Generic risk assessment – Human Health

CHLORFENAPYR
(CAS No. 122453-73-0)

An active ingredient in insecticide-treated nets

Prequalification Unit – Vector Control Products Assessment
Regulation and Prequalification Department
Access to Medicines and Health Products

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Contents

Acronym list

Abs-D	Dermal Absorption from Net Surface
Abs-O	Oral Absorption
ADI	Acceptable Daily Intake
aRfD	Acute Reference Dose
AT	Average Time
BMD	Benchmark Dose
$BMDL_{1SD}$	Benchmark Dose Lower Bound 1 Standard Deviation
BW	Body Weight
CHO	Chinese Hamster Ovary
cRfD	Chronic Reference Dose
DNA	Deoxyribonucleic Acid
DNT	Developmental Neurotoxicity
EC	European Commission
EFSA	European Food Safety Authority
EHA	Exposed Hand Area
ESA	Exposed Skin Area
FAO	Food and Agriculture Organization
FHM	Fraction Transferred from Hand to Mouth
FOB	Functional Observational Battery
GHS	United Nations Globally Harmonized System of Classification and Labelling of Chemicals
GRAM	Generic Risk Assessment Model
IARC	International Agency for Research and Cancer
IPCS	International Programme on Chemical Safety
IR	Ingestion Rate
ITN	Insecticide-Treated Net
JMPR	Joint Meeting on Pesticide Residues
LOAEL	Lowest Observed Adverse Effect Level
MOE	Margin of Exposure
NM	Net Mouthed
NOAEL	No Observed Adverse Effect Level
NoN	Number of Nets
NoW	Number of Washes
PCE	Polychromatic Erythrocytes
PND	Postnatal Day
PODs	Points of Departure
PQT/VCP	Prequalification Unit – Vector Control Products Assessment
RfD	Reference Dose
RSW	Release Rate
SE	Salivary Extraction Factor
SF	Surface Fraction

SN	Size of Net
TC	Total Concentration
TEM	Triethylenemelanine
Transl	Translodgeable Fraction
TSD	Tolerable Systemic Dose
TSD_{AC}	Tolerable Systemic Dose – acute
TWA	Time-Weighted Average
UF	Uncertainty Factor
USEPA	United States Environmental Protection Agency
VLH	Volume Liquid on Hand
VLS	Volume of Liquid on Skin
VolW	Volume of Washing Water
WHO	World Health Organization
WRI	Wash Resistance Index

1 Purpose

The purpose of this document is to present a human health hazard and risk assessment for chlorfenapyr-treated bednets (factory coated or incorporated). It is intended to be used by applicants, regulatory authorities and other stakeholders as an example of the implementation of the *Generic risk assessment model for insecticide-treated nets, 2nd edition (GRAM)* (WHO, 2018).

The product characteristics, including the fabric weight (40 g/m^2) concentration of chlorfenapyr (6.5 g active ingredient/kg net), and the wash resistance index (90%) were selected as representative values which exemplify currently prequalified insecticide-treated net (ITN) products.

The assessment assumes that the product is a uniformly treated chlorfenapyr ITN (coated or incorporated) with the following product characteristic values:

- Fabric weight: 40 g/m^2
- Concentration by weight of the net: 6.5 g chlorfenapyr/kg net
- Concentration by net area: 260 mg chlorfenapyr/m2
- Wash Resistance Index: 90%

Note: The selected values are not intended to put a limit on the possible concentration of chlorfenapyr in an ITN.

The selected values do not represent the maximum concentration of chlorfenapyr at which the assessed risks may become unacceptable.

In support of new product applications or change applications submitted to the World Health Organization (WHO) Prequalification Unit – Vector Control Products Assessment (PQT/VCP), applicants may include reference to this document as part of the product dossier; however, applicants must determine if the design of their product or certain characteristics would require altering the presented risk assessment to properly reflect and assess the proposed product.

2 Development of the risk assessment

The present human health risk assessment for chlorfenapyr was conducted according to the *Generic risk assessment model for insecticide-treated nets, 2nd edition* (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 may occur and the dose/exposure levels below which no adverse effects are observed. Authoritative evaluations may be used as starting points for the risk assessment. Examples of authoritative evaluations are: Joint Meeting on Pesticide Residues (JMPR) – Monographs and Evaluations; International Programme on Chemical Safety (IPCS): Concise International Chemical Assessment Documents, Environmental Health Criteria Documents; International Agency for Research and Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans: United States Environmental Protection Agency (USEPA) – Pesticide Evaluations; European Food Safety Authority (EFSA) – Pesticide Risk Assessments; European Chemicals Agency – Information on Chemicals. JMPR assessments, if available, are used by WHO for risk assessment unless a more recent authoritative evaluation exists.
- **Exposure assessment** may concern insecticide operators, applicators, residents of treated dwellingsand users of other treated buildings, bystanders, domestic animals, wildlife and the environment. Exposure is assessed in a “guideline scenario” which assumes that the insecticide is used accordingto the instructions given on the product label and in WHO guideline information. Conservative high endpoint estimates of the default distributions are used as defaults. No account is taken of intended misuse. All relevant routes of exposure are considered.
- **Risk characterization** is the final step in a risk assessment whereby estimates of exposure arecompared with acceptable exposure levels as defined in the hazard assessment for all relevantexposure scenarios.

The risk assessment for chlorfenapyr is based on the proposed uses of the ITN products, i.e., net used oversleeping areas.

2.1 Hazard assessment

The complete chlorfenapyr hazard assessment conducted to support this risk assessment is included in the appendix.

Oral exposure

In a rat metabolism study, fecal excretion was the major route of elimination (80% of recovered radioactivity) with low recoveries of the radioactive chlorfenapyr in urine and tissues. Most of the radioactivity was eliminated within 48 hours of dosing. Female rats had greater recovery of radioactivity (about 2X at the low dose) in the fat, carcass, and blood at all doses than did males. The highest recovery of radioactivity from a single organ was from the liver (0.15-0.48% of the administered dose). Parent compound was the major radioactive component found in excreta, accounting for approximately 40-70% of the administered doses. Minor amounts of eight primary and conjugated metabolites and four unidentified isolated components were detected, each at less than 10% of the dosed radioactivity. Liver and kidney contained several primary and conjugated metabolites and only minor levels of the parent compound (£8.3% of the radioactivity in the sample). Identified metabolites were minimally accumulated in tissues and primarily excreted in the urine (USEPA, 2020).

In a biliary excretion study following oral administration of 2 mg/kg chlorfenapyr to rats, tissues residues were 25-37%, urinary excretion was approximately 4-5 % and biliary excretion was around 18-20% at 24 hours post dosing. Based on these findings, the oral absorption value was determined to be at least 60% of the administered dose (ECHA, 2012). For the purposes of this generic risk assessment, the 100% default for oral absorption has been retained.

Dermal exposure

In an *in vivo* study, rats received dermal application of a formulation concentrate (BAS 306 02) at 2.4 mg/cm2 and 0.0217 mg/cm2. At 8, 24, and 120 hours, dermal absorption (tissues, excreta, surrounding skin, and application site) for the 2.4 mg/cm2 dose was 6.4%, 3.9%, and 3.6%, respectively. At 8, 24, and 120 hours, dermal absorption (tissues, excreta, surrounding skin, and application site) for the 0.0217 mg/cm2 dose was 13.1%, 10.7%, and 15.1%, respectively. Dermal absorption of 13% after 8 hours of exposure was calculated at the lowest dose tested (approximately 25 µg/cm2) based on excreta, cage wash, blood, plasma, carcass, application site, and the surrounding skin (USEPA, 2020).

In the *in vitro* studies, rat and human skins were exposed to a formulation concentrate (BAS 306 02) at 25, 100 or 250 µg/cm2. The total potentially absorbed dose for rat skin was 15.81%, 22.44%, and 11.12% at the low-, mid-, and high-doses. The total potentially absorbed dose for human skin was 1.42%, 0.16%, and 0.49% at the low-, mid-, and high-dose. Based on the results of these studies the USEPA calculated dermal absorption of 1.2% (USEPA, 2020).

$$\text{Abs-D} = \frac{\text{rat } \textit{in vivo} \text{ (13\%) x human } \textit{in vitro} \text{ (1.4\%)}}{\text{rat } \textit{in vitro} \text{ (15.8\%)}} = \mathbf{1.2}\%$$

Inhalation exposure

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

2.1.1 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).

