD 6-28). There were no effects on maternal reproductive parameters or signs of toxicity. There were no effects on fetal parameters or visceral and skeletal malformations and variations considered to be treatment related. Based upon this study, both maternal and developmental toxicity NOAEL were 1000 mg/kg bw/day (USEPA, 2020).

In a combined repeated dose/reproduction/developmental toxicity study designed according to OECD 422, no treatment-related effects were seen in male or female reproductive toxicity parameters. There were no treatment-related effects on gestational length, number of implantation sites, pup numbers,

pup survival, body weight gain to Day 21 *post-partum*, physical development or functional tests. No treatment-related findings were seen in the weanling offspring at necropsy. There were no adverse effects of treatment on functional or behavioral development, nor any adverse effects of treatment on motor activity data. For systemic toxicity, reproductive and developmental toxicity, the NOAEL was 15,000 ppm (983 mg/kg/day for males, and 1067 mg/kg/day for females). A LOAEL was not established.

2.5 Reproduction Toxicity

In a 2-generation reproductive toxicity study, Broflanilide, purity 98.67%, was administered to groups of 25 male and 25 female healthy young Wistar rats (F0 parental generation) in the diet at concentrations of 0, 30, 100, 300, 1500 and 15,000 ppm (equivalent to 0, 3, 8, 26, 127 and 1288 mg/kg bw/day in females). The parental systemic toxicity NOAEL was 3 mg/kg bw/day, and the LOAEL was established at 8 mg/kg bw/day based on increased adrenal weights with corroborative histopathologic findings with increased vacuolation and diffuse hypertrophy in the adrenal gland cortex in both sexes and both generations. For reproductive toxicity, the NOAEL was established at 8 mg/kg bw/day and the LOAEL was established at 26 mg/kg bw/day. For offspring toxicity, the NOAEL was established at 26 mg/kg bw/day and the LOAEL was established at 127 mg/kg bw/day based on decreased pup weight in F1 and F2 pups (USEPA, 2020).

2.6 Genotoxicity

In summary, over a range of standard test batteries, Broflanilide did not show any indication of genotoxicity *in vitro* or *in vivo*. All studies complied with USEPA and/or OECD testing guidelines and were fully GLP compliant.

Broflanilide tested with *Salmonella typhimurium* and *Escherichia coli* tester strains at concentrations up to and including the limit concentration of 10,000 µg/plate did not produce an increased number of reversions with or without S-9 metabolic activation. Broflanilide did not induce chromosome aberrations in an *in vitro* cytogenetic test using cultured Chinese hamster lung (CHL) cells at exposure levels up to and including 5000 µg/ml, with and without metabolic activation. In a Chinese hamster ovary (CHO) cells *in vitro* assay, Broflanilide was not mutagenic in the HPRT locus assay in the absence or the presence of metabolic activation. An *in vivo* bone marrow micronucleus test was performed with Broflanilide using male NMRI mice at dose levels up to and including the limit dose 2000 mg/kg bw. No increase in the mean frequency of micronucleated polychromatic erythrocytes was observed in the bone marrow of Broflanilide treated animals (USEPA, 2020).

2.7 Neurotoxicity

Acute and subchronic (90-day) neurotoxicity studies were conducted to assess the neurotoxicological potential of Broflanilide.

In an acute neurotoxicity study, male and female Wistar rats received a single oral administration of Broflanilide at dose levels of 200, 600 or 2000 mg/kg bw. There were no signs of neurotoxicity or systemic toxicity at any dose level. The neurotoxicity NOAEL was established at 2000 mg/kg bw and a LOAEL was not established (USEPA, 2020).

In a subchronic neurotoxicity study, male and female Wistar rats received Broflanilide in their diet at 0, 1500, 5000 or 15,000 ppm for 90-day. There was no indication of clinical (general clinical observation, FOB and motor activity) or neurohistopathologic effects. The neurotoxicity NOAEL was established at 15,000 ppm (equivalent to 1041 mg/kg bw/day and 1137 mg/kg bw/day in males and females, respectively); a LOAEL was not established (USEPA, 2020).

2.8 Absorption, Distribution, Metabolism, and Excretion (ADME)

Absorption, distribution, metabolism and elimination (ADME) studies on the product are not required by PQT/VCP, however ADME on the AI are considered and integrated into the hazard assessment.

