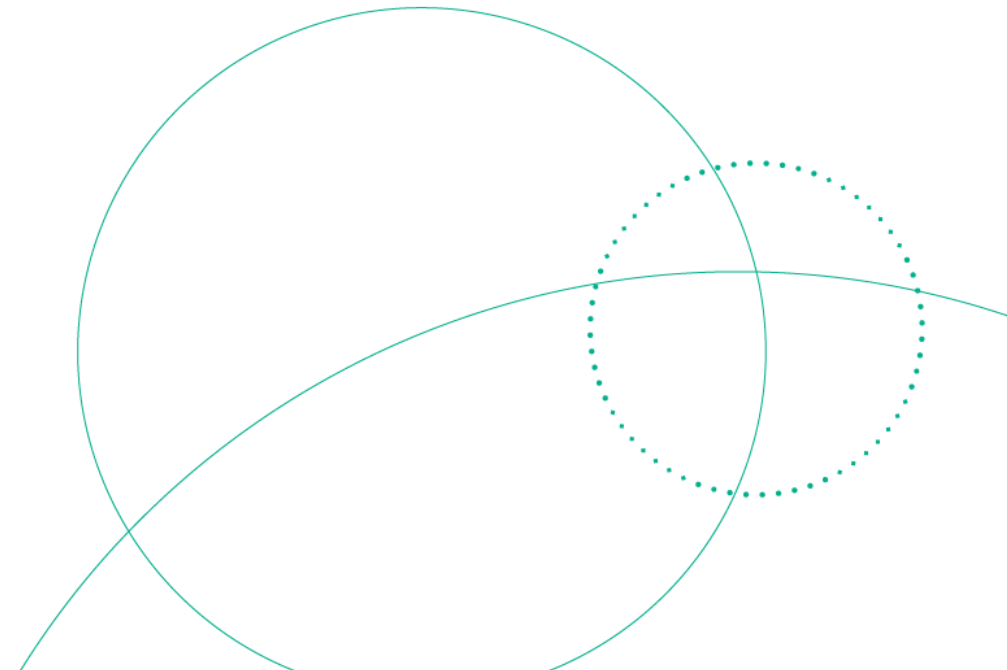
World Health Organization

WHO Prequalification Programme / Vector Control Product Assessment

WHO Public Assessment Report: WHOPAR Part 4

PermaNet Dual (Vestergaard Sàrl) P-03228

Safety Assessment



Contents

Acronyms

Abs	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
CP	Cyclophosphamide
cRfD	Chronic Reference Dose
DMBA	7,12-Dimethylbenz(a)anthracene
DMSO	Dimethyl Sulfoxide
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
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 Risk assessment summary

1.1 Introduction

The applicant, Vestergaard Sàrl (Switzerland), submitted a product dossier to the WHO PQT/VCP containing supporting data for the proposed product PermaNet Dual, a coated Insecticide Treated Net (ITN). The product, PermaNet Dual, is an ITN containing the active ingredients, Deltamethrin (CAS No. 52918-63-5) and Chlorfenapyr (CAS No. 122453-73-0) at nominal concentrations of 84 mg/m^2 net and 200 mg/m^2 net, respectively.

1.2 Product identification

Product Name:	PermaNet Dual
Other Names:	
Active Ingredient:	Deltamethrin and Chlorfenapyr
CAS No.:	52918-63-5, 122453-73-0
Product Type:	Insecticide Treated Net
Nominal Concentrations:	84 mg/m2 (Deltamethrin), 200 mg/m2 (Chlorfenapyr)

1.3 Active ingredient statement

Chemically, Deltamethrin (CAS No. 52918-63-5) is a Type II pyrethroid. It induces an insecticidal effect through disruption of the activity of the sodium channel in the nervous system (IRAC group 5). Chlorfenapyr (CAS No. 122453-73-0) is an N-substituted halogenated pyrrole. It is a pro-insecticide that is converted to its active metabolite by P450 monooxygenases mechanisms.

1.4 Supporting data base

Vestergaard Sàrl submitted a document prepared by Extera (Germany) that presented the exposure and risk assessment according to the 2nd edition of the *Generic Risk Assessment Model for Insecticide-Treated Nets (GRAM)*. To assess the risks associated with exposure to PermaNet Dual, the applicant used regulatory values (i.e., Reference Doses and Acceptable Daily Doses) for Deltamethrin and Chlorfenapyr previously established by WHO in 2003 and by JMPR in 2005, respectively (Mostert, 2021).

The United States Environmental Agency (USEPA) more recently conducted human health risk assessments for Deltamethrin in 2018 and for Chlorfenapyr in 2020. These risk assessments were conducted based on regulatory values established on the most sensitive toxicity endpoints of concern observed in the most sensitive species, population, and study. The PQT/VCP determined that the regulatory values established by the USEPA are more appropriate to assess the risks to adults, infants,

and children in the current exposure scenarios for the use of PermaNet Dual. The PQT/VCP risk assessment is presented in this document.

This human health risk assessment has been completed based on the "*Generic Risk Assessment Model for Insecticide Treated Nets, 2nd Edition"* (GRAM) (WHO, 2018).

1.5 Discussion and conclusion

The potential health risk of PermaNet Dual is acceptable for all populations (adults, children, infants, and children) sleeping under treated nets, for adults and children sleeping under and washing treated nets, and for infants and newborns sleeping under treated nets and exposed via breast milk. PermaNet Dual risk ratios are below the risk ratios (i.e., less than 1) established by the 2018 GRAM for all populations, routes of exposure (inhalation, dermal and oral) and all activities (sleeping under; washing and sleeping under; and sleeping under and exposed via breast milk).

2 Human health risk assessment

This human health risk assessment for PermaNet Dual is conducted according to the *"A Generic Risk Assessment Model for Insecticide-Treated Nets,* 2nd edition" (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 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.
2. **Exposure assessment** 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 endpoint estimates of the default distributions are used as defaults. No account is taken of intended misuse. All relevant routes of exposure are considered.
3. In **risk characterization,** estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure scenarios.

2.1 Hazard assessment

The toxicology database for Deltamethrin and Chlorfenapyr is adequate to determine the health hazard and to assess the risks associated with the proposed uses of PermaNet Dual as an ITN. Additionally, the human health risk assessment of Deltamethrin is discussed and summarized in the "*Generic Risk Assessment – Human Health – Deltamethrin (CAS No. 52918-63-5). An active ingredient in insecticide-treated nets*" published by WHO in 2021 (WHO, 2021). This GRA-Deltamethrin is intended to be used as an example of the implementation of the "*Generic Risk Assessment Model for Insecticide-Treated Nets, 2nd edition*" (GRAM) (WHO, 2018).

2.1.1 Product specific acute toxicity data

The applicant submitted acute toxicity studies conducted with the formulated product PermaNet Dual. All acute studies were conducted at Diligence Bio Private Ltd., Voluntariat Road, Thuthipet, Pondicherry, India, in accordance with the OECD and/or USEPA Test Guidelines and followed all Good Laboratory Practice (GLP) Regulations. The results from the acute toxicity studies are summarised in Table 1.

PermaNet Dual (Deltamethrin: 2.1g/kg + Chlorfenapyr: 5.0 g/kg) is practically non-toxic via the oral, dermal and inhalation routes of exposure. It is neither an eye nor skin irritant and is not a dermal sensitizer.

Table 1. Acute toxicity of PermaNet Dual				
Route of exposure	**Species**	**Toxicity**	**GHS category**	**Reference**
Oral	Rat	LD_{50} = >2000 mg/kg bw	5	Naidu, 2021a
Dermal	Rat	LD_{50} = >2000 mg/kg bw	5	Naidu, 2021b
Inhalation	Rat	LC_{50} = > 5.7 mg/L bw	3	Naidu, 2021c
Dermal irritation	Rabbit	Non-irritant	Not applicable	Naidu, 2021d
Eye irritation	Rabbit	Non-irritant	Not applicable	Naidu, 2021e
Dermal sensitization	Guinea pigs	Non-sensitizer	Not applicable	Naidu, 2021f

2.1.2 Active ingredients: Deltamethrin and Chlorfenapyr

2.1.2.1 Acute toxicity data of active ingredients

The acute toxicity profile of the two components of the product, Deltamethrin and Chlorfenapyr, are presented below in Table 2 (USEPA, 2018; 2020).

Deltamethrin is a Type II pyrethroid. Pyrethroids have historically been classified into two groups, Type I and Type II, based on chemical structure and toxicological effects. Pyrethroids disrupt the voltage-gated sodium channels in the nervous system, resulting in neurotoxicity. Deltamethrin is rapidly absorbed following an oral dose, and effects are typically observed within two to five hours after dosing.

