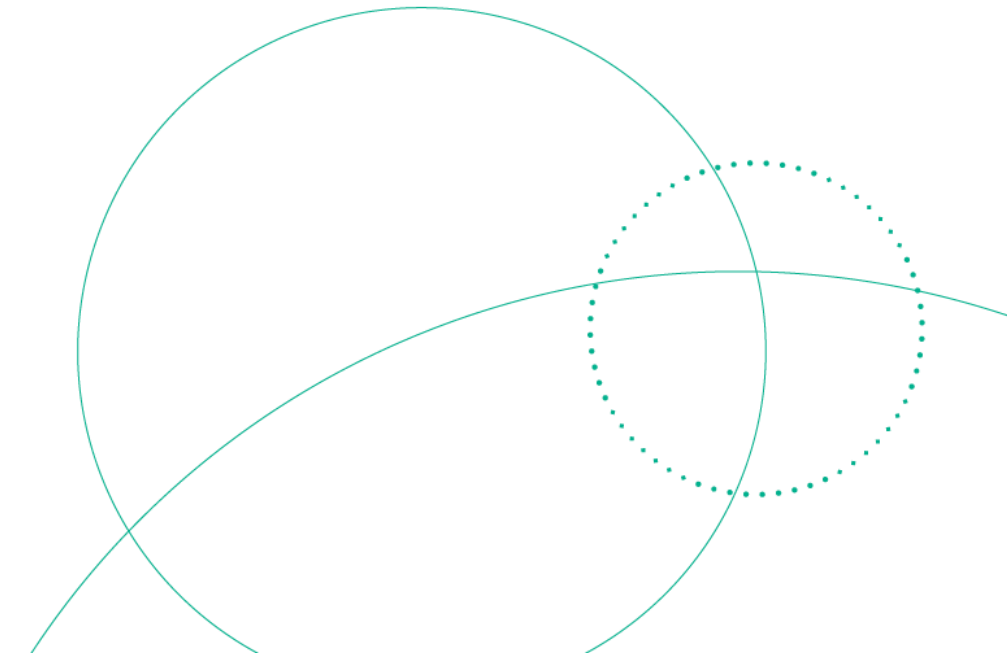
World Health Organization

WHO Prequalification Programme / Vector Control Product Assessment

WHO Public Assessment Report: WHOPAR Part 4

VECTRON T500 (Mitsui Chemicals Crop & Life Solutions, Inc.) P-03226

Safety Assessment



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1 Risk assessment summary

1.1 Introduction

The applicant, Mitsui Chemicals Agro, Inc. (Japan), submitted a product dossier to the WHO PQT/VCP containing supporting data for the proposed product VECTRON T500 for use as an Indoor Residual Spray (IRS). VECTRON T500 is a wettable powder (WP) packaged in 50g sachets. The active ingredient in VECTRON T500 is Broflanilide at 50% concentration.

1.2 Product identification

Product name:	VECTRON T500
Other names:	TENEBENAL 50 WP and Broflanilide 50% WP
Active ingredient:	Broflanilide
CAS no.:	1207727-04-5
Product type:	Indoor Residual Spray
Target application rate:	100 mg a.i./m^2
Spray concentration:	2.5 mg/ml
Volume applied:	40 ml/m^2

1.3 Active ingredient statement

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

1.4 Supporting data base

Acute toxicology studies with VECTRON T500 (Broflanilide 50 WP) were conducted at Biotoxtech Co. Ltd., Republic of Korea and Jeonbuk Branch Institute, KIT, KRICT, Republic of Korea, following OECD guidelines and GLP regulations. Under the United Nations Globally Harmonized System for Classification and Labelling of Chemicals (GHS, 2017), VECTRON T500 has low acute oral, dermal and inhalation toxicity (Category 5), is not an eye or skin irritant, and is not a skin sensitizer in mice and guinea pigs.

There is sufficient information on the toxicity of the active ingredient, Broflanilide technical, to conduct a human health hazard assessment and to assess the risks associated with the proposed uses of VECTRON T500.

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 children and infants.

This human health risk assessment has been completed based on the "*Generic Risk Assessment Model for Indoor Residual Spraying of Insecticides, 2nd Edition"* (GRAM) (WHO, 2018).

1.5 Discussion and conclusion

In this human health risk assessment, the estimated risk ratios for VECTRON T500 are based on the highest spray concentration of Broflanilide (maximum concentration 100 mg a.i./m^2).

The assessment supports the following conclusions:

- The existing toxicology database for VECTRON T500 and Broflanilide technincal is adequate for risk assessment and supports the proposed labelled uses of VECTRON T500 up to a concentration of 100 mg Broflanilide/m2.
- All risk ratios are less than 1, hence, do not exceed the level of concern.
- The use of Broflanilide formulated as wettable powder (50% WP) and used as an insecticide residual 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 breast milk.
- Therefore, the assessment of the submitted information supports the prequalification of the product VECTRON T500 for use as an indoor residual spraying insecticide.

2 Human health risk assessment

This human health risk assessment for VECTRON T500 is conducted according to the "*A Generic Risk Assessment Model for Indoor Residual Spraying of Insecticides, 2nd edition"* (GRAM) (WHO, 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 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).
2. **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.
3. In **risk characterization,** estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situation.

2.1 Hazard assessment

2.1.1 VECTRON T500

VECTRON T500 is practically non-toxic via the oral, dermal and inhalation routes of exposure. It is neither an eye nor a skin irritant and is not a dermal sensitizer. Acute studies were conducted at Biotoxtech Co. Ltd., Republic of Korea and Jeonbuk Branch Institute, KIT, KRICT, Republic of Korea, following OECD guidelines and GLP regulations. Acute toxicity studies conducted with VECTRON T500 are summarized in the following table.