Acute oral exposure

According to the risk assessment model, authoritative sources may be used as starting points for the risk assessment of insecticides used in long-lasting mosquito nets.

JMPR (2012) selected an oral POD of 3.0 mg/kg/day (NOAEL) based on depression of grooming and reactivity and decreased spontaneous motor activity at 10 mg/kg/day in a pharmacology study with mice.

USEPA (2020) selected an oral POD of 5.0 mg/kg/day based on increased deaths in pups on post-natal days 1-4 and decreased motor activity in pups at 10 mg/kg/day in a developmental neurotoxicity study in rats.

Chronic oral exposure

JMPR (2012) selected the oral POD of 2.8 mg/kg/day based on decreased body weight gain and vacuolation of the white matter of the brain at 16.6 mg/kg/day in a carcinogenicity study in mice.

USEPA (2020) selected the oral POD of 5.0 mg/kg/day from the reproduction toxicity study based on increased deaths in pups on post-natal days 1-4 and decreased motor activity in pups at 10 mg/kg/day in a developmental neurotoxicity study in rats.

2.1.2 Reference doses

Once PODs are developed, safety factors 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 an acceptable daily intake (ADI).

Acute reference dose (aRfD)

Chlorfenapyr was evaluated by the Food and Agriculture Organization/WHO JMPR (2012) at which time an aRfD of 0.03 mg/kg/day was established based on the POD of 3 mg/kg/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variation (see Table 1).

Table 1. JMPR aRfD

Population of concern	POD = NOAEL (mg/kg/day)	Uncertainty factor	Acute RfD (mg/kg/bw)	Toxicological endpoint of concern	Study selected	Reference
General population	3.0	100	0.03	Depression of grooming activity and decreased spontaneous motor activity at 10 mg/kg bw (LOAEL)	Pharmacology – rat	JMPR, 2012

USEPA (2020) established an aRfD of 0.05 mg/kg/day based on the POD of 5 mg/kg bw/day and an uncertainty factor of 100 to account for interspecies extrapolation and for intraspecies variation (USEPA, 2020) (see Table 2).

Table 2. USEPA aRfD

Population of concern	POD = NOAEL (mg/kg/day)	Uncertainty factor	Acute RfD (mg/kg/bw)	Toxicological endpoint of concern	Study selected	Reference
General population	5.0	100	0.05	Decreased motor activity	Developmental - rat	USEPA, 2020

Chronic reference dose (cRfD)

USEPA established an cRfD of 0.05 mg/kg/day based on the POD of 5 mg/kg bw/day and an uncertainty factor of 100 to account for interspecies extrapolation and for intraspecies variation (USEPA, 2020) (see Table 3).

Table 3. USEPA cRfD

Population of concern	POD = NOAEL (mg/kg/day)	Uncertainty factor	Acute RfD (mg/kg/bw)	Toxicological endpointof concern	Study selected	Reference
General population	5.0	100	0.05	Decreased motor activity	Developmental - rat	USEPA, 2020

Acceptable daily intake (ADI)

JMPR established and ADI of 0.03 mg/kg bw/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variation (JMPR, 2006) (see Table 4).

Table 4. JMPR – ADI

NOAEL (mg/kg/day)	Uncertainty factor	ADI (mg/kg/day)	Toxicological endpoint of concern	Study selected	Reference
2.8	100	0.03	Decreased body weight gain and vacuolation of the white matter of the brain at 16.6 mg/kg/day (LOAEL).	Carcinogenicity - mouse	JMPR, 2006

2.1.3 Selection of tolerable systemic dose (TSD)

Tolerable systemic doses (TSDs) are established for acute and long-term for risk assessments. Guidance values for acute exposure (TSDAC) and long-term (TSD) have already been set by international or national bodies such as JMPR, EU and/or USEPA; these include acute reference dose (aRfD) for assessing risk from acute exposure and acceptable daily intake (ADI) or chronic reference dose (cRfD) for assessing risk from long-term exposure.

The PQT/VCP selected the aRfD of 0.05 mg/kg/day established by the USEPA as the TSD for acute risk assessment (TSDAC).

The PQT/VCP selected the cRfD of 0.05 mg/kg/day established by the USEPA as the TSD for long-term risk assessment.

Although the POD established by the USEPA is slightly higher than that established by JMPR, the higher POD is chosen for both acute and chronic risk assessments due to the robust toxicological significance of the adverse effects observed in the most sensitive population subgroup (pups) in a study that examined developmental neurobehavior and neuropathology in the adults and offspring.

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) was conducted in accordance with the input parameters (default values) mainly taken from generic risk assessment model for insecticide-treated nets (WHO, 2018) and chemical-specific data. Exposure assessment includes the population (adults, children [6–11 years], toddlers [1–2 years], infants [<1year]), the routes of exposure (inhalation, dermal, oral and via breast milk) and the different scenarios (sleeping under, washing and sleeping under and washing treated nets). In the total exposure assessments, all relevant routes and different scenarios were summed up to derive the total systemic dose. Exposure is assessed in a “guideline scenario”, which assumes that the insecticide is used according to the instructions given on the product label and in WHO guideline information.

For exposure assessment, the total concentration (TC) of insecticide on the net and a default transfer coefficient of 6% for dislodgeable insecticide from net to skin, as proposed in the genericrisk assessment model (WHO, 2018), are used.

The concentration of the active ingredient in the net (TC) is derived from the WHO GRAM (2018)specification of the net (default variability of the concentration being +/- 25%).

$$TC = 125\% \text{ X Nominal concentration of the active ingredient g/kg net X weight of the net kg/m}^2$$

Using the selected product design attributes of 6.5g chlorfenapyr/kg net and 40 g/m^2 fabric weight, the TC is calculated as follows:

TC = 125% x 6.5 g/kg net x 0.040 kg/m2 x 1000 = 325 mg chlorfenapyr/m^2

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

Abs-D = Dermal from net surface (data derived = 1.2%)

Abs-O = Oral absorption (default) = 100%

AT = Average time (default = 365 days)

BW = Body weight (default = adult = 60 kg adult; 23.9 kg/child; 10 kg/toddler; 8 kg infant [less than 12 months]; 4.2 kg/newborn [birth to 1 month]

ESA = Exposed skin area (default = adult, 0.408; child, 0.225; toddler, 0.115; infant, 0.100 m^2)

EHA = Exposed hand area (default = 0.008 m^2/toddler; 0.007 m^2/infant)

FHM = Fraction transferred from hand to mouth (default = 0.164 [75th percentile])

NM = Net mouthed (default = 0.0014 m^2)

NoN = Number of nets washed per day (default = 5)

NoW = Number of washes per year (default = 20 washes/3 years)

RSW = Release rate (analytical data)

SE = Salivary extraction factor (default = 57%)

SN = Maximal actual size of the net (default = 15 m^2)

SF = Surface fraction (100 – wash resistance index %) = 10%

Transl = Translodgeable fraction (default = 6%)

TC = Total concentration of active ingredient on net surface (derived value)

VLH = Volume liquid on hand (default = 8.2 ml/adult; 4.3 ml/child)

VLS = Volume of liquid on skin (default = 36.7 ml/adult; 17.6 ml/child)

VolW = Volume of washing water (default = 4 litres)

WRI = Wash resistance index = 90%

1000 = conversion of mg to µg

Chlorfenapyr molecular mass = 407.6 g/mol

Chlorfenapyr vapor pressure = 9.81 $X10^{-3}$ mm Hg @ 20 °C

2.2.1 Exposure from sleeping under treated nets

The individual and cumulative exposures in adults, children, toddlers and infants via inhalation, dermal and oral routes are estimated and converted to total systemic exposures.

2.2.1.1 Inhalation exposure

Inhalation exposure from impregnated materials is expected to be negligible, since many pesticides that are used in impregnated materials have relatively low vapor pressure. As a result, inhalation exposure is not expected to result in appreciable exposure when compared with dermal or non-dietary ingestion exposure (USEPA, 2012; GRAM, 2018).

In order to assess the need to evaluate inhalation exposure, a worst-case scenario (a toddler staying 24 hours/day at a saturated vapor pressure concentration) to the pesticide can be estimated as follows (GRAM, 2018). Chlorfenapyr has a vapor pressure of <1.0 X 10^{-}7 mm hg at 20°C and a molecular weight of 407.6 g/mol (USEPA, 2001).