Neurotoxicity was observed throughout the database and clinical signs characteristic of Type II pyrethroids, such as increased salivation, altered mobility/gait, and tremors, were the most common effects observed. There is no evidence for dermal, developmental, reproductive, immunogenic, carcinogenic or genotoxic potential. **The toxicity profile of deltamethrin is presented in Appendix 1.**

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 and decreased motor activity in adults as well as in offspring following repeated exposure. 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 is no evidence for developmental, reproductive, or immunogenic or genotoxic potential. USEPA has classified Chlorfenapyr as showing "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." **The toxicity profile of chlorfenapyr is presented in Appendix 2**.

Table 2. Acute toxicity of Deltamethrin and Chlorfenapyr				
Route of exposure	**Deltamethrin**	**GHS category**	**Chlorfenapyr**	**GHS category**
Oral LD_{50} – Rat	>5000 mg/kg bw	5	1152 mg/kg bw	4
Dermal LD_{50} – Rabbit	> 2000 mg/kg bw	5	> 2000 mg/kg bw	5
Inhalation LC_{50} – Rat	>2.22 mg/L	3	1.9 mg/L bw	3
Primary Dermal Irritation – Rabbit	Non-irritant	Not applicable	Non-irritant	Not classified
Primary Eye Irritation – Rabbit	Moderate irritant	2B	Eye irritant	2
Skin Sensitization – Guinea pig	Non-sensitizing	Not applicable	Non-sensitizing	Not applicable

2.1.2.1.1 Oral absorption

- Deltamethrin: An oral absorption of 75% was used in the applicant's risk assessment (Mostert, 2021; RMS, 2011). In the 2021 GRA-Deltamethrin, a 100% oral absorption value was used as a default to represent a worst-case scenario (WHO, 2021). The worst-case scenario approach with 100% oral absorption is also used for Deltamethrin in the risk assessment of PermaNet Dual.

- Chlorfenapyr: 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 (RMS, 2012, Mostert, 2021).

2.1.2.1.2 Dermal absorption

- Deltamethrin: In the 2021 WHO GRA-Deltamethrin, a 1% dermal absorption factor was used as the default value for deriving the systemic doses. However, as discussed below, a data-driven dermal absorption factor is available for Deltamethrin. Dermal penetration studies have been conducted *in vitro* in rats with deltamethrin as an oil/water emulsion (EW) and as an emulsifiable concentrate (EC) in rat and human skin and in an *in vivo* study in rats. The results of these studies indicated that dermal absorption was somewhat lower for the EW 15 than for the EC 25. The main difference which is relevant to skin absorption is the solvent (water versus light aromatic solvent). The content of aromatic solvent is expected to enhance the degree of dermal absorption in comparison water-based formulations. For the solid formulations of deltamethrin a lower dermal absorption is expected since water and certain solvents favor it. Using data obtained in the dermal absorption studies on an aromatic solvent formulation, the dermal absorption of deltamethrin in humans was estimated to be 1.19% for the concentrate and 1.89% for the active substance when diluted in the spray solution. **Based on these results, the higher dermal absorption value of 2% is used in this risk assessment** (RMS, 2011, Mostert, 2021).

- Chlorfenapyr: In the *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/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. A dermal absorption factor (DAF) 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/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. Based on the results of these studies the USEPA calculated a dermal absorption factor (DAF) as follows (USEPA, 2020):

DAF = rat *in vivo* (13%) x human *in vitro* (1.4%) = 1.2%
rat *in vitro* (15.8%)

Based on these results, a dermal absorption value of 1.2% is used in this risk assessment. This value is lower than the 3.5% dermal absorption value used by the applicant in their risk assessment (Mostert, 2021).

2.1.2.1.3 Inhalation absorption

Toxicity via the inhalation route is assumed to be equivalent to toxicity via the oral route. Due to the lack of a long-term inhalation study, the oral exposure is used for risk assessment purpose.

2.1.3 Points of departure

Points of departure (PODs) (no observed adverse effect level [NOAEL]; Benchmark dose) are determined from the toxicological database based on the most sensitive endpoints. The PODs and toxicological endpoints of concern selected for risk assessment are considered protective of any potential adverse effects, including neuro-, developmental, reproductive, immune, and systemic toxicity as well as carcinogenicity for all populations including infants and children. 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.

2.1.3.1 Deltamethrin

2.1.3.1.1 Acute oral exposure

JMPR (2000) selected the oral POD of 5 mg/kg/day (NOAEL) from an acute neurotoxicity study in rats.

Since that assessment, Wolansky *et al.* (2006) investigated the effects of several pyrethroids on motor functions following a single oral administration to rats. Locomotor activity was measured at 1-4 hours after dosing utilizing a figure eight maze with motion photodetectors. The total locomotor activity was plotted versus administered pyrethroid amount. The USEPA considered this study as the most robust data set for assessing deltamethrin exposure and risk. The endpoint of decreased motor activity observed in Wolansky's study was selected by EPA as the POD for risk assessment. The USEPA's approach is the benchmark dose (BMD) analysis, using the benchmark dose lower bound ($BMDL_{1SD}$), as suggested for continuous endpoints in the USEPA's BMD guidance (USEPA, 2012).

Comparing the POD established from Wolansky's acute study with NOAELs obtained from repeated dosing studies, it is apparent that repeat exposures do not result in lower PODs. This observation is consistent with the general kinetic profile for pyrethroids. As a result, the oral $BMDL_{1SD}$ of 1.49 mg/kg/day is chosen as the acute POD for acute risk assessment in this document.

Acute oral POD = $BMDL_{1SD}$ of 1.49 mg/kg bw/day

2.1.3.1.2 Chronic oral exposure

JMPR (2000) selected the oral POD of 1.0 mg/kg bw/day (NOAEL) from a one-year dog study.

Deltamethrin is rapidly absorbed following an oral dose, and effects are typically observed within two to five hours after dosing. USEPA determined that it is not appropriate to assess chronic dietary risk due to a lack of increased toxicity with increased duration of exposure. Thus, the endpoint from the Wolansky acute neurotoxicity study is protective of the endpoints from the repeat dosing studies and, for the purposes of endpoint selection and exposure assessment. USEPA did not select a POD for chronic exposure and therefore a chronic risk assessment was not conducted. (USEPA, 2017, 2018).

The oral POD selected by JMPR was selected for chronic risk assessment and is deemed appropriate for chronic risk assessment.

Chronic oral POD = 1.0 mg/kg/day

2.1.3.2 Chlorfenapyr

2.1.3.2.1 Acute oral exposure

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 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.

Acute oral POD = 5 mg/kg bw/day

2.1.3.2.2 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 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 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. Consequently, this endpoint is the most appropriate to assess health risk to infants and children in the current exposure scenarios (e.g., sleeping under and washing treated nets). Furthermore, the chosen POD will adequately be protective of the adverse effects observed in other studies in the database.

2.1.4 Reference doses (RfD)

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), acceptable daily intake (ADI) or a safe margin of exposure (MOE).

2.1.4.1 Deltamethrin

2.1.4.1.1 Acute reference dose (aRfD)

JMPR 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. This is presented in Table 3.

Table 3. Deltamethrin: Acute reference dose (aRfD) established by JMPR

POD (mg/kg/day)	Uncertainty factor	aRfD (mg/kg)	Toxicological endpoint of concern	Study selected	Reference
5	100	0.05	FOB changes and locomotor activity at 15 mg/kg (LOAEL)	Acute neurotoxicity – Rat	JMPR, 2000

The USEPA established an **aRfD of 0.015 mg/kg bw** based on a $BMDL_{1SD}$ of 1.49 mg/kg/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities to establish an as shown below in Table 4.

Table 4. Deltamethrin: Acute reference dose (aRfD) established by USEPA

POD (mg/kg/day)	Uncertainty factor	aRfD (mg/kg)	Toxicological endpoint of concern	Study selected	Reference
$BMDL_{1SD}$ of 1.49	100	0.015	Decreased motor activity. BMD_{1SD} value = 2.48 mg/kg	Wolansky *et al.* 2006	WHO, 2021

2.1.4.1.2 Chronic reference dose (cRfD)

The USEPA did not establish a cRfD since the single-dose and repeated-dose studies with deltamethrin showed that repeat exposures did not result in lower PODs, i.e., there is no evidence of increasing toxicity with an increased duration of exposure. Therefore, the exposure assessments are conducted as a series of acute exposures, and these are protective scenarios in which exposure occurs for multiple days. Consequently, the acute RfD will be protective of risks from repeated exposures (USEPA, 2012 a, b, 2017).