Table 1. Acute toxicity of Broflanilide 50 WP

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat	$LD_{50} \geq 2000$ mg/kg bw	5	Biotoxtech J20066, 2020
Acute dermal toxicity	Rat	$LD_{50} \geq 2000$ mg/kg bw	5	Biotoxtech J20067, 2020
Primary dermal irritation	Rabbit	Not irritant	Not classified	Biotoxtech J20068, 2020
Primary Eye irritation	Rabbit	Slightly irritant/Reversible	Not classified	Biotoxtech J20069, 2020
Skin sensitization, Buehler	Guinea Pigs	Non-sensitizer	Not classified	Biotoxtech J20070, 2020
Skin sensitization, Local Lymph Node	Mouse	Non-sensitizer	Not classified	Biotoxtech J20071, 2020
Acute inhalation toxicity	Rat	$LC_{50} \geq 5$ mg/L/4 hours	5	KIT G220015, 2020

2.1.2 Active ingredient – Broflanilide

Broflanilide is a new active ingredient and toxicology studies have been evaluated by the US EPA (2020) and JMPR (2022). The US EPA has generated a human health hazard on Broflanilide (USEPA, 2020) and a

2022 annual summary report is available from JMPR (2022). The toxicity profile of Broflanilide is presented in Appendix 1. The complete Hazard Assessment of Broflanilide is presented in Appendix 2.

2.1.2.1 Acute studies

Broflanilide is of low toxicity following acute exposure. The acute oral and dermal LD_{50} are greater than 5000 mg/kg when tested in female or male and female rats, respectively, under the experimental conditions employed. 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. 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.

2.1.2.2 Sub-chronic studies

Subchronic toxicity studies on Broflanilide were conducted in 28- and 90-day oral route toxicity studies in rats, mice, and dogs. Additionally, 28-day repeat dose dermal exposure as well as 28-day repeat dose inhalation studies in rats were performed.

In summary, dermal application of Broflanilide to rats for 28 days did not result in overt signs of dermal or systemic toxicity. The dermal NOAEL was 1000 mg/kg bw/day. In a 4-week inhalation study in rats, the NOAEC was 31 mg/m^3 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). 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. A systemic NOAEL was established at 2.0 mg/kg bw/day and 2.2 mg/kg bw/day for male and female rats, respectively, after 90-days (USEPA, 2020). Under the conditions of a 90-day dog study, the NOAEL was 1000 mg/kg bw/day (highest dose tested), and the LOAEL was not established in beagle dogs (USEPA, 2020).

2.1.2.3 Chronic and carcinogenicity studies

Chronic studies with Broflanilide were conducted in rats, mice and dogs and carcinogenicity studies in rats and mice. In rats, there was evidence for carcinogenicity characterized as 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. For male rats, 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. In mice, there was no evidence of carcinogenicity at any dose level in either sex. The systemic NOAEL was established at 745 mg/kg bw/day for males and 172 mg/kg bw/day for female mice based on increased adrenal weight and slight increased incidence of ovarian cysts, adrenal hemopoiesis and inflammatory cell foci in the adrenal noted at 820 mg/kg bw/day (female systemic LOAEL). Broflanilide was given in capsules in the 1-year dog study at dose levels of 0, 100, 300 and 1000 mg/kg bw/day. The 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).

2.1.2.4 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.

2.1.2.5 Developmental toxicity

The developmental toxicity potential of Broflanilide was investigated in rats and rabbits. There were no developmental toxic effects noted in both species up to and including the highest guideline recommended dose of 1,000 mg/kg bw/day (USEPA, 2020).

2.1.2.6 Reproductive toxicity

In a 2-generation reproductive toxicity study, Broflanilide 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 (USEPA, 2020).

2.1.2.7 Neurotoxicity

Acute and subchronic (90-day) neurotoxicity studies were conducted to assess the neurotoxicological potential of Broflanilide. Broflanilide is not a neurotoxicant (USEPA, 2020).

2.1.2.8 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 (USEPA, 2020).

2.1.2.9 Immunotoxicity

In immunotoxicity studies, Broflanilide showed no signs of immunotoxicity when administered via the diet up to a concentration of 12,000 ppm over a period of 4 weeks to male Wistar rats (USEPA, 2020).

2.1.2.10 Absorption, distribution, metabolism, and excretion

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.

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 2.3% (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 (2020) for risk assessment.

2.1.3 Points of departure (POD) and reference doses (Rfd)

2.1.3.1 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).

2.1.3.2 Reference doses

Acute reference dose (aRfD)

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

aRfD: not established

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 to establish the cRfD.

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

Acceptable daily intake (ADI)

JMPR (2022) has established an acceptable daily intake at 0 – 0.02 mg/kg bw/day

ADI = 0.02 mg/kg bw/day

Dermal absorption factor

A POD was not selected for dermal risk assessment since there is no toxicological endpoint of concern. Based on an *in-vivo* dermal penetration study in male rats, a dermal absorption factor (DAF) is set up at 5% (USEPA, 2020).

2.1.3.3 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.

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

TSD = 0.03 mg/kg bw/day

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, 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 WHO-GRAM (second edition): "*Generic Risk Assessment Model for Indoor Residual Spraying of Insecticides" 2nd Edition (2018)*" and chemical-specific data. Exposure assessment includes operators mixing and loading, application of the insecticide product by spraying and washing and maintenance of the equipment, dermal exposure through contaminated surfaces, ingestion exposure from foodstuffs on surfaces, and exposure via breast milk. In the total exposure assessments, all relevant routes and different scenarios were summed up to derive the total systemic dose. Exposure is also assessed in a "lax standard scenario" (Appendix 3), 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 IRS without PPE.

VECTRON T500 is a mixture containing Broflanilide 50 WP (50%) and other ingredients (50%). VECTRON T500 is intended to be used for malaria control as an Indoor Residual Spray (IRS). The product is wettable powder (WP) packaged in 50 g sachets and will be applied exclusively on the inner walls of the houses/huts. The target dose of the product is 100 mg Broflanilide per m^2. This product should only be applied with the identified sprayers or those complying with WHO specifications fitted with a CFV that operates at 1.5 bar (~ 21 psi) and a flat fan type, 8002E nozzle. The volume applied per m^2 is 40 ml, hence the concentration of the spray solution is 2.5 mg a.i./ml (100 mg/m^2: 40 ml/m^2 = 2.5 mg a.i./ml).