2.8.1 Oral route studies

ADME studies were investigated in male and female rats with a series of metabolism studies. In absorption study in rats, from 68 to 87% was eliminated in the first 48 hours. The total absorption was 14-19% dose at the 5 mg/kg dose level and 2% dose at the 500 mg/kg dose level. Following daily oral doses, unchanged Broflanilide was identified as the major component in fecal extracts, accounting for 52.9-75.0% of dose during the first 24 hours. The half-life is in the range of 2-3 days. The default oral absorption of 100% was selected for risk assessment.

2.8.2 Dermal route studies

In an *in-vivo* dermal penetration study in male rats, the results indicated that 5.0% (low dose 1.25 $\mu g/cm^2$), 5.1% (mid-dose, 2.5 $\mu g/cm^2$) or 2.35 (high dose, 1000 $\mu g/cm^2$) of the applied radioactivity was absorbed after 120 hours. A dermal absorption of 5% was selected by the USEPA (2020) for risk assessment.

2.8.3 Inhalation route studies

Absorption via the inhalation route is assumed to be 100% that via the oral route. Due to the lack of a long-term inhalation study, oral exposure is used for risk assessment purposes.

3 Points of Departure (POD), Reference Doses (RfD), and Cancer Classification

3.1 Points of Departure

Points of departure (PODs) (No Observed Adverse Effect Level [NOAEL]; Benchmark Dose [BMD]) are determined from the toxicological database based on the most sensitive endpoints. Once PODs are developed, safety factors (SF) and uncertainty factors (UF) are used in conjunction with the PODs to derive a safe exposure level, generally referred to as reference dose (RfD) or acceptable daily intake (ADI).

3.2 Reference Doses

3.2.1 Acute Reference Dose (aRfD)

For Broflanilide, an acute RfD has not been established by regulatory agencies (USEPA, 2020; JMPR, 2022) since toxicological effects attributable to a single exposure were not identified in the toxicity data base including developmental toxicity studies in rats and rabbits. Therefore, PQT/VCP did not establish an aRfD for Broflanilide and no risk ratio is calculated for acute exposure.

aRfD: not established

3.2.2 Chronic Reference Dose (cRfD)

The USEPA (2020) selected the 2-generation reproductive toxicity study in rats with a NOAEL of 3 mg/kg bw/day and a LOAEL of 8 mg/kg bw/day based on increased adrenal weights with corroborative histopathological findings (increase vacuolation and diffuse hypertrophy in the adrenal gland cortex) in both sexes and both generations. This study is appropriate for the route of duration of exposure and for the population of concern. An uncertainty factor of 100X (10X for interspecies extrapolation and 10X for intraspecies variation) is applied.

cRfD = 3 mg/kg bw/day : 100 = 0.03 mg/kg bw/day

3.2.3 Acceptable Daily Intake (ADI)

JMPR (2022) established an ADI of 0.02 mg/kg bw, based on the LOAEL of 5.9 mg/kg bw/day in the two-year toxicity and carcinogenicity study in rats, and using an uncertainty factor of 100 for intra- and interspecies differences and an additional safety factor of 3 for using a LOAEL as the POD. This ADI is supported by the 90-day rat study NOAEL of 2.0 mg/kg bw/day, and the two-generation reproductive study with the parental NOAEL of 2.3 mg/kg bw/day (JMPR, 2022).

ADI = 0.02 mg/kg bw/day

3.3 Cancer Classification

The US EPA (2020) classified Broflanilide as “Likely to be Carcinogenic in Humans” based on Leydig cell tumors and all ovarian tumors combined (granuloma cell benign and malignant, luteomas, thecomas and sex cord stromal tumors). The linear slope factor (Q_1*) was calculated as 2.48 x 10^{-3} $(mg/kg\ bw/day)^{-1}$ based upon male rat testicular Leydig cell tumors.

JMPR (2022) concluded that Broflanilide is not carcinogenic in mice but is carcinogenic in rats based on increased incidence of ovarian tumors of sex cord stromal origin and uterus adenocarcinomas and an increase in the incidence of Leydig cell adenomas at 953 mg/kg bw/day. The Meeting also concluded that the upper bound of the ADI (0.02 mg/kg bw/day provides a margin of at least 4750 relative to the LOAEL (95 mg/kg bw/day) for the ovarian tumors observed in female rats.