2.1.4.1.3 Acceptable daily intake (ADI)

JMPR established an **ADI 0.01 mg/kg bw/day** based on a NOAEL of 1.0 mg/kg bw/day an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities as shown in Table 5.

Table 5. Deltamethrin: Acceptable daily intake (ADI) established by JMPR

POD (mg/kg/day)	Uncertainty factor	ADI (mg/kg)	Toxicological endpoint of concern	Study selected	Reference
1.0	100	0.01	Clinical signs of neurotoxicity	Chronic Toxicity-dog	JMPR, 2000

2.1.4.2 Chlorfenapyr

2.1.4.2.1 Acute reference dose (aRfD)

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 as shown below in Table 6.

Table 6. Chlorfenapyr: Acute reference dose (aRfD) established by JMPR

POD (mg/kg/day)	Uncertainty factor	aRfD (mg/kg)	Toxicological endpoint of concern	Study selected	Reference
3	100	0.03	Decreased spontaneous motor activity at 10 mg/kg.	Pharmacology - Mouse	JMPR, 2000

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 as shown below in Table 7.

Table 7. Chlorfenapyr: Acute reference dose (aRfD) established by USEPA

POD (mg/kg/day)	Uncertainty factor	aRfD (mg/kg)	Toxicological endpoint of concern	Study selected	Reference
5	100	0.05	Increased pup deaths on post-natal days 1-4 and decreased motor activity in pups at 10 mg/kg/day.	Developmental neurotoxicity - Rat	USEPA, 2020

2.1.4.2.2 Chronic reference dose (cRfD)

USEPA established an **cRfD 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 as shown below in Table 8.

Table 8. Chlorfenapyr: Chronic reference dose (cRfD) established by USEPA

POD (mg/kg/day)	Uncertainty factor	cRfD (mg/kg)	Toxicological endpoint of concern	Study selected	Reference
5	100	0.05	Increased pup deaths on post-natal days 1-4 and decreased motor activity in pups at 10 mg/kg/day.	Developmental neurotoxicity - Rat	USEPA, 2020

2.1.4.2.3 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 as shown in Table 9.

Table 9. Chlorfenapyr: Acceptable daily intake (ADI) established by JMPR

POD (mg/kg/day)	Uncertainty factor	ADI (mg/kg/day)	Toxicological endpoint of concern	Study selected	Reference
2.8	100	0.03	Decreases in body weight gain and vacuolation of the white matter of the brain	Carcinogenicity - Mouse	JMPR, 2012

2.1.5 Selection of tolerable systemic dose

A comparison of tolerable systemic doses (TSDs) used in the applicant's risk assessment (Mostert, 2021) and those selected by the WHO-PQT/VCP in this risk assessment are presented below in Table 10.

Table 10. Comparison of tolerable systemic doses used for risk assessment

Exposure scenario	Mostert, 2021	Reference	WHO PQT/VCP	Reference
Deltamethrin				
Acute	aRfD = 0.05 mg/kg bw	WHO, 2003	aRfD=0.015 mg/kg	GRA-Deltamethrin, 2021
Long-term	ADI = 0.01 mg/kg/day	WHO, 2003	ADI=0.01 mg/kg/day	GRA-Deltamethrin, 2021
Chlorfenapyr				
Acute	aRfD = 0.03 mg/kg	JMPR, 2005	aRfD=0.05 mg/kg	USEPA, 2020
Long-term	ADI = 0.03 mg/kg /day	JMPR, 2005	cRfD=0.05 mg/kg/day	USEPA, 2020

For Deltamethrin, PQT/VCP, has selected the aRfD established by USEPA as the TSD_{AC} for acute risk assessment since the lower aRfD value is based on the most sensitive toxicity endpoint, neurotoxicity, the principle toxicological effect of Deltamethrin observed in the most sensitive species (rat) following a single oral dose. The ADI established by the WHO is selected as the TSD for the long-term risk assessment.

For Chlorfenapyr, PQT/VCP, has selected the aRfD established by USEPA as the TSD_{AC} for acute risk assessment. The same value is also used as the TSD for long term risk assessment. Although this value (0.05 mg/kg/day) is numerically marginally higher than the JMPR ADI value (0.03 mg/kg bw/day), in the PQT/VCP opinion, it is appropriate for long term risk assessment since the adverse effects were seen in the most sensitive subpopulation (rat pups) in a study that examined developmental neurobehavior and neuropathology in pups following exposure to dams and thus is the most suitable toxicity endpoint of concern to assess health risk to infants and children in the current exposure scenarios.

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.

The exposure assessment (i.e., exposure calculations) was conducted in accordance with the input parameters (default values) mainly taken from the 2018 *A Generic Risk Assessment Model for Insecticide-Treated Nets* guidance and chemical specific data. Exposure assessment includes the population [adults, children (6-11 years), toddlers (1-2 years), infants (<1 year)], the routes of exposure (inhalation, dermal, oral, and via breast milk), and the different scenarios (sleeping under, washing, and sleeping 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. The concentration of the active ingredient in the net (TC) is

derived from the WHO (2018) specification of the net (default variability of the concentration being ± 25%). Conservative high-end point estimates of the default distributions are used as defaults.

The estimated systemic doses from Inhalation, dermal and oral (hand-to-mouth and direct contact) exposures due to sleeping under and washing treated PermaNet Dual nets, and from exposure through breast milk to deltamethrin are presented in **Appendix 3**.

The estimated systemic doses from Inhalation, dermal and oral (hand-to-mouth and direct contact) exposures due to sleeping under and washing treated PermaNet Dual nets, and from exposure through breast milk to chlorfenapyr are presented in **Appendix 4.**

2.2.1 Total (inhalation + dermal + oral) systemic dose due to sleeping under treated nets

The daily systemic exposure to the insecticides while sleeping under PermaNet Dual was calculated for inhalation, dermal, and oral routes of exposure. The results are presented in Table 11.

Table 11. Estimated total systemic dose due to sleeping under treated nets*

Population	Inhalation exposure	Dermal exposure (µg/kg bw/day)	Oral indirect exposure (hand to mouth) (µg/kg bw/day)	Oral direct exposure (µg/kg bw/day)	Total systemic dose (µg/kg bw/day)
Deltamethrin					
Adult	Negligible	0.027	Not Applicable	Not Applicable	0.027
Children	Negligible	0.038	Not Applicable	Not Applicable	0.038
Toddler	Negligible	0.046	0.015	0.268	0.329
Infants	Negligible	0.050	0.016	0.335	0.401
Chlorfenapyr					
Adult	Negligible	0.082	Not Applicable	Not Applicable	0.082
Children	Negligible	0.113	Not Applicable	Not Applicable	0.113
Toddler	Negligible	0.139	0.045	0.80	0.984
Infants	Negligible	0.151	0.049	1.01	1.21

* Data from Appendix 3 and 4

2.2.2 Total (dermal + oral) systemic exposure due to washing treated nets

The total systemic exposure from dermal and oral routes due to daily (acute) and repeated washing the treated nets. The results are presented in Table 12.

Table 12. Estimated total systemic dose from dermal + oral exposures due to washing nets*

Population	Dermal exposure (µg/kg bw/day)	Oral exposure (µg/kg bw/day)	Total systemic dose (µg/kg bw/day)
Deltamethrin			
Acute exposure (maximum)			
Adult	0.768	1.41	2.18
Children	0.928	1.86	2.79
Repeated exposure (TWA)			
Adult	0.014	0.115	0.129
Children	0.017	0.139	0.156
Chlorfenapyr			
Acute exposure (maximum)			
Adult	2.30	4.22	6.52
Children	2.78	5.57	8.35
Repeated exposure (TWA)			
Adult	0.042	0.343	0.385
Children	0.051	0.415	0.466

* Data from Appendix 3 and 4

2.2.3 Exposure via breast milk

The results for the maximum daily dose of the newborns and infants from the mother's exposure on the day she washes the family's nets (acute) and the from repeated washing (TWA) of the nets via breast milk are presented in Table 13.