Systemic dose = 0.328 × MM × VP

MM = molecular mass of the pesticide = 407.6 g/mol

VP, its vapor pressure at 20°C (Pa) = 1.7 X 10^{-}7

In the case of chlorfenapyr, the worst-case systemic dose following inhalation exposure is 0.23 µg /kg bw (0.328 x 407.6 x 0.00017= 0.023). This systemic dose is used to calculate the risk ratios for acute and long-term inhalation exposure to chlorfenapyr.

$$\text{Acute Risk Ratio} = \frac{\text{Systemic dose (0.023/µg/kg bw)}}{\text{TSD}_{AC}\ (0.05\ \text{mg/kg bw})} = 0.0005$$

$$\text{Long-term Risk Ratio} = \frac{\text{Systemic dose (0.023/µg /kg bw)}}{\text{TSD (0.05 mg/kg bw/day)}} = 0.0005$$

The ratio is less than 1 for both acute and long-term inhalation exposure scenarios.

Thus, for chlorfenapyr, while sleeping under a net the contribution of inhalation to total body exposure is so small that, in practice, it can be ignored.

2.2.1.2 Dermal exposure

The estimated time-weighted average (TWA) systemic dose due to potential dermal exposure from sleeping under the net is calculated using a data-derived Abs-D of 1.2 % established by the USEPA. Table 5 reflects the systemic doses for all populations due to dermal exposures from sleeping under treated nets.

$$\text{Systemic TWA dose} = \frac{\text{Abs-D x Transl x ESA x SF x TC}}{\text{BW}} \times 1000$$

Table 5. Estimated systemic dose (TWA) from dermal exposure from sleeping under treated nets

Population	Abs-D (%)	Transl (%)	ESA (m^2)	SF (%)	TC (mg/m^2)	BW (kg)	Systemic dose (µg/kg/ bw/day)
Adult	1.2	6	0.408	10	325	60.0	0.159
Children	1.2	6	0.225	10	325	23.9	0.220
Toddlers	1.2	6	0.115	10	325	10.0	0.269
Infants	1.2	6	0.100	10	325	8.0	0.293

Translodgeable = default = 6%
ESA = default value
SF= 100 – wash resistance index % = 10%
TC = 325 mg/m^2
BW = default values
1000 = conversion of mg to µg

2.2.1.3 Oral exposure to toddlers and infants

Oral exposure may occur from hand-to-mouth transfer and from direct mouthing activity such as mouthing, chewing and sucking in the case of infants and toddlers.

2.2.1.3.1 Indirect oral exposure – Hand-to-mouth transfer

It is assumed that hand-to-mouth transfer is significant only for toddlers and infants. The estimated daily systemic dose from hand-to-mouth transfer is calculated as indicated in Table 6.

$$\text{Systemic Dose} = \frac{\text{Abs-O x SE x Transl x EHA x FHM x SF x TC}}{\text{BW}} \times 1000$$

Table 6. Estimated systemic dose (TWA) from indirect oral exposure – Hand-to-mouth transfer

Population	Abs-O (%)	SE (%)	Transl (%)	EHA (m^2)	FHM	SF (%)	TC (mg/m^2)	BW (kg)	Systemic dose (µg/kg bw/day)
Toddlers	100	57	6	0.008	0.164	10	325	10.0	0.146
Infants	100	57	6	0.007	0.164	10	325	8.0	0.160

SE = default value = 57%
Transl = default value = 6%
EHA = default values
FHM = default value = 0.164
SF= 100 – wash resistance index % = 10%
TC = 325 mg/m^2
BW = default values
1000 = conversion of mg to µg

2.2.1.3.2 Direct oral exposure

Direct mouth contact is only relevant for toddlers and infants. The estimated systemic dose from direct mouth contact is indicated in Table 7.

$$\text{Systemic Dose} = \frac{\text{Abs-O x SE x NM x SF x TC}}{\text{BW}} \text{ x } 1000$$

Table 7. Estimated systemic dose (TWA) from direct oral exposure – Sleeping and mouthing, chewing and sucking

Population	Abs-O (%)	SE (%)	NM (m^2)	SF (%)	TC (mg/m^2)	BW (kg)	Systemic dose (µg/kg bw/day)
Toddlers	100	57	0.0014	10	325	10.0	2.60
Infants	100	57	0.0014	10	325	8.0	3.24

SE = default value = 57%
NM = default = 0.0014 m^2
SF= 100 – wash resistance index % = 10%
TC = 325 mg/m^2
BW = default values
1000 = conversion of mg to µg

2.2.1.4 Combined (inhalation + dermal + oral) exposure from sleeping under treated nets

A total daily systemic exposure to chlorfenapyr while sleeping under a treated net was calculated in Table 8 as the summation of the values for inhalation, dermal and oral routes of exposure given above.

Table 8. Estimated total systemic dose (µg/kg bw/day) from sleeping under treated nets

Population	Inhalation exposure	Dermal exposure	Oral Exposure		Total systemic dose (µg/kg bw/day)
			Indirect	Direct	
Adult	Negligible	0.159	Not Applicable	Not Applicable	0.159
Children	Negligible	0.220	Not Applicable	Not Applicable	0.220
Toddler	Negligible	0.269	0.146	2.60	3.015
Infants	Negligible	0.293	0.160	3.24	3.693

2.2.2 Washing treated nets

There is no risk associated with inhalation exposure from washing of treated nets since the inhalation route of exposure is not of concern. However, exposure due to dermal absorption and oral transfer from hands may occur during washing of nets. This exposure is estimated for adult and child only.

2.2.2.1 Dermal exposure during net washing

2.2.2.1.1 Acute (maximum) exposure

The estimated acute (maximum) systemic dose due to potential dermal exposure during washing of treated nets is presented in Table 9.

$$\text{Systemic dose (maximum)} = \frac{\text{Abs-D x NoN x VLS x SF x TC x SN}}{\text{VolW x BW}} \times 1000$$

Table 9. Estimated systemic dose (maximum) from dermal exposure - Washing treated nets

Population	Abs-D (%)	NoN (Nets)	VLS (mL)	SF (%)	TC (mg/m^2)	SN (m^2)	VolW (mL)	BW (kg)	Systemic dose (µg/kg bw/day)
Adults	1.2	5	36.7	10	325	15	4000	60.0	4.47
Children	1.2	5	17.6	10	325	15	4000	23.9	5.38

NoN = default = 5
VLS = default = 36.7 ml/adult and 17.6 ml/child)
SF= 100 – wash resistance index % = 10%
TC = 325 mg/m^2
SN = default = 15 m^2
VolW = default=4000 ml
BW = default values
1000 = conversion of mg to µg

2.2.2.1.2 Repeated (long-term) exposure

The estimated systemic dose (TWA) due to potential repeated dermal exposure during washing of treated nets is presented in Table 10.

$$\text{Systemic dose (TWA)} = \frac{\text{Abs-D x NoW x NoN x VLS x SF x TC x SN}}{\text{VolW x BW x AT}} \times 1000$$

Table 10. Estimated systemic dose (TWA) from repeated dermal exposure - Washing treated nets

Population	Abs-D (%)	NoW (washes)	NoN (Nets)	VLS (mL)	SF (%)	TC (mg/m^2)	SN (m^2)	VolW (mL)	BW (kg)	AT (days)	Systemic dose (µg/kg bw/day
Adults	1.2	20/3 years	5	36.7	10	325	15	4000	60.0	365	0.082
Children	1.2	20/3 years	5	17.6	10	325	15	4000	23.9	365	0.098

NoW= default =20/3 years
NoN = default=5
VLS = default = 36.7 ml/adult and 17.6 ml/child
SF= 100 – wash resistance index % = 10%
TC = 325 mg/m^2
SN = default =15 m^2
VolW = default=4000 ml
BW =default values
AT=default=365 days
1000 = conversion of mg to µg

2.2.2.2 Oral exposure during net washing

2.2.2.2.1 Acute exposure

The estimated acute (maximum) systemic dose due to potential oral exposure via hand-to-mouth activity during washing of treated nets is presented in Table 11.

$$\text{Systemic dose (maximum)} = \frac{\text{Abs-O x NoN x VLH x SF x TC x FHM x SN}}{\text{VolW x BW}} \times 1000$$