4 References

GHS, 2017. United Nations Globally Harmonized System of Classification and Labelling of Chemicals

JMPR (Joint FAO/WHO Meeting on Pesticide Residues), Summary report of 2022 annual JMPR, October 2022. https://www.fao.org/3/cc4115en/cc4115en.pdf

MCAG/BASF, 2020. Broflanilide "Joint Meeting on Pesticide Residues" (JMPR), Monograph Mammalian Toxicology, 24 November 2020.

US EPA (United States Environmental Protection Agency), 2020. Broflanilide: New Active Ingredient Human Health Risk Assessment. Office of Chemical Safety and Pollution Prevention, memorandum dated October 27, 2020.

4.3 Appendix C. Exposure (guideline and lax scenarios) and risk characterization

In the guideline scenario, 0.1 is used for the personal protective equipment (PPE) coefficient. In the lax scenario, 1.0 is used for the PPE coefficient. The results for the lax scenario of the GRAM are provided for information only. WHO does not recommend any application of space spray insecticides without appropriate PPE.

Table C1. Risk characterization for all populations and exposure scenarios

Activity	Operator exposure (dermal and inhalation) (µg /kg bw/day)	TSD (µg /kg bw/day)	Risk ratio
Total operator exposure – guideline scenarios			
Indoor Hand-Held Spray	0.950	30	0.031
Outdoor Hand-Held Spray	0.631	30	0.021
Vehicle Mounted Sprayer	0.630	30	0.021
Total operator exposure – lax scenarios			
Indoor Hand-Held Spray	9.508	30	0.316
Outdoor Hand-Held Spray	6.325	30	0.210
Vehicle Mounted Sprayer	6.308	30	0.210
Population	**Residential exposure (dermal, oral, and inhalation) (µg /kg bw/day)**	**TSD (µg /kg bw/day)**	**Risk ratio**
Total resident exposure – TWA scenario			
Adult	0.001	30	0.00003
Children	0.0023	30	0.00007
Toddler	0.0057	30	0.00019
Infant	0.0665	30	0.00221
Activity	**Operator-resident (combined exposure) (µg /kg bw/day)**	**TSD (µg /kg bw/day)**	**Risk ratio**
Operator-resident (adult) exposure – guideline scenario			
Indoor Hand-Held Spray	0.951	30	0.031
Outdoor Hand-Held Spray	0.632	30	0.021
Vehicle Mounted Sprayer	0.631	30	0.021
Operator-resident (adult) exposure – lax scenario			
Indoor Hand-Held Spray	9.509	30	0.316
Outdoor Hand-Held Spray	6.326	30	0.210
Vehicle Mounted Sprayer	6.309	30	0.210
Population	**Breast milk exposure residential (µg /kg bw/day)**	**TSD (µg /kg bw/day)**	**Risk ratio**
Guideline scenarios			
Newborn - TWA	0.091	30	0.00303

4.4 Appendix D. Broflanilide Cancer Classification and Quantification

4.4.1 Evidence for Carcinogenicity

In a carcinogenicity study, Crl:CD-1 (ICR) mice (51/sex/dose) were fed diets containing broflanilide at concentrations of 0, 200, 1500 or 7000 ppm for 78 weeks. These concentrations were equivalent to 0, 21, 157, and 745 mg/kg bw/day for males and 0, 22, 172, and 820 mg/kg bw/day for females, respectively. There was no evidence of carcinogenicity in male or female mice.

In a combined chronic/carcinogenicity study, Wistar [Crl:WI(Han)] rats (50/sex/dose) were fed diets containing broflanilide at concentrations of 0, 100, 300, 1500 or 15,000 ppm for 104 weeks. These concentrations were equivalent to 0, 4.5, 14, 70 and 709 mg/kg bw/day for males and 0, 5.9, 19, 95, and 953 mg/kg bw/day for females, respectively.

In males, histopathology revealed non-neoplastic lesions characterized as Leydig cell multifocal hyperplasia at 1,500 and 15,000 ppm dose groups. Neoplastic lesions were limited to an increased incidence of Leydig cell benign adenoma only at the highest dose tested (15,000 ppm; 709 mg/kg bw/day). In females, non-neoplastic lesions were limited to uterine glandular hyperplasia at doses above 300 ppm. There was an increase in animals with benign and malignant ovarian tumors of sex cord stromal origins (granulosa cell tumors, luteomas and thecomas) at 1500 ppm (95 mg/kg bw/day) and 15,000 ppm (953 mg/kg bw/day). In addition, there was an increase in the incidence of uterine adenocarcinomas and adrenal cell carcinomas at 15,000 ppm.