Table 13. Estimated systemic dose from exposure via breast milk*

Deltamethrin	
Subpopulation	**Acute exposure (maximum) (µg/kg bw/day)**
New-borns	0.250
Infants	0.132
TWA dose (µg/kg bw/day)	
New-borns	0.018
Infants	0.009
Chlorfenapyr	
Population	Acute exposure (maximum) (µg/kg bw/day)
New-borns	0.561
Infants	0.294
TWA dose ((µg/kg bw/day)	
New-borns	0.040
Infants	0.021

* Data from Appendix 3 and 4

2.3 Risk characterization

The purpose of risk characterization is to examine the probability of adverse effects occurring during the use of the insecticide under defined exposure conditions. Risk characterization consists of comparing the estimate of total exposure (i.e., Total Systemic Dose) with the Tolerable Systemic Dose (TSD) established in hazard assessment. The TSD is same as the ADI or the chronic RfD established for the active ingredients.

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

When the ratios are less than 1, the health risk is acceptable. Ratios are greater than 1 may indicated possible health risks in which case steps may be taken to reduce the risk such as changing the recommended operational conditions or the amount of active ingredient in the technical product. A risk-benefit analysis in which the risks of potential toxicity are compared with potential health benefits (disease prevention), may be needed in some cases (GRAM, 2018).

The ratios for all populations (adults, children, toddlers and infants) sleeping under the net, for adults and children washing the net, and for newborn/infants exposed via breast milk to Deltamethrin and chlorfenapyr are presented in Tables 14, 15, 16 and 17.

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 14.

Table 14. Exposure estimates and ratios for sleeping under treated nets

Subpopulation	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
Deltamethrin						
Adult	0.027	Not Applicable	Not Applicable	0.027	10	0.003
Children	0.038	Not Applicable	Not Applicable	0.038	10	0.004
Toddler	0.046	0.015	0.268	0.329	10	0.033
Infants	0.050	0.016	0.335	0.401	10	0.040
Chlorfenapyr						
Adult	0.082	Not Applicable	Not Applicable	0.082	50	0.002
Children	0.113	Not Applicable	Not Applicable	0.113	50	0.002
Toddler	0.139	0.045	0.80	0.984	50	0.019
Infants	0.151	0.049	1.01	1.21	50	0.024

TSD = Deltamethrin: 10 µg/kg bw/day (USEPA, 2018) ; Chlorfenapyr 50 µg/kg bw/day (USEPA, 2020)
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 presented in Table 15.

Table 15. Exposure estimates and ratios for washing treated nets

Subpopulation	Dermal exposure (µg/kg/day)	Oral exposure (µg/kg/day)	Total exposure (µg/kg/day)	TSDAC (µg/kg)	TSD (µg/kg/day)	Risk ratio
Deltamethrin						
Acute exposure (maximum)						
Adult	0.768	1.41	2.18	15	N/A	0.145
Children	0.928	1.86	2.79	15	N/A	0.186
Repeated exposure (TWA)						
Adult	0.014	0.115	0.129	N/A	10	0.013
Children	0.017	0.139	0.156	N/A	10	0.016
Chlorfenapyr						
Acute exposure (maximum)						
Adult	2.30	4.22	6.52	50	N/A	0.130
Children	2.78	5.57	8.35	50	N/A	0.167
Repeated exposure (TWA)						
Adult	0.042	0.343	0.385	N/A	50	0.008
Children	0.051	0.415	0.466	N/A	50	0.009

TSD_{AC} = Deltamethrin: 15 µg/kg bw/day (WHO 2021) ; Chlorfenapyr 50 µg/kg bw/day (USEPA, 2020)
TSD = Deltamethrin: 10 µg/kg bw/day (WHO 2021) ; Chlorfenapyr 50 µg/kg bw/day (USEPA, 2020)
Risk ratio = Total Exposure/TSD

2.3.3 Combined risk ratios for sleeping under nets and washing of nets

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

Table 16. Exposure estimates and ratios for all populations sleeping under and washing treated nets

Subpopulation	Sleeping under nets (combined) (µg/kg/day)	Washing of nets (combined) (µg/kg/day)	Total exposure (µg/kg/day)	TSDAC (µg/kg)	TSD (µg/kg/day)	Risk ratio
Deltamethrin						
Acute exposure (maximum)						
Adult	0.027	1.41	1.44	15	N/A	0.096
Children	0.038	1.86	1.90	15	N/A	0.127
Repeated exposure (TWA)						
Adult	0.027	0.115	0.142	N/A	10	0.014
Children	0.038	0.139	0.177	N/A	10	0.018
Chlorfenapyr						
Acute exposure (maximum)						
Adult	0.082	6.52	6.60	50	N/A	0.132
Children	0.113	8.35	8.46	50	N/A	0.169
Repeated exposure (TWA)						
Adult	0.082	0.385	0.467	N/A	50	0.009
Children	0.113	0.466	0.579	N/A	50	0.012

TSDAC= Deltamethrin: 15 µg/kg bw/day (WHO 2021) ; Chlorfenapyr 50 µg/kg bw/day (USEPA, 2020)
TSD = Deltamethrin: 10 µg/kg bw/day (WHO 2021); Chlorfenapyr50 µg/kg bw/day (USEPA, 2020) 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 17.

Table 17. Exposure estimates and ratios for populations sleeping under treated nets and consuming breast milk

Subpopulation	Total exposure sleeping under nets (dermal + oral indirect + oral direct) (µg/kg/day)	Breast milk exposure (µg/kg/day)	Total exposure (µg/kg/day)	TSDAC (µg/kg)	TSD (µg/kg /day)	Risk ratio
Deltamethrin						
Acute exposure (maximum)						
Newborns	N/A	0.250	0.250	15	N/A	0.017
Infants	0.313	0.132	0.445	15	N/A	0.030
Repeated exposure (TWA)						
Newborns	N/A	0.018	0.018	N/A	10	0.002
Infants	0.313	0.009	0.322	N/A	10	0.032
Chlorfenapyr						
Acute exposure (maximum)						
Newborns	N/A	0.561	0.561	50	N/A	0.0112
Infants	1.21	0.294	1.50	50	N/A	0.0300
Repeated exposure (TWA)						
Newborns	N/A	0.040	0.040	N/A	50	0.0008
Infants	1.21	0.021	1.23	N/A	50	0.0246

TSD_{AC} = Deltamethrin: 15 µg/kg bw/day (WHO 2021) ; Chlorfenapyr 50 µg/kg bw/day (USEPA, 2020)
TSD = Deltamethrin: 10 µg/kg bw/day (WHO 2021) ; Chlorfenapyr 50 µg/kg bw/day (USEPA, 2020)
Risk ratio = Total Exposure/TSD

2.3.5 Risk conclusions

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.

The risk characterisation summary is presented in Table 18.

Table 18. Summary of risk characterization for PermaNet Dual (Deltamethrin, 84 mg/m² net, + Chlorfenapyr 200 mg/m²)	
Activity/Population	**Risk acceptable / not acceptable**
Sleeping under net - inhalation exposure	
Adult	Negligible
Children	Negligible
Toddlers	Negligible
Infants	Negligible
Washing of nets - acute conditions	
Adult	Acceptable
Children	Acceptable
Washing of nets - repeated conditions	
Adult	Acceptable
Children	Acceptable
Sleeping under and washing of nets - acute conditions	
Adult	Acceptable
Children	Acceptable
Sleeping under and washing of nets - repeated conditions	
Adult	Acceptable
Children	Acceptable
Exposure via breast milk from mothers	
Infants (acute and chronic)	Acceptable
New-borns (acute and chronic)	Acceptable
Combined sleeping under net and breast milk	
Infants (acute and chronic)	Acceptable
New-borns (acute and chronic)	Acceptable

The potential health risk of PermaNet Dual is acceptable for all populations (adults, children, infants, and children) sleeping under treated nets, for adults and children sleeping under and washing treated nets, and for infants and newborns sleeping under treated nets and exposed via breast milk. PermaNet Dual risk ratios are below the risk ratios (i.e., less than 1) established by the 2018 GRAM for all populations, routes of exposure (inhalation, dermal and oral) and all activities (sleeping under; washing and sleeping under; and sleeping under and exposed via breast milk).

At the estimated exposure levels (less than TSD), synergistic action of any two compounds is unlikely. Furthermore, deltamethrin and chlorfenapyr have different modes of action and different target sites. In assessing the risk from exposure to mixtures of chemicals, International Programme for Chemical Safety (IPCS) recommends that dose-additivity is considered at the first tier of assessment (Meek et al., 2011). In this case, exposure to the combination of Deltamethrin and Chlorfenapyr remains below the TSD for acute and repeated exposures. The risk ratio is less than 1 for all populations (adults, children, toddlers, and infants) engaged in various activities (sleeping under; washing and sleeping under; and sleeping under and exposed via breast milk). Therefore, there is no concern for synergism from exposure to these two active ingredients.