Table 11. Estimated systemic dose (maximum) from acute oral exposure - Washing treated nets

Population	Abs-O (%)	NoN (Nets)	VLH (mL)	SF (%)	TC (mg/m^2)	FHM	SN (m^2)	VolW (mL)	BW (kg)	Systemic dose (µg/kg bw/day)
Adults	100	5	8.2	10	325	0.164	15	4000	60.0	13.65
Children	100	5	4.3	10	325	0.164	15	4000	23.9	17.98

NoN = default = 5
VLH = default = 8.2 ml/adult and 4.3 ml/child
SF= 100 – wash resistance index % = 10%
TC = 325 mg/m^2
FHM = default = 0.164
VolW = default = 4000 ml
BW = default values
1000 = conversion of mg to µg

2.2.2.2.2 Repeated (long-term) exposure

The estimated systemic dose (TWA) due to potential repeated oral exposure via hand-to-mouth activity during washing of treated nets is presented in Table 12.

$$\text{Systemic dose (TWA)} = \frac{\text{Abs-O x NoW x NoN x VLS x SF x TC x FHM x SN}}{\text{VolW x BW x AT}} \times 1000$$

Table 12. Estimated systemic dose (TWA) from repeated oral exposure - Washing treated nets

Population	Dermal absorption (%)	NoW (washes)	NoN (Nets)	VLS (mL)	SF (%)	TC (mg/m^2)	FHM	SN (m^2)	VolW (mL)	BW (kg)	AT (days)	Systemic dose (µg/kg bw/day
Adults	100	20/3 years	5	8.2	10	325	0.164	15	4000	60.0	365	0.249
Children	100	20/3 years	5	4.3	10	325	0.164	15	4000	23.9	365	0.328

NoN = default = 5
NoW = default = 20 washes/3 years
VLH = default= 8.2 ml/adult and 4.3 ml/child
SF= 100 – wash resistance index % = 10%
TC = 325 mg/m^2
FHM = default=0.164
SN =default = 15 m^2
Vol W = default=4000 ml
BW = default values
AT = default = 365 days
1000 = conversion of mg to µg

2.2.3 Combined (dermal + oral) exposure from washing treated nets

A total daily systemic exposure to chlorfenapyr while washing treated net was calculated in Table 13 as the summation of the values for dermal and oral routes of exposure given above.

Table 13. Estimated total exposure from dermal and oral routes due to washing treated nets

Subpopulation	Dermal Exposure (µg/kg bw/day)	Oral Exposure (µg/kg bw/day)	Total Systemic Dose (µg/kg bw/day)
Acute exposure (maximum)			
Adult	4.47	13.65	18.12
Children	5.38	17.98	23.36
Repeated exposure (TWA)			
Adult	0.082	0.249	0.331

Children	0.098	0.328	0.426

2.2.4 Exposure via breast milk

Newborns might be exposed to chlorfenapyr through breast milk of lactating mothers who sleep under the treated nets and/or wash the nets. Since data on the actual excretion in milk are not available, an upper bound of the exposure from the mother's milk can be roughly estimated from the physicochemical characteristics and kinetics of the pesticide (WHO, 2018). The estimated systemic dose to the newborn is calculated based on the estimated systemic dose to the mother. Estimates for systemic maximal and TWA doses from exposure via breast milk are calculated as follows:

$$\text{Systemic dose} = \frac{\text{Abs-O x Sol C} \times \text{dose (mother)} \times T½ \times \text{IR}}{\text{BW}}$$

Since inhalation exposure to the mother sleeping under the net is negligible, the maximum systemic doses and TWA doses are derived from dermal exposure sleeping under the net and oral exposure through washing of nets.

$Dose_{Mbw}$ (maternal dose) = Total exposure from sleeping under net + Total exposure from washing of net

$Dose_{Mbw}$ (maximum) = 0.159 + 18.12 µg/kg bw/day = 18.28 µg/kg bw/day

$Dose_{Mbw}$ (TWA) = 0.159 + 0.331 µg/kg bw/day = 0.49 µg/kg bw/day

The estimated maximum systemic dose from exposure via breast milk is shown in Table 14.

Table 14. Estimated maximum systemic dose from exposure via breast milk

Subpopulation	Abs-O (%)	SolC	Dose (ug/kg/day)	$T_{1/2}$ (days)	IR (kg/day)	BW (kg)	Systemic dose (µg/kg bw/day)
Newborns	100	0.361	18.28	2.5	0.66	4.2	2.60
Infants	100	0.361	18.28	2.5	0.66	8.0	1.36

The estimated TWA systemic dose from exposure via breast milk is shown in Table 15.

Table 15. Estimated systemic dose (TWA) from repeated exposure via breast milk

Subpopulation	Abs-O (%)	SolC	Dose (ug/kg/day)	$T_{1/2}$ (days)	IR (kg/day)	BW (kg)	Systemic dose (µg/kg bw/day)
Newborns	100	0.361	0.49	2.5	0.66	4.2	0.070
Infants	100	0.361	0.49	2.5	0.66	8.0	0.036

SolC = Solubility constant, default value
$T_{1/2}$ = First-order kinetics half time of chlorfenapyr in days, 2.5 days
Dose = Daily dose to the mother from repeated (TWA) and acute (maximum) dermal + oral exposure (from Table 12)
IR = default = 0.66 kg/day
BW = default values

2.3 Risk characterization

The purpose of risk characterization is to examine the probability of adverse effects occurring resulting 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).

$$\text{Ratio} = \frac{\text{Total exposed dose (µg kg bw/day)}}{\text{TSD (µg/kg bw/day)}}$$

When the active ingredient has significant acute toxicity, the aRfD is used as the TSD_{AC} to calculate risk ratios as shown below (WHO, 2018).

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

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 risk ratios for all the populations (adults, children, toddlers and infants) sleeping under treated nets and for adults and children washing the long-lasting bed nets treated with chlorfenapyr are presented in Tables 16–18.

2.3.1 Exposure estimates and risk ratios for sleeping under treated nets

The risk ratios for all populations sleeping under treated nets are presented in Table 16.

Table 16. Exposure estimates and risk ratios for all populations sleeping under chlorfenapyr-treated nets

Subpopulation	Inhalation exposure	Dermal exposure (µg/kg/day)	Oral indirect exposure (µg/kg/day)	Oral direct exposure (µg/kg/day)	Total exposure (µg/kg/day)	TSD (µg/kg/day)	Risk ratio
Adults	Negligible	0.159	Not applicable	Not applicable	0.159	50	0.003
Children	Negligible	0.220	Not applicable	Not applicable	0.220	50	0.004
Toddlers	Negligible	0.269	0.146	2.60	3.015	50	0.060
Infants	Negligible	0.293	0.160	3.24	3.693	50	0.079

Acute and repeated exposure TSD = 50 µg/kg bw/day
Risk ratio = Total exposure/TSD

2.3.2 Exposure estimates and risk ratios for washing treated nets

The risk ratios for all populations washing treated nets are depicted in Table 17.

Table 17. Exposure estimates and risk ratios for populations washing chlorfenapyr-treated nets

Subpopulation	Dermal exposure (µg/kg bw/day)	Oral exposure (µg/kg bw/day)	Total exposure (µg/kg bw/day)	Acute RfD (µg/kg bw)	TSD (µg/kg bw/day)	Risk ratio
Acute exposure (maximum)						
Adults	4.47	13.65	18.12	50	Not applicable	0.36
Children	5.38	17.98	23.36	50	Not applicable	0.47
Repeated exposure (TWA)						
Adult	0.082	0.249	0.331	Not applicable	50	0.006
Children	0.098	0.328	0.426	Not applicable	50	0.008

Acute and repeated exposure TSD= 50 µg/kg bw/day
Risk ratio = Total Exposure/TSD

2.3.3 Combined for sleeping under nets and washing nets

The combined risk ratios for all populations sleeping under and washing chlorfenapyr-treated nets are presented in Table 18.