4.4.2 Cancer Classification by Regulatory Agencies

USEPA: The USEPA classified broflanilide as “Likely to be Carcinogenic to Humans” based on Leydig cell tumors in male and ovarian tumors (granulosa cell benign and malignant, luteomas, thecomas and sex cord stromal tumors) in female rats in the chronic toxicity/carcinogenicity study and the lack of evidence for mutagenicity both *in vivo* and *in vitro* (USEPA, 2020).

JMPR: JMPR concluded that broflanilide is carcinogenic in rats based on increased incidence of Leydig cell adenomas and ovarian tumors of sex cord stromal origin and uterus adenocarcinomas. JMPR concluded that there was no evidence of mutagenicity (JMPR, 2022).

4.4.3 Assignment Of GHS Hazard Category for Carcinogens[1]

According to the *Globally harmonized system on classification and labelling of chemicals* carcinogen means a chemical substance or a mixture of chemical substances which induce cancer or increase its incidence. As shown in Table D1, substances and mixtures in this hazard class are assigned to one of two hazard categories. Category 1 has two subcategories.

Table D1. Carcinogenicity		
Category 1 **Known or Presumed Carcinogen**		**Category 2** **Suspected Carcinogen**
Subcategory1A	Subcategory 1B	

Known Human Carcinogen Based on human evidence	**Presumed Human Carcinogen** Based on demonstrated animal carcinogenicity	Limited evidence of human or animal carcinogenicity

[1][2]According to the GHS, chemicals are assigned to hazard categories based on strength of evidence for carcinogenicity and additional considerations (weight of evidence; WOE).
*"**The placing of a substance in Category 2 is done on the basis of** evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1. Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from **limited evidence of carcinogenicity in animal studies"*** (GHS Guide).

In accordance with the GHS classification scheme, the PQT/VCP determined that broflanilide would be classified under Category 2 (Suspected Carcinogen) because of limited evidence of carcinogenicity. Although three tumors were identified in the carcinogenicity rodent studies, Leydig cell, ovarian, and uterine carcinomas, these tumors were isolated to one species (rat), in some cases one dose (often near the limit dose), and as is the case with Leydig cell tumors (LCT), lacked robust human relevance. The following weight of evidence argument regarding the observed tumors substantiates the PQT/VCP determination.

The Leydig cell tumors (LCT) observed in male rats are not likely to pose a cancer hazard to humans based on the following considerations:

- In males, the observed Leydig cell tumors are benign with no progression to malignancy (i.e., there were no increases in carcinomas).
- Benign tumors were observed only at the highest dose tested (15,000 ppm or 709 mg/kg bw/day.
- In rodents (mice and rats), testicular Leydig cell adenomas result from the stimulation of the luteinizing hormone (LH). LH stimulates the growth and proliferation of Leydig cells in the rodents and to a lesser extent in humans. The reason for the increased susceptibility for LCT in rats results from quantitative and qualitative differences of Leydig cell response to LH stimuli. For example, rat Leydig cells contain >10-fold more LH receptors than humans, which causes greater sensitivity to slight changes in circulating cells (Katzung, 1995).
- In rats Leydig cell tumors (LCT) tend to be benign and occur late in two-year bioassay, with varying background incidences in the Sprague-Dawley (1-5%), Wistar (6%) and Fischer 344 (100%). In contrast, the incidence rate in humans of LCT is very low, only 0.4 per million (0.00004%) to 0.01% (Cook *et al,* 1999 and Mali *et al*. 2002).
- Because of the differences present between the human and the rat Leydig cells, non-genotoxic compounds that cause LCTs in rats have little relevance to humans (Clegg *et al*., 1997; Cook *et al*., 1999; Steinbach *et al*., 2015).

The degree of concern is minimal for the uterine adenocarcinoma and the adrenal cortical cell carcinomas, since they were observed only at the highest dose tested (15,000 ppm; 953 mg/kg bw/day) which is barely short of the limit dose of 1000 mg/kg bw/day.