The following abbreviations and default values are used throughout the exposure assessment:

Abs-D = Dermal absorption (5%, data derived)
Abs-P = Respiratory absorption (default = 100%)
Abs-O = Oral absorption (default = 100%)
AT = Average time (default = 365 days)
AV= Average proportion of spray residue on the wall during 6 months of first-order kinetics' decay with a half-time of 60 d (0.42)
BV = Breathing volume = 1.25 m3/hour
BW = Body weight (default = 60 kg/adult, 23.9 kg/children, 10 kg/toddlers)
C_{spray}= Concentration of the a.i in the spray in mg/ml (2.5 mg/ml)
CF= Concentration of formulation mg/ml (product label): 50% = 500 mg a.i./ml
Dose $_{Mbw}$=Daily dose to the mother (µg/kg bw/day)
ED = Exposure duration = 4 hours spraying per 8 hours working day
EF= Exposure frequency (6 days/week, 6 weeks per treatment round, 2 rounds/year=72 days/year)
ESA = Exposed skin areas
FHM = fraction of hand area mouthed (default = 0.164 – 75th percentile)
FEXS = Fraction extracted in saliva (default = 0.57)
IR=Ingestion rate of milk (default=0.66 kg/day)
ML= Amount of insecticide (a.i.) handled per day; default 12 loads per day, 10 L tank, concentration of the a.i. in the spray from the product label and dilution for spraying
NOD= Number of mixing operations per day (default=12)
PPE= Personal protective equipment.
Guideline scenario = 0.1 (90% protection); Lax standard scenario = 1 (no protection)
RPE = Respiratory protection = 0.1 for guideline scenario and 1.0 for lax standard scenario
SAF = Surface area of food in contact with the shelf (0.0169, 0.0126, 0.0124 and 0.0105 m2 for adults, children, toddlers, and infants, respectively). Half of food items are in contact with contaminated surfaces
Sol C = Solubility constant = 0.361 for lipid-soluble
SysD $_{TWA}$= TWA systemic dose (µg/kg bw/day)
SysD $_{MAX}$ = Maximal systemic dose (µg/kg bw/day)
TC_{WALL}= Target amount of the a.i. on the wall, 100 mg /m^2
Transl= Fraction translodged onto skin; default 8% of the amount on the surface
UE $_{SOL}$ = Unit exposure for handling wettable powder (default=9.7 mg/kg a.i.)
WS_{Dermal}=Volume of water on hands (default =166 ml/adult, 92 ml/children, 48 ml/toddlers, 41 ml/infants).
VS $_{dermal}$= volume of spray on hands = 8.2 ml

2.2.1 Occupational exposure

2.2.1.1 Operator exposure during mixing and loading of VECTRON T500

The estimated time weighted average (TWA) systemic dose from Broflanilide to operators due to potential dermal exposure from mixing and loading is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{UE_{SOL} \times PPE \times ML \times \text{Absorption (dermal)} \times EF \times 1000}{BW \times AT}$$

Table 2. Estimated long term systemic dose (TWA) to operator from dermal exposure during mixing and loading							
UE_{SOL} (mg/kg)	**PPE**	**ML**	**Dermal absorption (%)**	**EF (days)**	**BW (kg)**	**AT (days)**	**Systemic dose (µg/kg/day)**
Guideline scenario							
9.7	0.1	0.3	5	72	60.0	365	0.048

UE_{SOL}= 9.7 mg/kg a.i. handled for wettable powders
ML = 25 g a.i. diluted into 10 L spray tank; 12 tank loads per day; 25 g x 12 loads = 300 g or 0.3 kg
1000= mg to µg

The estimated maximal daily systemic dose to operators due to potential dermal exposure from mixing and loading is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{UE_{SOL} \times PPE \times ML \times \text{Absorption (dermal)} \times 1000}{BW}$$

Table 3. Estimated maximal daily systemic dose to operator from dermal exposure during mixing and loading					
UE_{SOL} (mg/kg)	**PPE**	**ML**	**Dermal absorption (%)**	**BW (kg)**	**Systemic dose (µg/kg/day)**
Guideline scenario					
9.7	0.1	0.3	5	60.0	0.243

UE_{SOL}= 9.7 mg/kg a.i. handled for wettable powders
ML = 25 g a.i. diluted into 10 L spray tank; 12 tank loads per day; 25 g x 12 loads = 300 g or 0.3 kg
1000= mg to µg

2.2.1.2 Operator exposure during application, washing, and maintenance

Dermal exposure

The estimated TWA systemic dose of Broflanilide to operators due to potential dermal exposure during application, washing and maintenance is calculated as follows:

$$\text{Systemic TWA dose} = \frac{VS_{dermal} \times C_{spray} \times PPE \times EF \times \text{Absorption (dermal)} \times 1000}{BW \times AT}$$

Table 4. Estimated long-term (TWA) systemic dose to operator from dermal exposure during application, washing, and maintenance							
VS_{dermal} (ml)	C_{Spray} (mg/ml)	PPE	EF (days)	Dermal absorption (%)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario							
8.2	2.5	0.1	72	5	60	365	0.337

VS_{dermal} = 8.2 ml
C_{spray} = Concentration of the active ingredient in the spray = 2.5 mg a.i./ml
1000= mg to µg

The estimated maximal systemic dose of Broflanilide to operators due to potential dermal exposure during application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{VS_{dermal} \times C_{spray} \times PPE \times Absorption\ (dermal)}{BW} \times 1000$$

Table 5. Estimated maximal systemic dose to operator from dermal exposure during application, washing, and maintenance					
VS_{dermal} (ml)	C_{Spray} (mg/ml)	PPE	Dermal absorption (%)	BW (kg)	Systemic dose (µg/kg/day)
Guideline scenario					
8.2	2.5	0.1	5	60	1.708

VS_{dermal} = 8.2 ml
C_{spray} = Concentration of the active ingredient in the spray = 2.5 mg a.i./ml
1000= mg to µg