Table 18. Exposure estimates and risk ratios for populations sleeping under and washing chlorfenapyr-treated nets

Sub population	Sleeping under nets (combined) (µg/kg/day)	Washing of nets combined (µg/kg/day)	Total exposure (µg/kg/day)	Acute RfD (µg/kg bw)	TSD (µg/kg/day)	Risk ratio
Acute exposure (maximum)						
Adults	0.159	18.12	18.28	50	N/A	0.366
Children	0.220	23.36	23.58	50	N/A	0.471
Repeated exposure (TWA)						
Adults	0.159	0.331	0.49	N/A	50	0.001
Children	0.220	0.426	0.65	N/A	50	0.013

Acute and repeated exposure TSD= 50 µg/kg bw/day
Risk ratio = Total Exposure/TSD

2.3.4 Combined exposure estimates for infants and newborns

The combined risk ratios for infants and newborns sleeping under treated nets and consuming breast milk are shown in Table 19.

Table 19. Exposure estimates and risk ratios for populations sleeping under chlorfenapyr-treated nets and consuming breast milk

Sub population	Total exposure sleeping under nets (dermal + oral indirect + oral direct) (µg/kg/day)	Breast milk exposure (µg/kg/day)	Total exposure (µg/kg/day)	Acute RfD (µg/kg /day)	TSD (µg/kg/day)	Risk ratio
Acute exposure (maximum)						
Newborns	N/A	2.60	2.60	50	N/A	0.052
Infants	3.69	1.36	5.05	50	N/A	0.101
Repeated exposure (TWA)						
Newborns	N/A	0.070	0.70	N/A	50	0.014
Infants	3.69	0.036	3.73	N/A	50	0.066

Acute and repeated exposure TSD= 50 µg/kg bw/day
Risk ratio = Total Exposure/TSD

2.4 Risk conclusion

The risk ratios are < 1 and the potential health risk is acceptable for all routes of exposure (inhalation, dermal and oral) for:

- Acute and repeated exposure for all populations sleeping under treated nets
- Acute and repeated exposure for all adults and children washing treated nets
- Acute and repeated exposure for adults and children sleeping under and washing the treated nets
- Acute and repeated exposure for infants and newborns exposed via breast milk and sleeping under nets

Table 20. Summary of risk characterization for chlorfenapyr-treated nets (up to 6.5 g/kg or 260 mg/m^2)

Activity/population	Risk acceptable/not acceptable
Sleeping under net – dermal exposure	
Adult	Acceptable
Children	Acceptable
Toddlers	Acceptable
Infants	Acceptable
Washing of nets – acute	
Adult	Acceptable
Children	Acceptable
Washing of nets – repeated conditions	
Adult	Acceptable
Children	Acceptable
Sleeping under and washing of nets – acute condition	
Adult	Acceptable
Children	Acceptable
Sleeping under and washing of nets – repeated conditions	
Adult	Acceptable
Children	Acceptable
Exposures via breast milk from mothers	
Infants (acute and chronic)	Acceptable
Newborn (acute and chronic)	Acceptable
Combined: sleeping under net and breast milk	
Infants (acute and chronic)	Acceptable
Newborn (acute and chronic)	Acceptable

3 Conclusion

Considering the selected product characteristics identified in section 1.0, the use of chlorfenapyr formulated as an ITN in the course of vector control does not present any unacceptable risk for adults, children, toddlers, and infants sleeping under the treated nets, or for adults and children both sleeping under and washing of treated nets, or for infants and newborns sleeping under the treated nets and exposed through breast milk. The calculated exposure levels were in all cases below the long-term tolerable systemic doses of chlorfenapyr and can be used safety for its intended use as a VCP ITN.

Appendix. Chlorfenapyr health hazard assessment

1 Introduction to chlorfenapyr

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 on these authoritative evaluations, focusing on the studies and endpoints applicable to the risk 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.

Chlorfenapyr (4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile) belongs to the class of arylpyrrole acaricides insecticides. It is a broad-spectrum insecticide that acts by uncoupling of oxidative phosphorylation in the mitochondria, thereby affecting the conversion of ADP to ATP, causing mortality of the insect. It is used in agriculture for application to fruiting vegetables and ornamentals, indoor and outdoor residential sites, food/feed handling areas, indoor and outdoor commercial sites, and indoor medical sites (USEPA, 2020).

There is sufficient information on the toxicity of chlorfenapyr to conduct a human health hazard assessment. Chlorfenapyr was evaluated by the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) (JMPR) most recently in 2012. A Human Health Risk Assessment was most recently conducted by the US Environmental Protection Agency (USEPA) in 2020 and the European Chemicals Agency (ECHA) published an Assessment Report in 2012. The toxicology database is adequate for purposes of PQT/VCP.

2 Hazard characterization

Only studies relevant to the hazard evaluation of vector control products 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, chlorfenapyr technical, to conduct a human health hazard assessment. Chlorfenapyr targets the central nervous system (CNS) inducing neurophysiological changes following subchronic and chronic dietary administration to mice and rats. Rats exhibited neurobehavioral changes on the day of dosing in the acute neurotoxicity study and decreased motor activity in adults as well as in offspring in the developmental neurotoxicity study. Several rat studies also noted effects in the liver (increased organ weights and tumors) at doses similar to or above those where CNS effects were seen. There was no evidence of increased susceptibility to offspring following *in utero* exposure to rats and rabbits. There was evidenced of increased susceptibility in the offspring in the two-generation reproduction study in rats. Chlorfenapyr did not show any evidence of mutagenicity in *in vitro* or *in vivo* studies. Chlorfenapyr is classified as "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential", but not sufficient to assess human carcinogenic potential" (USEPA, 2020).

2.1 Acute toxicity

Chlorfenapyr has low toxicity via the oral and dermal routes of exposure and mild to moderate toxicity via the inhalation route of exposure. Acute oral resulted in Category 4 as per the Globally Harmonized System of Classification (GHS). Acute dermal was classified as Category 5 and acute inhalation toxicity was classified as GHS Category 3. It is neither a skin irritant nor a dermal sensitizer (not classifiable) but did result in mild eye irritant and classified in Category 2B (USEPA, 2020) (Appendix 5.1, Table A1).

2.2 Subchronic toxicity

In a subchronic oral toxicity study with mice, doses of chlorfenapyr were administered via diet at dose levels of 0, 40, 80, 160, 320 ppm (equivalent to approximately 0, 7.1, 14.8, 27.6, 62.6 mg/kg bw/day for males, and 0, 9.2, 19.3, 40, and 78 mg/kg bw/day, respectively) for 90 days. The NOAEL was 14.8 mg/kg/day in males and 19.3 mg/kg/day in females and the LOAEL was 27.6 mg/kg/day in males and 40.4 mg/kg/day in females based on increased spleen weights (absolute and relative). Spongiform encephalopathy and significant changes in blood chemistry observed in both sexes at the high dose (78 mg/kg/day) (USEPA, 2020).

In a subchronic oral toxicity study with rats, chlorfenapyr technical was administered via diet at dose levels of 0, 150, 300, 600, 900, and 1200 ppm (approximately 0, 11.7, 24.1, 48.8, 72.5, and 94.5 mg/kg bw/day, respectively) for 90 days. The NOAEL was 24.1 mg/kg/day, and the LOAEL was 48.4 mg/kg/day based on spongiform myelopathy in the brain and spinal cord of male rats, and increased liver weight in males and females, increased absolute liver weight in females and decreased hemoglobin in females (USEPA, 2020).

In a subchronic dietary toxicity study with purebred Beagle dogs, chlorfenapyr (purity 95.4%) was fed to four groups of four males and four females for 90 days at dietary doses levels of 0, 60, 120, and approximately 247 ppm (equivalent to 0, 2.1. 3.9, and 6.7 mg/kg bw/day for males and 0, 2.2, 4.5, and 6.8 mg/kg bw/day for females). The NOAEL was 6.7 mg/kg/day, the highest dose tested. A LOAEL was not established (USEPA, 2020).

In a subchronic inhalation toxicity study with 15 male and 15 female Wistar rats per test group were exposed, nose-only, to dust aerosols of chlorfenapyr (purity 97.8%) for 6 hours per working day, 5 days/week, for approximately 90 days. Of the 15 animals/sex/group, 10 were part of the main group and were terminated 1 day after the exposure period. The 5 remaining animals per group were terminated after a recovery period of 28 days. The concentrations were 0 (control air), 5, 20, 40, and 80 mg/m^3. The NOAEL was 20 mg/m^3 and the LOAEL was 40 mg/m^3 based on visually accelerated respiration, increased white blood cell and lymphocyte counts, and changes in clinical parameters in both sexes. Mortality observed in males at 80 mg/m^3 (USEPA, 2020).