2.4 Conclusion

Risk characterization indicates that 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 via breast milk, the calculated exposure levels were in all cases below both short-term and long-term tolerable systemic doses of Deltamethrin and Chlorfenapyr.

The assessment of the available information on safety indicates that the ITNproduct, PermaNet Dual, containing Deltamethrin at 84 mg/m^2 net and Chlorfenapyr at 200 mg/m^2 net with a fabric weight of 40 g/m^2 and the wash resistance indices of 96.8% for Deltamethrin and 93.3% for Chlorfenapyr can be used safely for its intended use as a vector control product. The assessment of the submitted information supports the prequalification of the product PermaNet Dual.

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4 Appendices

4.1 Appendix 1. Toxicity profile of Deltamethrin

A summary of acute toxicity information is shown in Table A1. A summary of subchronic toxicity, genotoxicity, neurotoxicity, reproductive and developmental toxicity and chronic/carcinogenicity is shown in Table A2.

Table A1. Acute toxicity of Deltamethrin

Deltamethrin – toxicity profile: acute toxicity		
Study type	**Species; dose levels; guidelines**	**Results**
Acute oral LD50	Wistar rats (female) OECD 423 50, 300, 2000 mg/kg bw	50 < LD50 < 300 mg/kg bw GHS: Category 3
Acute oral LD50	Sprague Dawley rats (both sexes) OECD 401 — Single dose of 5000 mg/kg bw in 1% methylcellulose	LD50 > 5000 mg/kg bw GHS: Category 5
Acute dermal LD50	Wistar rats (both sexes) OECD 402, single dose tested 2000 mg/kg bw	LD50 > 2000 mg/kg bw GHS: Category 4
Acute inhalation LC50 (aerosol; whole body)	Sprague Dawley rats (both sexes) OECD 403, 4-hour; 1.0, 1.8 and 2.3 mg/L	LC50/4 hours = 2.2 mg/L GHS: Category 3
Primary dermal irritation	New Zealand rabbits (female) OECD 404 — limit test (0.5 g)	Non-irritating GHS: Not classified
Primary eye irritation	New Zealand rabbits (female) OECD 405 — limit test (0.1 g)	Slight irritant GHS: Category 2B
Skin sensitization – maximization test	Guinea pigs (female) OECD 406	Non-sensitizer GHS: Not classified
Skin sensitization – Buehler test	Guinea pigs (female) OECD 406	Non-sensitizer GHS: Not classified

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

Deltamethrin – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Test material; purity; dose levels; design**	**Results**
Sub-chronic toxicity		
21-day dermal, rats	Technical (99.6%) dissolved in PEG 400; 0, 100, 300 and 1000 mg/kg bw/day	NOAEL dermal = 1000 mg/kg bw/day NOAEL systemic = 1000 mg/kg bw/day
13-week dietary, Crl:CD (SD) BR rats	Technical (98.9%) mixed in diet at 0, 30, 300, 3000 and 6000 ppm. Each group consisted of 20 rats/sex.	NOAEL = 300 ppm (corresponding to 24 and 30 mg/kg bw/day for males and females, respectively) LOAEL = 1000 ppm (supplemental study) corresponding to 72 and 84 mg/kg bw/day for males and females, respectively
13-week oral gavage, Sprague Dawley rats	Doses at 0, 0.1, 1.0, 2.5 and 10 mg/kg bw/d. Each group consisted of 20 rats/sex.	NOAEL = 1 mg/kg bw/day LOAEL = 2.5 mg/kg bw/day

Table A2. Subchronic, chronic, carcinogenicity, and other toxicity studies with Deltamethrin		
Deltamethrin – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Test material; purity; dose levels; design**	**Results**
12-week dietary, CD-1 mice	Technical (99.7%) mixed in diet at 0, 30, 300, 3000, and 6000 ppm. Each group consisted of 10 mice/sex.	NOAEL = 300 ppm (corresponding to 62 and 77 mg/kg bw/d for males and females, respectively). LOAEL = 3000 ppm (decreased food consumption and body weight.
13-week oral (capsule), beagle dogs	Technical dissolved in PEG 200. Gelatin capsule with 0, 0.1, 1.0, 2.5 and 10 mg/kg bw/ day. Each group consisted of five dogs/sex except control and low dose groups had three dogs/sex.	A recovery group with two males and three females from the three highest dosage groups for an additional 20 weeks. Neurological examinations conducted at five and 12 weeks after dosing. NOAEL = 1 mg/kg bw/day LOAEL = 2.5 mg/kg bw/day (abnormal electroencephalogram-gram patterns) Unsteadiness, body tremors, jerking movements and neurological effects at 10 mg/kg bw/day.
13-week oral (capsule), beagle dogs	Technical (98.9%) given in capsule at 0, 2, 10, and 50 mg/kg bw/day. Control and highest dose groups had 6 dogs/sex. Other groups had only three dogs/sex.	NOAEL = 10 mg/kg bw/day LOAEL = 50 mg/kg bw/day (reduced body weight gains). No treatment-related findings at neurological examinations.
Developmental and reproductive toxicity		
Developmental toxicity, Sprague Dawley rats	Dose levels: 0, 0.1, 1 or 10 mg/kg bw/day given by gavage on gestational days (GD) 6–15.	Dev. Tox NOAEL = > 10 mg/kg bw/day (highest dose tested) Dev. Tox LOAEL = not established
Developmental toxicity, rats	Dose levels: 0, 1.25, 2.5 or 5.0 mg/kg bw/day dissolved in corn oil given by gavage on GD 7–20	Maternal NOAEL = 2.5 mg/kg bw/day Maternal LOAEL = 5 mg/kg bw/day (reduced BW) Dev. Tox NOAEL = 5 mg/kg bw/day (highest dose tested) Dev. Tox LOAEL = not established
Developmental toxicity, New Zealand rabbits	Dose levels: 0, 1, 4 or 16 mg/kg bw/day dissolved in sesame oil given by gavage on GD 6–19	Dev. Tox NOAEL = 16 mg/kg bw/day (highest dose tested) Dev. Tox LOAEL = not established
Developmental toxicity, KBL New Zealand rabbits	Dose levels: 0, 3, 10 or 32 mg/kg bw/day dissolved in corn oil given by gavage on GD 6–28 post-coitum	Maternal NOAEL = 10 mg/kg bw/day Maternal LOAEL = 32 mg/kg bw/day (decreased BW) Dev. Tox NOAEL = 32 mg/kg bw/day (highest dose tested) Dev. Tox LOAEL = not established
Post-natal developmental toxicity, Sprague Dawley rats	Dose levels: 0, 2.5 or 5.0 mg/kg bw/day dissolved in corn oil given by gavage	Test material given from gestation day 7 to lactation day 15. Dams were allowed to deliver and rear the young. Post-natal measurements on pups (body weight, eye-opening, startle reflex, air righting, etc.). No effects on parturition, litter size, pup viability and behavioral parameters.

Table A2. Subchronic, chronic, carcinogenicity, and other toxicity studies with Deltamethrin		
Deltamethrin – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Test material; purity; dose levels; design**	**Results**
Developmental neurotoxicity, Wistar rats	Dose levels: 0, 20, 80 or 200 ppm (Corresponding to 0, 1.64, 6.78 or 16.1 mg/kg bw/day)	Test material given in the diet from GD 6 through to lactation day 21. Reproductive parameters were not affected. Maternal NOAEL = 80 ppm Maternal LOAEL = 200 ppm (reduced body weight gain) Dev Neurotox NOAEL = 200 ppm (16.1 mg/kg bw/day) Dev Neurotox LOAEL = not established
Multigeneration reproduction, Charles River rats	Dose levels: 0, 2, 20 or 50 mg/kg bw in the diet	3-generation reproduction Parental systemic NOAEL = 20 mg/kg bw/day Parental systemic LOAEL = 50 mg/kg bw/day (decreased body weight and food consumption) Parental reproductive NOAEL = 50 mg/kg bw/day Offspring NOAEL = 50 mg/kg bw/day (highest dose tested)
2-generation reproduction, Charles River rats	Dose levels: 0, 5, 20, 80 or 320 ppm in diet	Parental systemic NOAEL = 80 ppm (4.2 mg/kg bw/day) Parental systemic LOAEL = 320 ppm (18 mg/kg bw/day; reduced body weight gain and feed consumption) Offspring NOAEL = 80 ppm (11 mg/kg bw/day) Offspring LOAEL = 320 ppm (reduced BW, increased mortality, clinical signs) Reproductive NOAEL = 320 ppm (18 mg/kg bw/day)
Neurotoxicity		
Acute neurotoxicity, Sprague Dawley rats	Dose level: 0, 5, 15 or 50 mg/kg bw/day dissolved in corn oil given by gavage as a single dose	Neuropathy NOAEL = 50 mg/kg bw/day (highest dose tested) Neuropathy LOAEL = not established
Acute neurotoxicity, Long Evans rats (Non-guideline but acceptable study; Wolansky et al., 2006)	Dose level: single oral dose of deltamethrin in corn oil at 0, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg — Groups of eight rats/dose	Motor activity measured two hours after dosing BMD = 2.48 BMDL = 1.49 Results used to derive PODs
13-week neurotoxicity study, rats	Dose levels: 0, 50, 200 or 800 ppm in the diet (Corresponding to 0, 4, 16, and 58 mg/kg bw/day)	Systemic NOAEL = 50 ppm Systemic LOAEL = 200 ppm (hypersensitivity to noise) Neuropathy NOAEL = 800 ppm (54-58 mg/kg bw/day) Neuropathy LOAEL = not established