Inhalation exposure

The estimated TWA systemic dose of Broflanilide to operators due to potential inhalation exposure during application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{10^{-3} \times TC_{WALL} \times RPE \times BV \times ED \times Abs\text{-}P \times EF}{BW \times AT} \times 1000$$

Table 6. Estimated long-term (TWA) systemic dose to operator from inhalation exposure during application, washing and maintenance								
TC_{WALL} (mg/m²)	RPE	BV (m³/hr)	ED (hours)	Abs-P (%)	EF (days)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario								
100	0.1	1.25	4	100	72	60	365	0.164

TC_{WALL} = Target concentration = 100 mg/m2
1000= mg to µg

The estimated maximal systemic dose of Broflanilide to operators due to potential inhalation exposure during application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{10^{-3} \times TC_{WALL} \times RPE \times BV \times ED \times Abs}{BW} \times 1000$$

Table 7. Estimated maximal systemic dose to operator from inhalation exposure during application, washing and maintenance						
TC_{WALL} (mg/m2)	**RPE**	**BV (m^3/hr)**	**ED (hours)**	**Abs-P (%)**	**BW (kg)**	**Systemic dose (µg/kg/day)**
Guideline scenario						
100	0.1	1.25	4	100	60	0.833

TC_{WALL} = Target concentration = 100 mg/m2
1000= mg to µg

2.2.1.3 Total operator exposure

Estimated total systemic exposure from dermal exposure from mixing and loading and from dermal and inhalation exposure from application, washing and maintenance.

Table 8. Estimated total operator exposure from dermal and inhalation exposure				
Scenario	**Dermal exposure**		**Inhalation exposure**	**Estimated systemic dose (µg/kg/day)**
	Mixing/Loading (µg/kg/day)	**Application/Washing/ Maintenance (µg/kg/day)**	**Application/Washing/ Maintenance (µg/kg/day)**	
Estimated TWA				
Guideline	0.048	0.337	0.164	0.549
Estimated maximal				
Guideline	0.243	1.708	0.833	2.784

2.2.2 Residential exposure

2.2.2.1 Dermal exposure due to touching of contaminated surfaces

The estimated TWA dermal exposure due to touching of contaminated surfaces is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{0.15 \times TC_{WALL} \times AV \times Transl \times ESA \times Abs\text{-}D \times 1000}{BW}$$

The estimated maximal dermal exposure due to touching of contaminated surfaces is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{0.15 \times TC_{WALL} \times Transl \times ESA \times Abs\text{-}D \times 1000}{BW}$$

Table 9. Estimated systemic dose from dermal exposure due to touching of contaminated surfaces							
Population	**TC_{WALL} (mg/m^2)**	**Transl (%)**	**AV**	**ESA (m^2)**	**Dermal absorption (%)**	**BW (kg)**	**Systemic dose (µg/kg/day)**
TWA scenario							
Adults	100	8	0.42	0.308	5	60	0.129
Children	100	8	0.42	0.153	5	23.9	0.161
Toddlers	100	8	0.42	0.133	5	10	0.334
Infants	100	8	0.42	0.394	5	8	1.242
Maximal scenario							
Adults	100	8	N/A	0.308	5	60	0.308
Children	100	8	N/A	0.153	5	23.9	0.384
Toddlers	100	8	N/A	0.133	5	10	0.796
Infants	100	8	N/A	0.394	5	8	2.957

AV = Average proportion of spray residue on the wall during 6 months of first order kinetic decay (default = 0.42)
Transl= Fraction translodged onto skin (default = 8%)
ESA = 0.308 m^2/adults; 0.153 m^2/child; 0.133 m^2 /toddlers and 0.394 m^2/infants.
1000= mg to µg

2.2.2.2 Ingestion exposure from contaminated foodstuffs

The estimated TWA exposure due to ingestion of contaminated foodstuffs from surfaces is calculated as follows:

$$\text{Sys-}D_{TWA} = \frac{0.30 \times 0.5 \times AV \times TC_{WALL} \times Transl \times SAF \times Abs\text{-}O \times 1000}{BW}$$

The estimated maximal exposure due to ingestion of contaminated foodstuffs from surfaces is calculated as follows:

$$\text{Sys-}D_{MAX} = \frac{0.30 \times 0.5 \times TC_{WALL} \times Transl \times SAF \times Abs\text{-}O \times 1000}{BW}$$

Table 10. Estimated ingestion exposure of contaminated foodstuffs from surfaces							
Population	**TC_{WALL} (mg/m^2)**	**AV**	**Transl (%)**	**SAF (m^2)**	**Abs-O (%)**	**BW (kg)**	**Systemic dose (µg/kg/day)**
TWA scenario							
Adults	100	0.42	8	0.0169	100	60	0.142
Children	100	0.42	8	0.0126	100	23.9	0.265
Toddlers	100	0.42	8	0.0124	100	10	0.625
Infants	100	0.42	8	0.0105	100	8	0.661
Maximal scenario							
Adults	100	N/A	8	0.0169	100	60	0.338
Children	100	N/A	8	0.0126	100	23.9	0.633
Toddlers	100	N/A	8	0.0124	100	10	1.489
Infants	100	N/A	8	0.0105	100	8	1.575

AV = Average proportion of spray residue on the wall during 6 months of first order kinetic decay (default = 0.42)
Transl = fraction translodgeable to foods (default = 8%) of amount present on surfaces
1000= mg to µg

2.2.2.3 Ingestion exposure of toddlers via hand-to-mouth behavior

The estimated TWA ingestion exposure of toddlers via hand to mouth behavior is calculated as follows:

$$\underline{SysD\text{-}_{TWA} = 0.15 \times AV \times TC_{WALL} \times Transl \times ESA \times F_{HM} \times F_{EXS} \times Abs\text{-}O} \times 1000$$
$$BW$$

The estimated maximal ingestion exposure of toddlers via hand to mouth behavior is calculated as follows:

$$\underline{SysD\text{-}_{MAX} = 0.15 \times TC_{WALL} \times Transl \times ESA \times F_{HM} \times F_{EXS} \times Abs\text{-}O} \times 1000$$
$$BW$$