The degree of concern is elevated in female rats for the ovarian tumors of sex cord origin observed at the 1500 ppm (95 mg/kg bw/day) and 15,000 ppm (953 mg/kg bw/day) since the increases at these

doses (12/50 at 1500 ppm and 13/50 at 15,000 ppm) reached statistical significance when compared[3] to the controls (4/50).

4.4.4 GRAM Guidance

Section 4.1.5 of the GRAM for Indoor and Outdoor Space Spraying of Insecticides provides guidance for *Insecticides not recommended for use in space spraying* (GRAM, 2018).

Compounds meeting the criteria of carcinogenicity, mutagenicity or reproductive toxicity categories 1A and 1B of the *Globally harmonized system of classification and labelling of chemicals* or GHS (UN, 2015) can be regarded as highly hazardous pesticides (HHPs) (JMPR, 2008).

Dose–response assessment is an essential part of hazard assessment for deriving health-based guidance values and for the assessment of risks. Different methods are available. The standard NOAEL approach can be regarded as a simplified form of dose–response analysis, identifying a dose assumed to be without appreciable adverse effects (GRAM, 2018).

However, it is generally considered that compounds that are both genotoxic and carcinogenic are particularly likely to exert effects at very low doses: even if studies indicate apparent NOAELs, these should not be used for risk characterization.

When setting tolerable systemic dose levels (TSDs) for non-cancer effects, critical NOAELs/LOAELs (or BMDs) are derived from acute or long-term toxicity studies. These values are then divided by uncertainty factors (UFs). Thus, a TSD can be derived from long-term oral toxicity studies (GRAM, 2018):

$$TSD = \frac{NOAEL/\ LOAEL/BMD}{UF}$$

A TSD is usually expressed in mg/kg body weight/day.

Typically, a 100-fold UF is used which includes a 10X for interspecies extrapolation and 10X for intraspecies variation. However, sometimes, the use of additional UFs is justified and can include the following:

- When LOAEL is used instead of NOAEL, an additional UF (e.g. 3 or 10) is usually incorporated.

- When a NOAEL from a sub-chronic study (in the absence of a chronic study) is used to derive a TSD for long-term exposure, an additional UF (e.g. 3–10) is usually incorporated to take account of the attendant uncertainties.

- **If the critical NOAEL relates to** serious, irreversible toxicity, such as developmental abnormalities or **cancer induced by a non-genotoxic mechanism**, especially if the dose–response is shallow.

• When there are exposed subgroups, which may be extra-sensitive to the effects of the compound (e.g. neonates because of the incompletely developed metabolism).

• If the database is limited.

On the other hand, if the NOAEL/LOAEL is derived from human data, the UF for interspecies differences need not be considered.

4.4.5 TSD_{cancer}

The GRAM does not provide guidance on assessing potential cancer risk resulting from exposure to pesticide chemicals indicating evidence of carcinogenicity in experimental animals.

Consequently, the following method will be used to derive a TSD for non-genotoxic cancer risk assessment when the pesticide is not considered highly hazardous (TSD_{cancer}).

When setting the TSD_{cancer}, the critical dose for cancer risk assessment will be the dose that did not cause a treatment-related and/or statistically significant increase in tumor incidence when compared to the concurrent controls. **This dose is defined as the non-tumorigenic dose. This dose will be used as the Point of Departure (POD) for lack of carcinogenic effects** along with the uncertainty factors (UFs). Thus, a TSD_{cancer} can be derived for cancer risk assessment.

In accordance with the GRAM, typically, a 100-fold UF is used for deriving TSD_{acute} and/or $TSD_{long\text{-}term}$ for calculating risk ratios for non-cancer.

In establishing the TSD_{cancer}, for pesticide chemicals that induce cancer by a non-genotoxic mechanism, PQT/VCP follows the guidance provided in the GRAM section of the UF:

A total uncertainty factor of 1000 will be used in deriving the TSD_{cancer}. The 1000 UF include, (beyond the conventional 100 UF for the interspecies and intraspecies), an additional 10x to the non-tumorigenic dose. The additional 10x UF is deemed appropriate because there is high level of confidence that the combination of the hazard and exposure assessments is adequately protective of any potential carcinogenic risk.

$$TSD_{cancer} = \frac{\text{Non-tumorigenic POD (mg/kg bw/day)}}{1000\ UF}$$

A TSD_{cancer} is usually expressed in mg/kg bw/day.