Table A2. Subchronic, chronic, carcinogenicity, and other toxicity studies with Deltamethrin		
Deltamethrin – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Test material; purity; dose levels; design**	**Results**
Genotoxicity		
Bacterial reverse mutation assay (Ames assay)	Dose levels: 0, 2, 10, 50, 200, 500, 1000 and 5000 ug/plate Salmonella strains	Not mutagenic in all Salmonella typhimurium tested in both presence and absence of metabolic activation (S9-mix)
Chromosomal aberration assay, human lymphocytes (in vitro)	Dose levels: 0, 16.6, 26.3 and 50.8 ug/ml	Did not induce micronuclei in human lymphocytes in both presence and absence of S9-mix
Unscheduled DNA synthesis, rat hepatocytes	Dose levels: 0, 42, 130, 420, 1300 and 4200 ug/ml. Vehicle control (acetone) and positive control were used.	Did not induce unscheduled DNA synthesis in rat hepatocytes
In-vivo micronucleus test, mice	Dose level: single oral dose of 16 mg/kg bw dissolved in corn oil. Positive and negative controls were used.	No statistically significant increase in the frequency of micronuclei at any sample times up to 72 hours post-dosing
In-vivo micronucleus assay, mice	Dose levels: 0, 9.25, 18.5, and 37 mg/kg bw dissolved in corn oil given by gavage for two days.	Did not induce micronuclei in the bone marrow
Dominant lethal assay, male mice	Dose levels: 3 mg/kg bw for 7 days; 6 or 15 mg/kg as a single dose; 10 male mice/ group; Positive control used (Thio-TEPA)	Did not induce dominant lethal mutations in male mice
Chronic-carcinogenicity		
Chronic/carcinogenicity, CD-1 mice	Dose levels: 0, 10, 100, 1000 or 2000 ppm (Equivalent to 0, 1.5, 16, 160 and 310 mg//kg bw/day) 50 CD-1 mice/sex/group	Systemic NOAEL = 100 ppm Systemic LOAEL = 1000 ppm (skin ulceration) Not carcinogenic in the mouse
Chronic/carcinogenicity, rats	Dose levels: 0, 25, 125, 500 and 800 ppm (Equivalent to 0, 1.1, 5.4, 22 and 36 mg/kg bw/day). 70 rats/sex/group.	Systemic NOAEL = 25 ppm Systemic LOAEL = 125 ppm (hepatotoxicity) Not carcinogenic in the rat
Chronic/carcinogenicity CD-rats	Dose levels: 0, 2, 20, and 50 ppm mixed in corn oil (Equivalent to 0, 0.1, 0.8 and 2.1 mg/kg bw/day). 90 rats/sex/group. Corn oil group had 60 rats/sex.	Systemic NOAEL = 50 ppm (2.1 mg/kg bw/day for males and 2.8 mg/kg bw/day for females) Systemic LOAEL = not established Not carcinogenic in the rat
One-year oral (capsule), beagle dogs	Technical (98.9%) given in capsule at 0, 1, 10, or 50 mg/kg bw/day. Each group consisted of four dogs/sex.	NOAEL = 1 mg/kg bw/day LOAEL = 10 mg/kg bw/day (unsteadiness gait, splayed limbs/digits; reduced body weight, tremor)
Two-year dietary, beagle dogs	Dose levels: 0, 1, 10 and 40 ppm suspended in corn oil in the diet. eight animals/sex/group.	No treatment related effects noted on neurological, systemic or pathological examinations The systemic NOAEL ≥ 40 ppm (1.13 mg/kg bw/day for males and 0.98 mg/kg bw/day for females) Not carcinogenic in the dog

Source: JMPR, 2000; USEPA 2015, 2017, 2018

4.2 Appendix 2. Toxicity profile of Chlorfenapyr

A summary of acute toxicity information is shown in Table A3. A summary of subchronic toxicity, genotoxicity, neurotoxicity, reproductive and developmental toxicity and chronic/carcinogenicity is shown in Table A 4.

Table A3. Acute toxicity of Chlorfenapyr

Chlorfenapyr– acute toxicity profile			
Study type	**Species**	**Results**	**GHS category**
Acute Ora lLD50	Rat	LD50 = 441 mg/kg (males) LD50 = 1152 mg/kg (females)	4
Acute Dermal LD50	Rabbit	LD50 = >2000 mg/kg	5
Acute Inhalation LC50	Rat	LC50 = 0.83mg/L (males) LC50 = > 2.7 mg/L (females)	3
Primary dermal irritation	Rabbit	Non-irritant	None
Primary eye irritation	Rabbit	Mild irritant	2
Skin sensitization	Guinea pigs	Non-sensitizer	Not applicable

Table A4. 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.
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.
In vivo dermal-penetration – Rat	49315901 (2005) Acceptable/guideline 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.

4.3 Appendix 3. Exposure assessment: Deltamethrin

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.

Default values used are those required in the 2018 GRAM, except for the following:

- Target concentration (TC): 125% x 2.1 g deltamethrin/kg net x 40 g net/m^2 = 105 mg/m^2
- Dermal absorption: Data-driven 2% dermal absorption factor (Mostert, 2021)
- Oral absorption: 100% default
- Surface fraction (SF): 3.2% based on the wash resistance index of 96.8% (Mostert, 2021)

4.3.1 Inhalation exposure from sleeping under treated nets

Deltamethrin has a vapor pressure of 1.5x10^{-8} mm Hg at 25° C and a molecular weight of 505.4 (USEPA, 2020). The worst-case systemic dose after inhalation exposure of 0.000003 mg/kg bw (0.328 x 505.4 x 1.5x10^{-8}) is less than 1% of the long-term Tolerable Systemic Dose of 0.01 mg/kg/day. Thus, inhalation exposure is negligible and can be ignored.

4.3.2 Dermal exposure from sleeping under treated nets

Table A5. Deltamethrin estimated systemic dose via skin from sleeping under treated nets							
Population	**Dermal absorption (%)**	**Transl (%)**	**ESA (m^2)**	**SF (%)**	**TC (mg/m^2)**	**BW (kg)**	**Systemic dose (µg/kg bw/day)**
Adult	2	6	0.408	3.2	105	60.0	0.027
Children	2	6	0.225	3.2	105	23.9	0.038
Toddlers	2	6	0.115	3.2	105	10.0	0.046
Infants	2	6	0.100	3.2	105	8.0	0.050
Systemic dose via dermal exposure = Absorption (Dermal) x Transl x ESA x SF x TC ÷ BW x 1000 (conversion of mg to ug)							

4.3.3 Oral exposure to toddler and infants due to sleeping under treated nets.

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.

4.3.3.1 From hand-to-mouth transfer

The estimated systemic dose due to oral exposure via hand-to-mouth transfer is calculated as follows:

Table A6. Deltamethrin estimated systemic dose from hand-to-mouth transfer sleeping under treated nets									
Population	**Oral Absorption (%)**	**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	3.2	105	10.0	0.015
Infants	100	57	6	0.007	0.164	3.2	105	8.0	0.016
Systemic Dose = Absorption (oral) SE x Transl x EHA x FHM x SF x TC ÷ BW x 1000 (conversion of mg to ug)									

4.3.3.2 From direct mouth contact

The estimated systemic TWA dose due to oral exposure via mouthing, chewing, and sucking is calculated as follows:

Table A7. Deltamethrin estimated systemic dose due to direct mouth contact sleeping under treated nets							
Population	**Oral absorption (%)**	**SE (%)**	**NM (m^2)**	**SF (%)**	**TC (mg/m^2)**	**BW (kg)**	**Systemic dose (µg/kg bw/day)**
Toddlers	100	57	0.0014	3.2	105	10.0	0.268
Infants	100	57	0.0014	3.2	105	8.0	0.335
Systemic Dose = Absorption (oral) SE x NM x SF x TC ÷ BW x 1000 (conversion of mg to ug)							

4.3.4 Sleeping under treated nets – total combined (inhalation + dermal + oral) systemic dose

A total daily systemic exposure to deltamethrin while sleeping under a treated net was calculated in Table A8 as summation of the values for inhalation, dermal and oral routes of exposure given above.