Table 11. Estimated ingestion exposure of toddlers via hand-to-mouth behavior

Conc. on surface to wall target conc.	TC_{WALL} (mg/m^2)	AV	Transl (%)	ESA (m^2)	FHM	FEXS	Abs-O (%)	BW	Systemic dose (µg/kg/day)
TWA scenario									
0.15	100	0.42	8	0.023	0.164	0.57	100	10	0.108
Maximal scenario									
0.15	100	N/A	8	0.023	0.164	0.57	100	10	0.258

AV = Average proportion of spray residue on the wall during 6 months of first order kinetic decay (default = 0.42)
F_{HM} = fraction of hand area mouthed (default = 0.164 – 75th percentile)
F_{EXS} = Fraction extracted in saliva (default = 0.57)
BW = 10 kg (toddlers)
ESA = 0.023 m^2 /toddlers for hands
1000= mg to µg

2.2.2.4 Total residential exposure

Table 12. Estimated total residential systemic dose from dermal, ingestion, and hand-to-mouth exposure

Population	Dermal exposure (Contaminated Surfaces) (µg/kg/day)	Ingestion contaminated foods (from surfaces) (µg/kg/day)	Hand to mouth (µg/kg/day)	Estimated systemic dose (ug/kg bw/day)
TWA scenario				
Adults	0.129	0.142		0.271
Children	0.161	0.265		0.426
Toddlers	0.334	0.625	0.108	1.067
Infants	1.242	0.661		1.903
Maximal scenario				
Adults	0.308	0.338		0.646
Children	0.384	0.633		1.017
Toddlers	0.796	1.489	0.258	2.543
Infants	2.957	1.575		4.532

2.2.2.5 Combined exposure for resident operator

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

Combined Exposure = Total Operator Exposure + Total Residential exposure

Table 13. Combined exposure for resident operator			
Population	**Total operator exposure (µg/kg/day)**	**Total residential exposure (µg/kg/day)**	**Total combined exposure (µg/kg/day)**
TWA exposure – guideline			
Adult	0.549	0.271	0.820
Maximal daily dose – guideline			
Adult	2.784	0.646	3.430

2.2.3 Exposure via breast milk

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 post-spraying. WHO does not approve nor recognize a scenario where a nursing or lactating mother is working as an operator, therefore, this scenario has not been evaluated.

Estimates for systemic TWA and maximal doses from exposure via breast milk are calculated as follows:

$$\text{Systemic dose TWA} = \frac{\text{SolC} \times \text{Dose (mother)} \times T_{1/2} \times \text{IR} \times \text{Absorption}}{\text{BW}}$$

Table 14. Estimated systemic dose from exposure to breast milk (residential exposure)							
Population	**SolC**	**Dose (µg/kg bw)**	**$T_{1/2}$ (days)**	**IR (kg/day)**	**Oral absorption (%)**	**BW (kg)**	**Systemic dose (µg/kg/day)**
TWA							
Newborns	0.361	0.271	2	0.66	100	4.2	0.0307
Maximal daily dose							
Newborns	0.361	0.646	2	0.66	100	4.2	0.0733

Sol C = Solubility constant = 0.361 for water soluble
Dose = Daily dose to the mother ((residential exposure)
$T_{1/2}$= First order kinetics half-life of clothianidin, 2 day (JMPR, 2001)
IR= (default value=0.53 kg/day for the first month and 0.68 kg/day for the first 12 months

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).

$$\text{Ratio} = \frac{\text{Estimated maximal daily systemic dose (µg kg bw/day)}}{\text{TSD (µg kg bw/day)}}$$

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).

Table 15. Risk characterization for all populations and exposure scenarios

Population	Operator exposure (dermal and inhalation) (µg/kg bw/day)	TSD (µg/kg bw/day)	Risk ratio
Total operator exposure – TWA scenario			
Adult – guideline	0.549	30	0.02
Total operator exposure – maximal scenario			
Adult – guideline	2.784	30	0.09
Total operator/residential exposure – TWA scenario			
Adult – guideline	0.820	30	0.03
Adult – maximal	3.430	30	0.11
Population	**Residential exposure (dermal and foodstuffs) (µg/kg bw/day)**	**TSD (µg/kg bw/day)**	**Risk ratio**
Total exposure – TWA scenario			
Adult	0.271	30	0.01
Children	0.426	30	0.01
Toddler	1.067	30	0.04
Infant	1.903	30	0.06
Total exposure – maximal scenario			
Adult	0.646	30	0.02
Children	1.017	30	0.03
Toddler	2.543	30	0.08
Infant	4.532	30	0.15
TWA Total exposure – breast milk – residential			
Newborn	0.0307	30	0.001
Maximal daily dose – breast milk – residential			
Newborn	0.0733	30	0.002

For operators (mixing/loading/applying/maintenance), the risk ratios are all below 1.

For adult resident scenario (dermal exposure through surfaces and ingestion of foodstuffs), the risk ratios are below 1 for all populations of concern.

For resident operator, 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 Conclusions

The use of Broflanilide formulated as wettable powder (50% WP) and used as IRS 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.

3 References

Biotoxtech Co. No. J20066, 2020. Acute oral toxicity study of Broflanilide 50 WP in Sprague Dawley Rats (Acute Toxic Class Method).

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Biotoxtech Co. No. J20068, 2020. Acute skin irritation/corrosion study of Broflanilide 50 WP in New Zealand rabbits.

Biotoxtech Co. No. J20069, 2020. Acute eye irritation/corrosion study of Broflanilide 50 WP in New Zealand rabbits.

Biotoxtech Co. No. J20070, 2020. Skin sensitization study of Broflanilide 50 WP in Harley Guinea pigs (Buehler Test).

Biotoxtech Co. No. J20071, 2020. Skin sensitization test of Broflanilide 50 WP in CBA/J mice (local lymph node assay:BrdU-ELISA).

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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.

WHO, 2018. "*A Generic Risk Assessment Model for Indoor Residual Spraying of Insecticides, 2nd edition*" (GRAM).