4.4.6 TSD_{cancer} for Broflanilide

Groups of Wistar [Crl:WI(Han)] rats (50/sex/dose) were fed diets containing broflanilide at 0, 4.5, 17, 70 and 709 mg/kg bw/day for males and 0, 5.9, 19, 95, and 953 mg/kg bw/day for females for 104 weeks.

In males, treatment-related LCT were seen only at a very high dose 709 mg/kg bw/day and as discussed above, the biological significance of this finding to humans is questionable. .

In females, treatment-related increases were seen in ovarian tumors at 95 mg/kg bw/day and 953 mg/kg bw/day dose groups as well as treatment-related tumors of the uterus and adrenals only at 953 mg/kg bw/day. Of these three tumor types, both USEPA and JMPR considered only the ovarian tumors

to be of significance in their conclusions on the carcinogenic potential of broflanilide (JMPR, 2022; USEPA, 2020a).

No treatment-related tumors were seen at 70 mg/kg bw/day in males and at 19 mg/kg bw/day in females.

Therefore, the non-tumorigenic dose (19 mg/kg bw/day) in female rats will be used as the POD along with a 1000-fold UF to derive the TSD_{cancer}.

$$TSD_{cancer} = \frac{19 \text{ mg/kg bw/day}}{1000 \text{ UF}} = \mathbf{0.019 \text{ mg/kg bw/day}}$$

4.4.7 Cancer Risk Characterization

Cancer risk characterization consists of the comparison of estimates of time-weighted average (TWA) exposure with TSD_{cancer} defined above for all relevant exposure situations and populations.

$$\text{Cancer Risk Ratio} = \frac{\text{Estimated TWA systemic dose (mg/kg bw/day)}}{TSD_{cancer} \text{ (mg/kg bw/day)}}$$

In calculating the cancer risk ratio, WHO/PQT is able to characterize potential cancer risk within the context of exposure scenarios defined in the exposure assessment for Optica ULV and consider mitigative measures, if needed. When cancer risk ratios are <1, this indicates that the risks associated with the use of the product, as assessed, are below levels of concern. Application of product- and chemical-specific data as well as model default values are used to inform the risk assessment.

The long-term (TWA) exposure estimates are compared to the TSD_{cancer} and are presented in the following tables.

4.4.7.1 Risk Estimates for Operator and Operator/Resident (Adult) – Guideline Scenario

Table D2. Risk characterization for Operators and Aggregate Operator-Resident (adult) Exposure

Activities	Operator exposure (dermal, oral, inhalation) (µg/kg bw/day)	TSD_{Cander} (µg/kg bw/day)	Cancer Risk ratio
Total operator exposure – TWA scenario			
Indoor Hand-Held Spray	0.950	19	0.05
Outdoor Hand-Held Spray	0.631	19	0.03
Vehicle Mounted Sprayer	0.630	19	0.03
Total operator/residential exposure – TWA scenario			
Indoor Hand-Held Spray	0.951	19	0.05
Outdoor Hand-Held Spray	0.632	19	0.03
Vehicle Mounted Sprayer	0.631	19	0.03

4.4.7.2 Risk Estimates for Residents/Bystanders

Table D3. Risk characterization for all Resident/Bystander Exposure			
Population	**Resident/Bystander exposure (dermal, oral, inhalation) (µg/kg bw/day)**	**TSD_{Cancer} (µg/kg bw/day)**	**Cancer Risk ratio**
Total exposure – TWA scenario			
Adult	0.001	19	0.00005
Children	0.0023	19	0.0001
Toddler	0.0057	19	0.0003
Infant	0.0665	19	0.0035
Newborns	0.091*	19	0.0048

*breast milk exposure only

For operators' exposure activities (indoor, outdoor, and vehicle mounted), under the guideline scenario where workers wear appropriate personal protective equipment (PPE) the cancer risk ratios are all below 1.
For residential exposure scenario (dermal exposure through touching contaminated surfaces, oral exposure through ingestion of contaminated food stuff and toddler hand-to-mouth, and inhalation exposure), the cancer risk ratios are below 1 for all populations of concern.

For resident operators, the cancer risk ratios are all below 1.

4.4.8 References

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