Table A8. Deltamethrin estimated total systemic dose (µg/kg bw/day) due to sleeping under treated nets					
Population	**Inhalation exposure**	**Dermal exposure**	**Oral (indirect) exposure**	**Oral (direct) exposure**	**Total systemic dose (µg/kg bw/day)**
Adult	Negligible	0.027	Not applicable	Not applicable	0.027
Children	Negligible	0.038	Not applicable	Not applicable	0.038
Toddler	Negligible	0.046	0.015	0.268	0.329
Infants	Negligible	0.050	0.016	0.335	0.401

4.3.5 Estimation of systemic dose during washing deltamethrin treated nets.

There is no risk associated with inhalation exposure from washing of treated nets. 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.

4.3.5.1 Dermal exposure during washing of treated nets

The estimated systemic dose (maximum) from acute dermal exposure from washing of nets is depicted in Table A9.

4.3.5.1.1 From acute (maximum) exposure

Table A9. Deltamethrin estimated systemic dose (maximum) from acute dermal exposure due to washing treaded nets									
Population	**Dermal absorption (%)**	**NoN (Nets)**	**VLS (mL)**	**SF (%)**	**TC (mg/m²)**	**SN (m²)**	**VolW (mL)**	**BW (kg)**	**Systemic dose (µg/kg bw/day)**
Adults	2	5	36.6	3.2	105	15	4000	60.0	0.768
Children	2	5	17.6	3.2	105	15	4000	23.9	0.928
Systemic Dose (Maximum) = Absorption (Dermal) x NoN-x VLS x SF x TC x SN ÷ (VolW × BW) x1000 (conversion of mg to ug)									

4.3.5.1.2 From repeated (TWA) exposure

Table A10. Deltamethrin estimated systemic dose (TWA) from repeated dermal exposure due to washing treated nets											
Population	**Dermal absorption (%)**	**NoW (washes)**	**NoN (Nets)**	**VLS (mL)**	**SF (%)**	**TC (mg/m²)**	**SN (m²)**	**VolW (mL)**	**BW (kg)**	**AT (days)**	**Systemic dose (µg/kg bw/day)**
Adults	2	20/3 years	5	36.6	3.2	105	15	4000	60.0	365	0.014
Children	2	20/3 years	5	17.6	3.2	105	15	4000	23.9	365	0.017
Systemic Dose (TWA)=Absorption (Dermal) x NoW × NoN × VLS × SF × TC × SN ÷ (VolW × BW × AT) x1000 (conversion of mg to ug)											

4.3.5.2 Oral exposure during net washing.

Estimated systemic dose from acute oral (maximum) exposure is presented in Table A11.

4.3.5.2.1 *From acute (maximum) exposure*

Table A11. Deltamethrin estimated systemic dose from acute oral (maximum) exposure due to washing of nets										
Population	**Oral absorption (%)**	**NoN (Nets)**	**VLS (mL)**	**SF (%)**	**TC (mg/m²)**	**FHM**	**SN (m²)**	**VolW (mL)**	**BW (kg)**	**Systemic dose (µg/kg bw/day)**
Adults	100	5	8.2	3.2	105	0.164	15	4000	60.0	1.41
Children	100	5	4.3	3.2	105	0.164	15	4000	23.9	1.86
Systemic Dose (Maximum)= Absorption (Oral) NoN-x VLH x SF x TC x FHM x SN ÷ (VolW × BW) x1000 (conversion of mg to ug)										

4.3.5.2.2 *From repeated (TWA) exposure*

Table A12. Deltamethrin estimated systemic dose (TWA) from repeated oral exposure due to washing of nets												
Population	**Oral absorption (%)**	**NoW (washes)**	**NoN (Nets)**	**VLS (mL)**	**SF (%)**	**TC (mg/m²)**	**FHM**	**SN (m²)**	**VolW (mL)**	**BW (kg)**	**AT (days)**	**Systemic dose (µg/kg bw/day)**
Adults	100	20/3 years	5	36.6	3.2	105	0.164	15	4000	60.0	365	0.115
Children	100	20/3 years	5	17.6	3.2	105	0.164	15	4000	23.9	365	0.139
Systemic Dose (TWA)=Absorption (Oral) x NoW × NoN × VLS × SF × TC × SN ÷ (VolW × BW × AT) x1000 (conversion of mg to ug)												

4.3.5.3 Total systemic exposure due to washing of treated nets.

Table 9 depicts the estimated total systemic dose from washing of nets.

Table A13. Deltamethrin estimated total systemic dose from washing of 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	0.768	1.41	2.18
Children	0.928	1.86	2.79
Repeated exposure (TWA)			
Adult	0.014	0.115	0.129
Children	0.017	0.139	0.156

4.3.5.3.1 *Exposure via breast milk*

Pregnant and lactating women may sleep under the ITN and likely wash the nets. Infants may, therefore, be exposed through breast milk.

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

$$\text{Systemic dose TWA} = \frac{\text{Absorption (75\%) x SolC} \times \text{dose (mother)} \times T½ \times \text{IR}}{\text{BW}} \times 100$$

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

Mother dose = Dermal exposure/sleeping under net + total exposure/washing of net

Mother dose Maximum = 0.027 + 2.18 µg/kg bw/day = 2.21 µg/kg bw/day

Mother dose (TWA) = 0.027 + 0.129 µg/kg bw/day = 0.156 µg/kg bw/day

The estimated maximum systemic dose from exposure via breast milk is shown in Table A14.

Table A14. Deltamethrin estimated maximum systemic dose from exposure via breast milk

Population	Oral absorption (%)	SolC	Dose (µg /kg/day)	$T_{1/2}$ (days)	IR (kg/day)	BW (kg)	Systemic dose (µg/kg bw/day)
New-borns	100	0.361	2.21	2	0.66	4.2	0.250
Infants	100	0.361	2.21	2	0.66	8.0	0.132

$T_{1/2}$ First-order kinetics half-life of deltamethrin in days, 38.5 hours (NPIP, 2011); round off to 2 days
The estimated TWA systemic doses from exposure via breast milk is presented in A15.

Table A15. Deltamethrin estimated TWA systemic dose from exposure to breast milk

Population	Oral absorption (%)	SolC	Dose (µg/kg/day)	$T_{1/2}$ (days)	IR (kg/day)	BW (kg)	Systemic dose (µg/kg bw/day)
New-borns	100	0.361	0.156	2	0.66	4.2	0.018
Infants	100	0.361	0.156	2	0.66	8.0	0.009

4.4 Appendix 4. Exposure assessment: Chlorfenapyr

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.

Default values used are those required in the 2018 GRAM, except for the following:

- Target concentration (TC): 125% x 5.0 g chlorfenapyr/kg net x 40 g net/m^2 x 1000 = 250 mg/m^2
- Dermal absorption: Data-driven 1.2% dermal absorption factor (USEPA, 2020)
- Oral absorption: 60% (Mostert, 20221)
- Surface fraction (SF): 6.7% based on the wash resistance index of 93.3% (Mostert, 2021)

4.4.1 Inhalation exposure from sleeping under treated nets.

Chlorfenapyr has a vapor pressure of $1.7x10^{-7}$ at $25^{O}C$ and a molecular weight of 407.615. The worst-case systemic dose after inhalation exposure is 0.000023 mg/kg bw (0.328 x 407.615 x $1.7x10^{-7}$). This is less than 1% of the long term Tolerable Systemic Dose of 0.05 mg/kg/day. Thus, inhalation exposure is negligible and can be ignored.

4.4.2 Dermal exposure from sleeping under treated nets

Dermal absorption: A data-derived dermal absorption factor of 1.2% is used for deriving the systemic dose. This value is lower than the 3.5% value used by the applicant's assessment.