4 Appendices

4.1 Appendix 1. 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
Skin sensitization, Maximization Test	Guinea Pig	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, rats	NOAEL = 1000 (HDT)	USEPA, 2020
4-week inhalation (nose only) study, rats Nominal conc: 30 mg/m³, 200 mg/m³ and 1000 mg/m³ Actual conc: 0, 31, 193, and 940 mg/m³	NOAEC = 31 mg/m³ LOAEC = 193 mg/m³ based on increased adrenal weight, increased incidence of ovary vacuolation, and increased incidence of adrenal vacuolation in both sexes	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	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, 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 90-day study with the LOAEL established at the lowest concentration tested at 500 ppm	NOAEL = 2.0 mg/kg bw/day (males) and 2.2 mg/kg bw/day (females)	USEPA, 2020
90-day oral (capsule) study, dogs Doses: 0, 100, 300 and 1000 mg/kg bw/day	NOAEL = 1000 mg/kg bw/day LOAEL= not established	USEPA, 2020

Table A2. Summary of subchronic, chronic, and carcinogenicity studies with Broflanilide		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
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 the 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 dog study (capsules) 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 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 (pulse exposure) and 5.47 to 700 ug/ml (continuous exposure	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 A4. Summary of developmental toxicity and reproductive studies with Broflanilide		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
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
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

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

4.2 Appendix 2. Hazard assessment

Executive summary

VECTRON T500 is an Indoor Residual Spray (IRS) product for the control of mosquitoes vectoring malaria manufactured by Mitsui Chemicals Agro, Inc. (Japan). Other synonyms include TENEBENAL™ 50 WP and Broflanilide 50% WP.

The active ingredient in VECTRON T500 is Broflanilide (CAS No. 1207727-04-5) at a concentration of 50%.

Acute toxicology studies with VECTRON T500 (Broflanilide 50 WP) were conducted at Biotoxtech Co. Ltd., Republic of Korea and Jeonbuk Branch Institute, KIT, KRICT, Republic of Korea, following OECD

guidelines and GLP regulations. Under the United Nations Globally Harmonized System for Classification and Labelling of Chemicals (GHS, 2017), VECTRON T500 has low acute oral, dermal and inhalation toxicity (Category 5), is slightly irritant to the eye but is not a skin irritant. It is not a skin sensitizer in mice and guinea pigs.

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.

I. Background information

The formulation VECTRON T500 is a mixture containing Broflanilide 50 WP (50%) and other ingredients (50%). VECTRON T500 is intended to be used for malaria control as Indoor Residual Spraying (IRS). The product is wettable powder (WP) packaged in 50 g sachets and will be applied exclusively on the inner walls of the houses/huts. The target dose of the product is 100 mg a.i. (Broflanilide) per m^2.

Chemically, Broflanilide (CAS No. 1207727-04-5) is a meta-diamides, isoxazolidines insecticide developed by Mitsui Chemicals Agro, 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).

II. Toxicity information on VECTRON T500 (Broflanilide 50% WP)

Mitsui Chemical Agro, Inc. (Japan) submitted seven acute toxicity studies conducted with Broflanilide 50 WP. All acute studies were conducted at Biotoxtech Co. Ltd., Republic of Korea, and Jeonbuk Branch Institute, KIT, KRICT, Republic of Korea, following OECD guidelines and GLP regulations. The results are summarized in Table A6.

Table A6. Acute toxicity of Broflanilide 50 WP				
Route of exposure	**Species**	**Toxicity**	**GHS category**	**Reference**
Acute oral toxicity	Rat	LD_{50} > 2000 mg/kg bw	5	Biotoxtech J20067, 2020
Acute dermal toxicity	Rat	LD_{50} > 2000 mg/kg bw	5	Biotoxtech J20067, 2020
Acute inhalation toxicity	Rat	LC_{50} > 5 mg/L/4 hours	5	KIT G220015, 2020
Primary dermal irritation	Rabbit	Not irritant	Not classified	Biotoxtech J20067, 2020
Primary eye irritation	Rabbit	Mild irritant/reversible	Not classified	Biotoxtech J20067, 2020
Skin sensitization, local lymph node	Mouse	Non-sensitizer	Not classified	Biotoxtech J20067, 2020
Skin sensitization, Buehler	Guinea Pigs	Non-sensitizer	Not classified	Biotoxtech J20067, 2020

Under GHS classification (2017), Broflanilide 50 WP is practically non-toxic via the oral, dermal and inhalation routes of exposure. It is not a skin irritant and is not a dermal sensitizer in both guinea pigs and mice. The effects on the eye are classified as “mild irritant” and reversible.

III. Toxicity information on Broflanilide

Broflanilide is a new active ingredient and toxicology studies have been evaluated by JMPR and the US EPA. A human health hazard on Broflanilide (USEPA, 2020) and a summary report (JMPR, 2022) are available.

III.A. Acute toxicity

Broflanilide is of low toxicity following acute exposure. The acute oral and dermal LD_{50} are greater than 5000 mg/kg when tested in female or male and female rat, respectively, under the experimental conditions employed. 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. 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

The results of acute toxicity studies with Broflanilide are depicted in Table A7.

Table A7. 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
Skin sensitization, Maximization Test	Guinea Pig	Non-sensitizer	Not classified	USEPA, 2020

III.B. Subchronic toxicity

(Note: only studies relevant to the hazard and risk assessment of Broflanilide are discussed)

Subchronic toxicity studies on Broflanilide were conducted in 28- and 90-day oral route toxicity studies in rats, mice, and dogs. Additionally, 28-day repeat dose dermal exposure as well as 28-day repeat dose inhalation studies in rats were conducted.

III.B.1 Dermal study

Dermal application of Broflanilide to male and female Wistar rats for 28-days (6 hours/day; 5 days/week for 4 weeks) 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 NOAEL (No Observed Adverse Effect Level) was 1000 mg/kg bw/day.

III.B.2. Inhalation study

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 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).