In a subchronic dermal toxicity study, chlorfenapyr technical was applied to the skin of rats for 28 days at doses of 0, 100, 300, and 1000 ppm (approximately 0, 72.1, 205.5, 835 mg/kg bw/day). The NOAEL was 205.5 mg/kg/day, and the LOAEL was 835 mg/kg/day based on clinical signs consisting of slight to moderate urine smearing of the anogenital region for several days in female rats and liver weight increases (absolute and relative) in both sexes (USEPA, 2020).

2.3 Chronic toxicity and carcinogenicity

In a chronic dietary toxicity study with Beagle dogs, chlorfenapyr technical was administered via capsule at dose levels of 0, 60, 120, or 240 ppm (equivalent to 0, 2.1, 4.0, 8.7 mg/kg bw/day for males and 0, 2.3, 4.5, 10.1 mg/kg bw/day for females) for one year. The NOAEL was selected at 4.0 mg/kg/day in males and 4.5 mg/kg/day in females and the LOAEL was 8.7 mg/kg/day in males and 10.1 mg/kg/day in females based on decreased body weight in both sexes (USEPA, 2020).

In a combined chronic toxicity/carcinogenicity study, four groups of 65 male and 65 female Sprague-Dawley rats were administered chlorfenapyr (purity 94.5%) for 24 months via diet at dose levels of 0, 60, 300, or 600 ppm (achieved intake of 0, 2.9, 15, or 30.8 mg/kg bw/day for males and 0, 3.6, 18.6, and 37 mg/kg bw/day for females, respectively). An interim/chronic termination was also conducted on 10 rats/sex/dose group after 12 months treatment. The systemic NOAEL was 15 mg/kg/day, and the LOAEL was 30.8 mg/kg/day based on anemia. In female rats, the systemic NOAEL was 3.6 mg/kg/day and the LOAEL was 18.6 mg/kg/day based on decreased body weights. There was no evidence of carcinogenicity (USEPA, 2020).

In a carcinogenicity study with CD-1 albino mice, chlorfenapyr (purity 94.5%) was fed to four groups of 65 males and 65 females for 18 months at dietary concentrations of 0, 20, 120, or 240 ppm (achieved intakes were 0, 2.8, 16.6, or 34.5 mg/kg bw/day for males and 0, 3.7, 21.9, or 4.5 mg/kg bw/day for females, respectively). The systemic NOAEL was 2.8 mg/kg/day in males and 3.7 mg/kg/day in females and the LOAEL was 16.6 mg/kg/day in males and 21.9 mg/kg/day in females based on brain vacuolation and scabbing of the skin (USEPA, 2020). There was no evidence of carcinogenicity.

2.4 Developmental

In a prenatal developmental toxicity study with Sprague-Dawley rats, pregnant females were administered 0, 25, 75, or 225 mg/kg bw/day of chlorfenapyr (purity 94.5%) via gavage in vehicle 0.5% carboxymethylcellulose on day 6 through day 15 of gestation. For maternal toxicity, the NOAEL was 225 mg/kg/day, the highest dose tested. A LOAEL for maternal toxicity was not established. For developmental toxicity, the NOAEL was 225 mg/kg/day; a developmental LOAEL was not established. There was no evidence of developmental toxicity (USEPA, 2020).

In a prenatal developmental toxicity study, four groups of 20 artificially inseminated female New Zealand White rabbits were administered chlorfenapyr (purity 94.5%) by gavage in vehicle 0.5% carboxymethylcellulose at a dose level of 0, 5, 15, or 30 mg/kg bw/day from day 7 through 19 of gestation. Animals were sacrificed on day 29 of gestation. For maternal toxicity, the NOAEL was 30 mg/kg/day, the highest dose tested. A LOAEL for maternal toxicity was not established. For developmental toxicity, the NOAEL was 30 mg/kg/day; a developmental LOAEL was not established. There was no evidence of developmental toxicity (USEPA, 2020).

2.5 Reproduction toxicity

In reproductive and fertility study with Sprague-Dawley rats, chlorfenapyr (purity 94.5%) was administered daily via diet at concentrations of 0, 60, 300, or 600 ppm (approximately 0, 5, 22, or 44 mg/kg bw/day, respectively). The parental generations were treated during a premating period of 10-11 weeks and continued through day 20 of mating and then a post-mating period. Mated females continued treatment during gestation, lactation, and post-weaning periods until termination. F_1 and F_2 litters were culled on postnatal day 4. For parental toxicity, the NOAEL was 22 mg/kg/day in males and 24.5 mg/kg/day in females and the LOAEL was 44 mg/kg/day in males and 48.3 mg/kg/day in females based on decreases in body weights in both sexes. For reproductive toxicity, the NOAEL was 48.3 mg/kg/day; a LOAEL was not established. There was no evidence of reproductive toxicity. For offspring toxicity, the NOAEL was 4.5 mg/kg/day in males and 5 mg/kg/day in females and the LOAEL was 22.2 mg/kg/day in males and 24.5 mg/kg/day in females based on decreases in pup body weights (USEPA, 2020).

2.6 Genotoxicity

In a bacterial reverse mutation assay, chlorfenapyr was negative in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, TA 1538 and *Escherichia coli* strain WP2 uvrA – exposed up to cytotoxicity (50 µg/plate) with or without metabolic activation (USEPA, 2020).

In an *in vitro* mammalian cell mutation assay, chlorfenapyr was negative up to a cytotoxic and precipitating concentration (500 µg/mL) in the presence of S9 activation or the solubility limit (250 µg/mL) without S9 activation (USEPA, 2020).

In an *in vitro* chromosomal aberration assay, chlorfenapyr was negative up to 100 µg/mL without metabolic activation or 25 µg/mL with metabolic activation; higher doses with or without S9 activation were cytotoxic (USEPA, 2020).

In an *in vitro* chromosomal aberration assay with Chinese hamster lung cells, chlorfenapyr was negative up to a precipitating level without S9 activation (225 µg/mL) or a concentration range of 3.5-14.1 µg/mL with metabolic activation. Higher S9-activated doses (≥28 µg/mL) were cytotoxic (USEPA, 2020).

In a micronucleus assay with mice, chlorfenapyr was negative in mice administered single oral gavage doses of 7.5-30 mg/kg (males) or 5-20 mg/kg (females). Clinical toxicity (deaths in males and diarrhea in females) was seen at the HDT. There was however no evidence of cytotoxicity for the target organ (USEPA, 2020).

In an unscheduled DNA synthesis, chlorfenapyr was negative for inducing unscheduled DNA synthesis in primary rat hepatocyte cultures exposed up to concentrations greater than 30 µg/mL (USEPA, 2020).

2.7 Neurotoxicity

In an acute neurotoxicity study with rats, a single bolus dose of chlorpenapyr (purity 94.5%) was administered via gavage, to 10 Sprague-Dawley CD rat/sex/dose at dose levels of 0, 45, 90, or 180 mg/kg bw. The LOAEL was 45 mg/kg/day, the lowest dose tested based on decreased motor activity on day of dosing. A NOAEL was not established (USEPA, 2020).

In a subchronic neurotoxicity study with rats, chlorfenapyr was fed to four groups of 25 Sprague-Dawley rat for 52 weeks via diet at doses on 0, 60, 300, or 600 ppm (achieved doses were 0. 2.6. 13.6, 28.2 mg/kg bw/day for males and 0, 3.4, 18, and 37.4 for females, respectively). The NOAEL was 2.6 mg/kg/day in males and 3.4 mg/kg/day in females and the LOAEL was 13.6 mg/kg/day in males and 18 mg/kg/day in females based on the presence of alterations in the myelin of the CNS in male rats, decreased body-weight, food efficiency, absolute food consumption in females and water consumption in males (USEPA, 2020).

In a developmental neurotoxicity study with Wistar rats, chlorfenapyr was administered via gavage in 0.5% carboxymethylcellulose to 40 pregnant female rats/dose from gestation day 6 (GD 6) through lactation day 10 (LD 10). A functional observational battery was performed on 10 dams/dose on GD 7, GD 14, LD 7, and LD 14. On postnatal day 4, litters were culled (four animals per sex) and the test material was administered via gavage from PND 11 through PND 21. For maternal toxicity, the NOAEL was 15 mg/kg/day; a LOAEL was not established. For developmental neurotoxicity, the NOAEL was 5 mg/kg/day and the LOAEL was 10 mg/kg/day based on increased pup deaths and decreased motor activity. In pups at the high dose 15 mg/kg/day, vacuolation of the white matter and decreased hippocampus size were observed in several areas of the brain of 22-day old pups (USEPA, 2020).