Surface fraction (SF): 6.7% based on the wash resistance index of 93.3% (Mostert, 2021)

Table A16. Chlorfenapyr estimated systemic dose via skin from sleeping under treated nets

Population	Dermal absorption (%)	Transl (%)	ESA (m^2)	SF (%)	TC (mg/m^2)	BW (kg)	Systemic dose (µg/kg bw/day)
Adult	1.2	6	0.408	6.7	250	60.0	0.082
Children	1.2	6	0.225	6.7	250	23.9	0.113
Toddlers	1.2	6	0.115	6.7	250	10.0	0.139
Infants	1.2	6	0.100	6.7	250	8.0	0.151
Systemic dose = Absorption (Dermal) x Transl x ESA x SF x TC ÷ BW x 1000 (conversion of mg to ug)							

4.4.3 Oral exposure to toddler and infants due to sleeping under treated nets

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.

4.4.3.1 From hand-to-mouth transfer

The estimated systemic dose due to oral exposure via hand-to-mouth transfer is calculated as follows:

Table A17. Chlorfenapyr estimated systemic dose from hand-to-mouth transfer sleeping under treated nets

Population	Absorption (%)	SE (%)	Transl (%)	EHA (m^2)	FHM	SF (%)	TC (mg/m^2)	BW (kg)	Systemic dose (µg/kg bw/day)
Toddlers	60	57	6	0.008	0.164	6.7	250	10.0	0.045
Infants	60	57	6	0.007	0.164	6.7	250	8.0	0.049
Systemic Dose = Absorption (oral) SE x Transl x EHA x FHM x SF x TC ÷ BW x 1000 (conversion of mg to ug)									

4.4.3.2 From direct mouth contact

The estimated systemic TWA dose due to oral exposure via mouthing, chewing, and sucking is calculated as follows:

Table A18. Chlorfenapyr estimated systemic dose due to direct mouth contact sleeping under treated nets							
Population	**Absorption (%)**	**SE (%)**	**NM (m^2)**	**SF (%)**	**TC (mg/m^2)**	**BW (kg)**	**Systemic dose (µg/kg bw/day)**
Toddlers	60	57	0.0014	6.7	250	10.0	0.80
Infants	60	57	0.0014	6.7	250	8.0	1.01
Systemic Dose = Absorption (oral) SE x NM x SF x TC ÷ BW x 1000 (conversion of mg to ug)							

4.4.3.3 Sleeping under treated nets – total combined (inhalation + dermal + oral) systemic dose

A total daily systemic exposure to deltamethrin while sleeping under a treated net was calculated in Table A19 as summation of the values for inhalation, dermal and oral routes of exposure give above.

Table A19. Chlorfenapyr estimated total systemic dose (µg/kg bw/day) due to sleeping under treated nets					
Population	**Inhalation exposure**	**Dermal exposure**	**Oral (indirect) exposure**	**Oral (direct) exposure**	**Total systemic dose (µg/kg bw/day)**
Adult	Negligible	0.082	Not Applicable	Not Applicable	0.082
Children	Negligible	0.113	Not Applicable	Not Applicable	0.113
Toddler	Negligible	0.139	0.045	0.80	0.984
Infants	Negligible	0.151	0.049	1.01	1.21

4.4.3.4 Estimation of systemic dose during 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.

4.4.3.4.1 Dermal exposure during washing of treated nets

The estimated systemic dose (maximum) from acute dermal exposure from washing of nets is depicted in Table A20.

4.4.3.4.2 From acute (maximum) exposure

Table A20. Chlorfenapyr estimated systemic dose (maximum) from acute dermal exposure due to washing treaded nets									
Population	**Absorption (%)**	**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	36.6	6.7	250	15	4000	60.0	2.30
Children	1.2	5	17.6	6.7	250	15	4000	23.9	2.78
Systemic Dose (Maximum) = Absorption (Dermal) x NoN-x VLS x SF x TC x SN ÷ (VolW × BW) x1000 (conversion of mg to ug)									

4.4.3.4.3 *From repeated (TWA) exposure*

Table A21. Chlorfenapyr estimated systemic dose (TWA) from repeated dermal exposure due to washing treated nets											
Population	**Absorption (%)**	**NoW (washes)**	**NoN (Nets)**	**VLS (mL)**	**SF (%)**	**TC (mg/m²)**	**SN (m²)**	**VolW (mL)**	**BW (kg)**	**AT (days)**	**Systemic dose (µg/kg bw/day)**
Adults	1.2	20/3 years	5	36.6	6.7	250	15	4000	60.0	365	0.042
Children	1.2	20/3 years	5	17.6	6.7	250	15	4000	23.9	365	0.051
Systemic Dose (TWA)=Absorption (Dermal) x NoW × NoN × VLS × SF × TC × SN ÷ (VolW × BW × AT) x1000 (conversion of mg to ug)											

4.4.3.5 Oral exposure during net washing

Estimated systemic dose from acute oral (maximum) exposure is presented in Table A22.

4.4.3.5.1 *From acute (maximum) exposure*

Table A22. Chlorfenapyr estimated systemic dose from acute oral (maximum) exposure due to washing of nets										
Population	**Absorption (%)**	**NoN (Nets)**	**VLS (mL)**	**SF (%)**	**TC (mg/m²)**	**FHM**	**SN (m²)**	**VolW (mL)**	**BW (kg)**	**Systemic dose (µg/kg bw/day)**
Adults	60	5	8.2	6.7	250	0.164	15	4000	60.0	4.22
Children	60	5	4.3	6.7	250	0.164	15	4000	23.9	5.57
Systemic Dose (Maximum)= Absorption (Oral) NoN-x VLH x SF x TC x FHM x SN ÷ (VolW × BW) x1000 (conversion of mg to ug)										

4.4.3.5.2 *From repeated (TWA) exposure*

Table A23. Chlorfenapyr estimated systemic dose (TWA) from repeated oral exposure due to washing of nets											
Population	**Absorption (%)**	**NoW (washes)**	**NoN (Nets)**	**VLS (mL)**	**SF (%)**	**TC (mg/m²)**	**FHM**	**SN (m²)**	**VolW (mL)**	**BW (kg)**	**AT (days)**	**Systemic dose (µg/kg bw/day)**
Adults	60	20/3 years	5	36.6	6.7	250	0.164	15	4000	60.0	365	0.343
Children	60	20/3 years	5	17.6	6.7	250	0.164	15	4000	23.9	365	0.415
Systemic Dose (TWA)=Absorption (Oral) x NoW × NoN × VLS × SF × TC × SN ÷ (VolW × BW × AT) x1000 (conversion of mg to ug)											

4.4.4 Total systemic exposure due to washing of treated nets.

Table A24 depicts the estimated total systemic dose from washing of nets.

Table A24. Chlorfenapyr estimated total systemic dose from washing of 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	2.30	4.22	6.52
Children	2.78	5.57	8.35
Repeated exposure (TWA)			
Adult	0.042	0.343	0.385
Children	0.051	0.415	0.466

4.4.5 Exposure via breast milk

Pregnant and lactating women may sleep under the ITN and likely wash the nets. Infants may therefore be exposed through breast milk. Estimates for systemic maximum and TWA doses from exposure via breast milk are calculated as follows:

$$\text{Systemic dose TWA} = \frac{\text{Absorption (60\%) x SolC} \times \text{dose (mother)} \times T_{½} \times \text{IR x 100}}{\text{BW}}$$

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

Mother dose = Dermal exposure/sleeping under net + total exposure/washing of net

Mother dose Maximum = 0.082+ 6.52µg/kg bw/day = 6.60 µg/kg bw/day

Mother dose (TWA) = 0.082 + 0.385 µg/kg bw/day = 0.467 µg/kg bw/day

The estimated maximum systemic dose from exposure via breast milk is shown in Table A25.

Table A25. Chlorfenapyr estimated maximum systemic dose from exposure via breast milk

Population	Oral absorption (%)	SolC	Dose (µg /kg/day)	$T_{1/2}$ (days)	IR (kg/day)	BW (kg)	Systemic dose (µg/kg bw/day)
New-borns	60	0.361	6.60	2.5	0.66	4.2	0.561
Infants	60	0.361	6.60	2.5	0.66	8.0	0.294

The estimated TWA systemic doses from exposure via breast milk is presented in Table A26.

Table A26. Chlorfenapyr estimated TWA systemic dose from exposure to breast milk

Population	Oral absorption (%)	SolC	Dose (µg/kg/day)	$T_{1/2}$ (days)	IR (kg/day)	BW (kg)	Systemic dose (µg/kg bw/day)
New-borns	60	0.361	0.467	2.5	0.66	4.2	0.040
Infants	60	0.361	0.467	2.5	0.66	8.0	0.021