III.B.3. Subchronic - rodents

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 a 90-day 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/day for males and 0, 32.3, 230, and 1148 mg/kg/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, 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).

III.B.4. Subchronic – dogs

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 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 (the limit dose), and the LOAEL was not established in beagle dogs (USEPA, 2020).

III.C. Chronic toxicity and carcinogenicity

The chronic toxicity potential of Broflanilide was evaluated in rats, mice, and dogs.

III.C.1. Rats

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 at all doses tested; in luteomas and granuloma cell tumors in the ovaries; uterine adenocarcinomas, and adrenal cortex carcinomas in females.

III.C.2. Mice

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 inclusion 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, the systemic NOAEL was established at 745 mg/kg bw/day for males and 172 mg/kg bw/day for female mice based on increased adrenal weight and slight increased incidence of ovarian cysts, adrenal hemopoiesis and inflammatory cell foci in the adrenal noted at 820 mg/kg bw/day (female systemic LOAEL). There was no evidence of carcinogenicity at any dose level in either sex.

III.C.3. Dogs

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, the 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).

A summary of chronic and carcinogenic studies with Broflanilide is depicted in Table A8.

Table A8. Summary of subchronic, chronic and carcinogenicity studies with Broflanilide

Study dose levels	Results (mg/kg bw/day)	Reference
28-day dermal study, rats	NOAEL = 1000 (HDT)	USEPA, 2020
4-week inhalation (nose only) study, rats Nominal conc: 30 mg/m³, 200 mg/m³ and 1000 mg/m³	NOAEC = 31 mg/m³ LOAEC = 193 mg/m³	USEPA, 2020

Table A8. Summary of subchronic, chronic and carcinogenicity studies with Broflanilide		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
Actual conc: 0, 31, 193, and 940 mg/m^3	based on increased adrenal weight, increased incidence of ovary vacuolation, and increased incidence of adrenal vacuolation in both sexes	
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	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, 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 90-day study with the LOAEL established at the lowest concentration tested at 500 ppm	NOAEL = 2.0 mg/kg bw/day (males) and 2.2 mg/kg bw/day (females)	USEPA, 2020
90-day oral (capsule) study, 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 tumors in ovaries, and findings of uterine adenocarcinoma, adrenal cortex carcinomas, etc.	USEPA, 2020
78 Week Dietary Combined Chronic Carcinogenicity Study in the 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 dog study (capsules) 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

Cancer risk assessment

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.

III.D. 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 (USEPA, 2020).

III.E. Reproductive 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 (USEPA, 2020).

A summary of the findings in developmental and reproductive toxicity is depicted in Table A9.

Table A9. Summary of developmental and reproductive developmental studies with Broflanilide		
Study dose levels	**Results (mg/kg bw/day)**	**Reference**
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 Offspring LOAEL = 127 mg/kg bw/day (decreased pup weights in F1 and F2 generations).	USEPA, 2020
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 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

III.F. Neurotoxicity

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

In an acute neurotoxicity study via gavage exposure, no signs of neurotoxicity or systemic toxicity were seen at any dose level, including a limit dose of 2000 mg/kg bw.

In a subchronic neurotoxicity study in rats, there was no indication of clinical (general clinical observation, FOB, and motor activity) or neurohistopathologic effects. The neurotoxicity NOAEL was established at the limit concentration of 15,000 ppm (equivalent to 1041 mg/kg bw/day and 1137 mg/kg bw/day in males and females, respectively). The NOAEL and LOAEL for these studies are summarized in Table A10.

Table A10. 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**

III.G. 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.

III.H. Immunotoxicity

In the immunotoxicity study, Broflanilide showed no signs of immunotoxicity when administered via the diet to at concentrations of 0 ppm, 1200 ppm, 4000 ppm and 12,000 ppm over a period of 4 weeks to male Wistar rats. The NOAEL for systemic and immunotoxicity was set at 12,000 ppm (1020 mg/kg bw/d), the highest dose tested. A LOAEL was not identified.

III.I. Absorption, distribution, metabolism, and excretion (ADME)

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, 2% dose at the 500 mg/kg dose level (C-ring), and 16-23% dose at the 5 mg/kg dose level (B-ring). 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.

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 2.3% (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 (2020) for risk assessment.

IV. Toxicological point of departures for risk assessments

The Points of Departure (PODs) 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 tabulated below. Exposure durations are: Short-(1-7 days); Intermediate-1-6 months); and Long-term (greater than 6 months). 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), acceptable daily intake (ADI) or a safe margin of exposure (MOE).

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

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

Acceptable daily intake (ADI):

Broflanilide has been evaluated by JMPR and a summary report available in October 2022.

ADI = 0.02 mg/kg bw/day

Dermal exposure (short term and intermediate term):

The USEPA did not select a POD 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 Broflanilide at 1000 mg/kg/day, 5 days/week for 21 days to rats. There was also no toxicity observed following acute dermal exposure to Broflanilide 50% up to a dose of 2000 mg/kg. Therefore, quantification of dermal risk is not required. The dermal absorption factor (DAF) is set up at 5% (USEPA, 2020).

Dermal RfD = Not established

Dermal Absorption Factor (DAF) = 5%

Inhalation exposure (short-term and intermediate-term):

The USEPA selected the 4-week inhalation study with Broflanilide in Wistar rats to establish the inhalation reference dose. In this study, the NOAEC was 31 mg/m^3 and the LOAEC was 193 mg/m^3 corresponding to 0.031 mg/L and 0.193 mg/L, respectively, based on increased adrenal weight,

increased incidence of adrenal vacuolation in both sexes, increased ovarian weights and increased incidence of ovary vacuolation in females. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the lack of pharmacodynamic interspecies differences and a 10X for intraspecies variations (US EPA, 2020).

Inhalation RfC = 31 mg/m^3/ 30 = 1.03 mg/m^3

The toxicological PODs and reference doses are summarized in Table A11.