2.8 Special study

A study on the pharmacological potential of chlorfenapyr was performed on mice with the purpose of evaluating the central nervous system, respiratory and cardiovascular systems, autonomic nervous system, gastrointestinal system, skeletal muscle and blood coagulation. A single oral dose of 3, 10, 30, or 100 mg/kg bw was administered to three male mice. A NOAEL of 3 mg/kg bw was selected based on depression of grooming behavior and reactivity, and increased frequency of prone position and slight diarrhea at the LOAEL of 10 mg/kg bw (JMPR, 2012).

2.9 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.

2.9.1 Oral route studies

In a rat metabolism study, fecal excretion was the major route of elimination (80% of recovered radioactivity) with low recoveries of the radioactive chlorfenapyr in urine and tissues. Most of the radioactivity was eliminated within 48 hours of dosing. Female rats had greater recovery of radioactivity (about 2X at the low dose) in the fat, carcass, and blood at all doses than did males. The highest recovery of radioactivity from a single organ was from the liver (0.15-0.48% of the administered dose). Parent compound was the major radioactive component found in excreta, accounting for approximately 40-70% of the administered doses. Minor amounts of eight primary and conjugated metabolites and four unidentified isolated components were detected, each at less than 10% of the dosed radioactivity. Liver and kidney contained several primary and conjugated metabolites and only minor levels of the parent compound (£8.3% of the radioactivity in the sample). Identified metabolites were minimally accumulated in tissues and primarily excreted in the urine (USEPA, 2020).

In a biliary excretion study following oral administration of 2 mg/kg chlorfenapyr to rats, tissues residues were 25-37%, urinary excretion was approximately 4-5 % and biliary excretion was around 18-20% at 24 hours post dosing. Based on these findings, the oral absorption value was determined to be at least 60% of the administered dose (ECHA, 2012).

2.9.2 Dermal route studies

In an *in vivo* study, rats received dermal application of a formulation concentrate (BAS 306 02) at 2.4 mg/cm^2 and 0.0217 mg/cm^2. At 8, 24, and 120 hours, dermal absorption (tissues, excreta, surrounding skin, and application site) for the 2.4 mg/cm^2 dose was 6.4%, 3.9%, and 3.6%, respectively. At 8, 24, and 120 hours, dermal absorption (tissues, excreta, surrounding skin, and application site) for the 0.0217 mg/cm^2 dose was 13.1%, 10.7%, and 15.1%, respectively. Dermal absorption of 13% after 8 hours of exposure was calculated at the lowest dose tested (approximately 25 µg/cm^2) based on excreta, cage wash, blood, plasma, carcass, application site, and the surrounding skin (USEPA, 2020).

In the *in vitro* studies, rat and human skins were exposed to a formulation concentrate (BAS 306 02) at 25, 100 or 250 µg/cm^2. The total potentially absorbed dose for rat skin was 15.81%, 22.44%, and 11.12% at the low-, mid-, and high-doses. The total potentially absorbed dose for human skin was 1.42%, 0.16%, and 0.49% at the low-, mid-, and high-dose. Based on the results of these studies the USEPA calculated dermal absorption of 1.2% (USEPA, 2020).

$$\text{Abs-D} = \frac{\text{rat } \textit{in vivo} \text{ (13\%) x human } \textit{in vitro} \text{ (1.4\%)}}{\text{rat } \textit{in vitro} \text{ (15.8\%)}} = 1.2\%$$

2.9.3 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)

JMPR (2012) selected an oral POD of 3.0 mg/kg/day (NOAEL) based on depression of grooming and reactivity and decreased spontaneous motor activity at 10 mg/kg/day in a pharmacology study with mice.

USEPA (2020) selected an oral POD of 5 mg/kg/day from the reproduction toxicity study based on increased deaths in pups on post-natal days 1-4 and decreased motor activity in pups at 10 mg/kg/day in a developmental neurotoxicity study in rats.

$$\text{Acute oral POD} = 5 \text{ mg/kg bw}$$

JMPR established an aRfD of 0.03 mg/kg bw based on a POD of 3 mg/kg/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities.

USEPA established an aRfD of 0.05 mg/kg bw based on a POD of 5 mg/kg/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities.

$$\text{aRfD} = 5 \text{ mg/kg bw} \div 100 = 0.05 \text{ mg/kg/day}$$

3.2.2 Chronic reference dose (aRfD)

JMPR (2012) selected the oral POD of 2.8 mg/kg/day based on decreased body weight gain and vacuolation of the white matter of the brain at 16.6 mg/kg/day in a carcinogenicity study in mice.

USEPA (2020) selected the oral POD of 5 mg/kg/day from the reproduction toxicity study based on increased deaths in pups on post-natal days 1-4 and decreased motor activity in pups at 10 mg/kg/day in a developmental neurotoxicity study in rats.

Chronic oral POD = 5 mg/kg bw/day

Although the POD established by the USEPA is slightly higher than that established by JMPR, the higher POD is chosen for both acute and chronic risk assessments due to the toxicological significance of the adverse effects observed in the most sensitive population subgroup (pups) in a study that examined developmental neurobehavior and neuropathology.

USEPA **established a cRfD of 0.05 mg/kg bw/day based** on a POD of 5 mg/kg/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities.

cRfD = 5 mg/kg bw/day ÷ 100 = 0.05 mg/kg/bw/day

3.2.3 Acceptable daily intake (ADI)

JMPR established an ADI of 0.03 mg/kg bw/day based on a NOAEL of 2.8 mg/kg bw/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities.

ADI = 2.8 mg/kg bw/day ÷ 100X = 0.03 mg/kg bw/day

3.3 Cancer classification

Classified as “suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential” (USEPA, 2020).

4 Toxicity profile tables

4.1 Acute toxicity

Table A1. Acute toxicity of chlorfenapyr technical

Route of exposure	Species	Toxicity	GHS category	Reference
Acute oral toxicity	Rat Purity 94.5%	LD_{50} = 441 mg/kg (males) LD_{50} = 1152 mg/kg (females) LD_{50} = 626 mg/kg/bw (combined)	4	USEPA, 2020
Acute dermal toxicity	Rabbit Purity 94.5%	LD_{50} >2000 mg/kg (male and female)	5	USEPA, 2020
Acute Inhalation	Rat Purity 94.5% 4 h, dust, whole body	LC_{50} = 0.83mg/L (males) LC_{50} > 2.7 mg/L (females) LC_{50} = 1.9 mg/L (combined)	3	USEPA, 2020
Dermal irritation	Rabbit Purity 94.5%	Non-irritant	Not classified	USEPA, 2020
Eye irritation	Rabbit Purity 94.5%	Mild irritant Corneal opacity, iritis, and conjunctivitis present at 48 h. All animals recovered by Day 7.	2B	USEPA, 2020
Skin sensitization	Guinea pig Purity 94.5% Buehler Method	Non-sensitizer	Not classified	USEPA, 2020

4.2 Subchronic, chronic, and carcinogenicity studies

Table A2. Subchronic, chronic, carcinogenicity, and other toxicity studies with chlorfenapyr

Chlorfenapyr – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Dose levels; design**	**Results**
Subchronic- toxicity		
90-Day oral – Rat	0, 150, 300, 600, 900, 1200 Ppm. Equivalent to 0, 11.7, 24.1, 48.4, 72.5, 94.5 mg/kg/day	NOAEL =24.1 mg/kg/day. LOAEL = 48.4 mg/kg/day based on spongiform myelopathy in the brain and spinal cord of male rats, and increased liver weight in males and females, increased absolute liver weight in females and decreased hemoglobin in females.
90-Day oral – Mouse	0, 40, 80, 160, 320 ppm Equivalent to 0, 7.1, 14.8, 27.6, 62.6 mg/kg/day in males and 0, 9.2, 19.3, 40, 78 mg/kg/day in females.	NOAEL = 14.8/19.3 mg/kg/day (M/F). LOAEL = 27.6/40.0 mg/kg/day (M/F) based on increased spleen weights (absolute and relative). Spongiform encephalopathy and significant changes in blood chemistry observed in both sexes at the HDT.
90-Day oral – Dog	0, 60, 120, ~247 ppm Equivalent to 0, 2.1, 3.9, 6.7 mg/kg/day in males and 0, 2.2, 4.5, 6.8 mg/kg/day in females.	NOAEL = 6.7/6.8 mg/kg/day (M/F). LOAEL not established.
28-Day dermal toxicity (rat)	0, 100, 300, 1000 ppm. Equivalent to 0, 72.1, 205.5, 835 mg/kg/day	NOAEL = 205.5 mg/kg/day. LOAEL = 835 mg/kg/day based on clinical signs consisting of slight to moderate urine smearing of the anogenital region for several days in female rats and liver weight increases (absolute and relative) in both sexes.
90-day inhalation – Rat	0, 5, 20, 40, 80 mg/m^3	NOAEL = 20 mg/m^3. LOAEL = 40 mg/m^3 based on visually accelerated respiration, increased white blood cell and lymphocyte counts, and changes in clinical parameters in both sexes. Mortality observed in males at 80 mg/m^3.
Developmental and reproductive toxicity		
Developmental – Rat	0, 25, 75, 225 mg/kg/day	Maternal NOAEL = 225 mg/kg/day. Maternal LOAEL not established. Developmental NOAEL = 225 mg/kg/day. Developmental LOAEL not established.
Developmental – Rabbit	0, 5, 15, 30 mg/kg/day	Maternal NOAEL = 30 mg/kg/day. Maternal LOAEL not established. Developmental NOAEL = 30 mg/kg/day. Developmental LOAEL not established.
Reproduction and fertility effects – Rat	0, 60, 300, 600 ppm Equivalent to 0, 4.5, 22.2, 44.0 mg/kg/day in males and 0, 5.0, 24.5, 48.3 mg/kg/day in females	Parental NOAEL = 22.2/24.5 mg/kg/day (M/F). Parental LOAEL = 44.0/48.3 mg/kg/day (M/F) based on decreased body weight. Offspring NOAEL = 4.5/5.0 mg/kg/day (M/F). Offspring LOAEL = 22.2/24.5 mg/kg/day (M/F) based on decreased pup weights. Pup deaths were considered adverse at the high-dose in the F_2 generation. Reproductive NOAEL = 44.0/48.3 mg/kg/day (M/F). Reproductive LOAEL not established.
Neurotoxicity		
Acute neurotoxicity screening battery – Rat	0, 45, 90, 180 mg/kg	NOAEL = not established. LOAEL = 45 mg/kg/day based on decreased motor activity on day of dosing.
Chronic neurotoxicity screening battery – Rat	0, 60, 300, 600 ppm Equivalent to 0, 2.6, 13.6, 28.2 mg/kg/day in males and 0, 3.4, 18.0, 37.4 mg/kg/day in females	NOAEL = 2.6/3.4 mg/kg/day (M/F). LOAEL = 13.6/18.0 mg/kg/day (M/F) based on the presence of alterations in the myelin of the CNS in male rats, decreased body-weight, food efficiency, absolute food consumption (females) and water consumption (males).
Developmental neurotoxicity – Rat	0, 5, 10, 15 mg/kg/day	Maternal NOAEL = 15 mg/kg/day. Maternal LOAEL not established. Developmental NOAEL = 5 mg/kg/day. Developmental LOAEL = 10 mg/kg/day based on increased pup deaths and decreased motor activity.

Chlorfenapyr – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Dose levels; design**	**Results**
Chronic toxicity/carcinogenicity		
Chronic – Dog	0, 60, 120, 240 ppm Equivalent to 0, 2.1, 4.0, 8.7 mg/kg/day in males and 0, 2.3, 4.5, 10.1 mg/kg/day in females	NOAEL = 4.0/4.5 mg/kg/day (M/F). LOAEL = 8.7/10.1 mg/kg/day (M/F) based on decreased body-weight.
Carcinogenicity – Mouse	0, 20, 120, 240 ppm Equivalent to 0, 2.8, 16.6, 34.5 mg/kg/day in males and 0, 3.7, 21.9, 44.5 mg/kg/day in females	NOAEL = 2.8/3.7 mg/kg/day (M/F). LOAEL = 16.6/21.9 mg/kg/day (M/F) based on brain vacuolation and scabbing of the skin). No evidence of carcinogenicity.
Combined chronic toxicity/ carcinogenicity – Rat	0, 60, 300, 600 ppm Equivalent to 0, 2.9, 15.0, 30.8 mg/kg/day in males and 0, 3.6, 18.6, 37.0 mg/kg/day in females	NOAEL = 15 mg/kg/day (males). LOAEL = 30.8 mg/kg/day based on anemia. NOAEL = 3.6 mg/kg/day (females). LOAEL = 18.6 mg/kg/day based on decreased body-weight in females. "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" based on significant trends in liver tumors (adenomas and combined adenomas/carcinomas), malignant histiocytic sarcomas, and testicular cell tumors in male rats and uterine polyps in female rats seen at the highest dose.
Genotoxicity		
Bacterial reverse mutation	S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537, TA 1538, and E. coli strain WP2 uvrA – exposed up to cytotoxicity (50 µg/plate, +/- S9).	Negative
In vitro mammalian cell gene mutation	(500 µg/mL) in the presence of S9 activation or the solubility limit (250 µg/mL) without S9 activation	Negative
In vitro mammalian chromosome aberration	100 µg/mL –S9 or 25 µg/mL +S9; higher doses with or without S9 Activation.	Negative
In vitro chromosome aberration assay in Chinese hamster lung cells	Up to a precipitating level without S9 activation (225 µg/mL) or a concentration range of 3.5-14.1 µg/mL +S9. Higher S9-activated doses (≥28 µg/mL) were cytotoxic.	Negative
Mammalian micronucleus (mouse)	Mice administered single oral gavage doses of 7.5-30 mg/kg (males) or 5-20 mg/kg (females).	Negative
Unscheduled DNA synthesis	Primary rat hepatocyte cultures exposed up to severely toxic concentrations (≥30 µg/mL).	Negative
Metabolism and dermal absorption		
Metabolism and pharmacokinetics – Rat	20, 200 mg/kg/day	Low recoveries of the radioactive dose in urine and tissues indicated limited absorption. More than 80% of the doses were eliminated in the feces. Most of the radioactivity was eliminated in the feces and urine within 48 hours of dosing. After 7 days, 89-121% of the dosed radioactivity was recovered. At sacrifice, female rats had greater recovery (about twice) in the carcass, blood, and fat at all doses than did males. The highest recovery of radioactivity from a single organ was from the liver (0.15-0.48% of dose). Parent compound was the major component found in excreta (40-70% of administered doses). Based on the metabolites identified, the major deposition route of orally administered chlorfenapyr is fecal excretion of unaltered parent compound. Metabolites are minimally accumulated in tissue and excreted primarily in urine.

Chlorfenapyr – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Dose levels; design**	**Results**
In vivo dermal-penetration –Rat	Formulation concentrate (BAS 306 02 I) at 2.4 mg/cm^2 and 0.0217 mg/cm^2	At 8, 24, and 120 hours, dermal absorption (tissues, excreta, surrounding skin, and application site) for the 2.4 mg/cm^2 dose was 6.4%, 3.9%, and 3.6%, respectively. At 8, 24, and 120 hours, dermal absorption (tissues, excreta, surrounding skin, and application site) for the 0.0217 mg/cm^2 dose was 13.1%, 10.7%, and 15.1%, respectively.
In vitro dermal-penetration (rat and human skin)	Formulation concentrate (BAS 306 02 I) at 25, 100, and 250 µg/cm^2	The total potentially absorbed dose for rat skin (calculated as the sum of the total absorbed dose and total dose associated with the skin) was 15.81%, 22.44%, and 11.12% at the low-, mid-, and high-doses. The total potentially absorbed dose for human skin was 1.42%, 0.16%, and 0.49% at the low-, mid-, and high-doses.
Pharmacological study - Mouse	Vehicle control, 0.3, 1, 3, 10, 30, 100 mg/kg bw	NOAEL = 3 mg/kg bw LOAEL = 10 mg/kg bw depression of grooming behavior and reactivity, increased frequency of prone position and slight diarrhea.

(USEPA, 2020; JMPR, 2012)

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WHO Prequalification of Vector Control Products
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