Table A11. Points of departure and reference doses

Exposure scenario	POD (mg/kg/day)	UF	Reference dose	Toxicological endpoint of concern	Study selected
Acute exposure aRfD	Not selected		N/A	Not of toxicological concern after acute exposure	N/A
Chronic exposure cRfD	3 mg/kg	100	0.03 mg/kg/day	Increased adrenal weights with corroborative histopathological findings (increase vacuolation and diffuse hypertrophy in the adrenal gland cortex) in both sexes and both generations.	2 generation reproduction study in rats
Inhalation exposure (All durations)	31 mg/m^3 (0.031 mg/L)	30	1.03 mg/m^3 (0.001 mg/L)	Increased adrenal weight, increased incidence of adrenal vacuolation in both sexes, increased ovarian weights and increased incidence of ovary vacuolation in females.	4-week inhalation study in rats
Dermal exposure	Not selected		N/A	Not of toxicological concern after repeated dermal exposure	

V. Conclusion and recommendation

Acute toxicity studies have been conducted on VECTRON T500 and a summary of these studies and references are provided. Under GHS classification, VECTRON T500 has low acute oral, dermal and inhalation toxicity (Category 5), is not an eye or skin irritant, and is not a skin sensitizer.

The toxicological data base for Broflanilide is complete. The toxicity profile can be characterized for all effects including developmental toxicity, reproductive toxicity, chronic toxicity, immunotoxicity, genotoxicity, and neurotoxicity.

The existing toxicology database is adequate to support the proposed labelled uses of VECTRON T500 an Indoor Residual Spray (IRS) product for the control of mosquitoes vectoring malaria.

VI. References

Biotoxtech Co. No. J20066, 2020. Acute oral toxicity study of Broflanilide 50 WP in Sprague Dawley Rats (Acute Toxic Class Method).

Biotoxtech Co. No. J20067, 2020. Acute dermal dose toxicity study of Broflanilide 50 WP in Sprague Dawley Rats (Fixed Dose Procedure).

Biotoxtech Co. No. J20068, 2020. Acute skin irritation/corrosion study of Broflanilide 50 WP in New Zealand rabbits.

Biotoxtech Co. No. J20069, 2020. Acute eye irritation/corrosion study of Broflanilide 50 WP in New Zealand rabbits.

Biotoxtech Co. No. J20070, 2020. Skin sensitization study of Broflanilide 50 WP in Harley Guinea pigs (Buehler Test).

Biotoxtech Co. No. J20071, 2020. Skin sensitization test of Broflanilide 50 WP in CBA/J mice (local lymph node assay:BrdU-ELISA).

Jeonbuk Branch Institute, KIT, KRICT No. G220015, 2020. Broflanilide 50 WP: Acute Inhalation Toxicity Study in Sprague Dawley Rats.

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.

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 3. 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 IRS without appropriate PPE.

Table A12. Risk characterization for all populations and exposure scenarios

Population	Operator exposure (dermal and inhalation) (µg /kg bw/day)	TSD (µg /kg bw/day)	Risk ratio
Total operator exposure – guideline scenarios			
Adult – TWA	0.549	30	0.02
Adult – max	2.784	30	0.09
Total operator exposure – lax scenarios			
Adult – TWA	5.492	30	0.18
Adult – max	27.842	30	0.93
Population	**Residential exposure (dermal and foodstuffs) (µg /kg bw/day)**	**TSD (µg /kg bw/day)**	**Risk ratio**
Total resident exposure – TWA scenario			
Adult	0.271	30	0.01
Children	0.426	30	0.01
Toddler	1.067	30	0.04

Table A12. Risk characterization for all populations and exposure scenarios			
Infant	1.903	30	0.06
Total resident exposure – maximal scenario			
Adult	0.646	30	0.02
Children	1.017	30	0.03
Toddler	2.543	30	0.08
Infant	4.532	30	0.15
Population	**Operator-resident (combined exposure) (µg /kg bw/day)**	**TSD (µg /kg bw/day)**	**Risk ratio**
Operator-resident exposure – guideline scenario			
Guideline – TWA	0.820	30	0.03
Guideline – max	3.430	30	0.11
Operator-resident exposure – Worst case scenario [(a)]			
Lax – TWA	5.763	30	0.19
Lax – max	28.488	30	0.83
Population	**Breast milk exposure residential (µg /kg bw/day)**	**TSD (µg /kg bw/day)**	**Risk ratio**
Guideline scenarios			
Newborn - TWA	0.0307	30	0.001
Newborn - Max	0.0733	30	0.002

(a): Worst Case Scenario = Operator (Lax scenario - max) + Resident (Guideline scenario) since Lax scenario applies only to operator

The values given in Table A13 are only for risk illustration purposes of a worst-case scenario. This scenario assumes the operator is also a nursing/lactating resident. Even under this scenario, which is neither recognized nor accepted by WHO, the risk estimate is still acceptable (< 1).

Table A13. Estimated systemic dose from exposure to breast milk							
Population	**SolC**	**Exposed Dose (µg/kg bw)**	**$T_{1/2}$ (days)**	**IR (kg/day)**	**Oral Absorption (%)**	**BW (kg)**	**Systemic dose (µg/kg/day)**
Worst case – TWA							
Newborns	0.361	5.763	2	0.66	100	4.2	0.654
Worst case – maximal daily dose							
Newborns	0.361	28.488	2	0.66	100	4.2	3.232
Risk estimate – breast milk exposure – worst case scenario [(a)(b)]							
Population		**Operator resident breast milk exposure dose (µg/kg/day)**			**TSD (µg/kg/day)**		**Risk ratio**
Newborn – TWA		0.654			30		0.021
Newborn – Max		3.232			30		0.107

Sol C = Solubility constant = 0.361 for water soluble
$T_{1/2}$= First order kinetics half-life of clothianidin, 2 day (JMPR, 2001)
IR= (default value=0.53 kg/day for first month and 0.68 kg/day for first 12 months
Exposed dose = Operator (Lax dose maximal) + Residential (Guideline Max dose)
(a): Worst Case Scenario = Operator (Lax scenario - max) + Resident (Guideline scenario) since Lax scenario applies only to operator
(b): The scenario of nursing/lactating mother working as an operator is neither recognized nor accepted by WHO