Generic risk assessment – Human Health

PERMETHRIN
(CAS No. 52645-53-1)

A long-lasting mosquito net treated with permethrin

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

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Contents

Acronym list

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
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
MOE	Margin of Exposure
NM	Net Mouthed
NOAEL	No Observed Adverse Effect Level

NoN	Number of Nets
NoW	Number of Washes
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 permethrin-treated nets (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* (WHO, 2018).

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

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

- fabric weight: 40 g/m^2
- concentration by weight of net: 20 g permethrin/kg net
- concentration by net area: 800 mg permethrin/m^2
- wash resistance index: 90%[1]

Note: The selected values are not intended to put a limit on the possible concentration of n permethrin in an ITN. The selected values do not represent the maximum concentration of permethrin 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 permethrin was conducted according to *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 dwellings and users of other treated buildings, bystanders, domestic animals, wildlife and the environment. Exposure is assessed in a "guideline scenario" which assumes that the 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.
- **Risk characterization** is the final step in a risk assessment whereby estimates of exposure are compared with acceptable exposure levels as defined in the hazard assessment for all relevant exposure scenarios.

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

1 The measured wash resistance index is determined for all products individually. The measured value is used to estimate the exposure as part of the Surface Fraction (SF).

2.1 Hazard assessment

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

Oral exposure

Absorption and metabolism of permethrin is rapid and extensive, with only 6% of the administered dose being recovered unmetabolized in the faeces. Consequently, oral absorption is assumed to be 100%.

Dermal exposure

The comparative *in vitro* dermal penetration study using human and rat skin showed that 18% of an applied dose was absorbed through rat skin and 2.3% through human skin, which indicates that *in vitro* rat skin is 6.6 times more permeable than *in vitro* human skin. Therefore, a dermal absorption factor of 21.7/6.6 = 3.3% is considered appropriate for risk assessment.

Inhalation exposure

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 purposes.

2.1.1 Points of departure

Points of departure (PODs) (no observed adverse effect level [NOAEL]; benchmark dose) are determined from the toxicology database based on the most sensitive endpoints.

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 selected the oral POD of 150 mg/kg bw (NOAEL) based on clinical signs of neurotoxicity n in rats following a single oral dose in an acute oral toxicity study (JMPR, 2002).

The USEPA (2015, 2018) considered the acute neurotoxicity study in rats by Wolansky et al. (2006) 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 for all dietary (acute), non-occupational (incidental oral and inhalation) and occupational exposure (inhalation) scenarios.

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 PODs 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 44 mg/kg/day is chosen as the acute POD for acute risk assessment in this document.

Acute oral POD = $BMDL_{1SD}$ of 44 mg/kg bw

Chronic oral exposure

Permethrin is rapidly absorbed from the gastrointestinal tract and extensively metabolized following an oral dose, and effects are typically observed within 2 to 5 hours after dosing. Like other pyrethroids, it is not appropriate to assess chronic dietary risk due to a lack of increased toxicity with increased duration of exposure. Therefore, 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, only single-day risk assessments need to be conducted (USEPA, 2018).

Chronic oral POD = Not applicable

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

Acute reference dose (aRfD)

Permethrin was evaluated by the Food and Agriculture Organization/WHO JMPR (2002), at which time an aRfD of 1.5 mg/kg bw was established based on the POD of 150 mg/kg bw 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	150	100	1.5	Clinical signs of neurotoxicity	Acute neurotoxicity – rat	JMPR, 2002

The USEPA (2012) used the $BMDL_{1SD}$ of 44 mg/kg/day from the Wolansky study (2006) and an uncertainty factor of 100 to account for interspecies extrapolation and 10X for intraspecies variation to establish an aRfD of 0.44 mg/kg/day (USEPA, 2012 a,b, 2017) (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	BMDL = 44	100	0.44	Decreased motor activity	Wolansky et al., 2006	USEPA, 2012 a,b, 2017

Chronic reference dose (cRfD)

The USEPA did not establish a cRfD since the single-dose and repeated-dose studies with permethrin 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, risk estimates derived from use of the acute study are protective of risk from repeated exposures (USEPA, 2012 a,b, 2017).

cRfD = Not established

Acceptable daily intake

Permethrin was evaluated by the FA0/WHO JMPR in1999 at which time an ADI of (ADI) of 0.05 mg/kg bw was established based on a NOAEL of 5 mg/kg/day in the 2-year study in rats and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variation. The clinical signs and changes in body and organ weights and blood chemistry at 25 mg/kg/day in the 2-year study in rats. This was supported by a NOAEL of 5 mg/kg/day based on the reduced body weight at 100 mg/kg/day in a one-year study in dogs (see Table 3).

Table 3. JMPR – ADI

NOAEL (mg/kg/day)	Uncertainty factor	ADI (mg/kg/day)	Toxicological endpoint of concern	Study selected	Reference
5.0	100	0.05	Clinical signs and changes in body weight and organ weights at 25 mg/kg/day (LOAEL) in rats. Supported by reduced body weight in dogs at 100 mg/kg/day.	2-year rat 1-year dog	JMPR, 1999

2.1.3. Selection of tolerable systemic dose (TSD)

The PQT/VCP selected the aRfD of 0.44 mg/kg/day established by the USEPA as the TSD for acute risk assessment (TSD_{AC}). The USEPA considered the findings in the acute neurotoxicity study in rats reported by Wolansky et al. (2006) to be the most robust data set for assessing the acute toxicity of permethrin exposure and risk.

The PQT/VCP selected the ADI of 0.05 mg/kg/day established by the JMPR (1999) as the TSD for long-term risk assessment and the ADI is appropriate for assessing repeated toxicity of permethrin exposure and risk.

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 the amount of dislodgeable insecticide from net to skin, as proposed in the generic risk 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% x Nominal concentration of the active ingredient mg/kg net x weight of the net kg/m^2

Using the selected product design attributes of 20 g permethrin/kg net and 40 g/m^2 fabric weight, the TC is calculated as follows:

$$TC = 125\% \times 20000 \text{ mg/kg net} \times 40 \text{ g/m}^2 = 1000 \text{ mg/m}^2$$

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

Abs = Dermal absorption from net surface (3.3% data-derived)
Abs-o = Oral absorption (default = 100%)
AT = Average time (default = 365 days)
BW = Body weight (default = 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
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% [75th percentile])
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) = 1000 mg/m^2
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 liters)
WRI = Wash resistance index = 90%
1000 = Conversion of mg to µg
Permethrin Molecular Mass = 391.28 g/mol
Permethrin Vapor Pressure = 2.15x10-8 mm Hg

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 From inhalation exposure

Permethrin has a vapor pressure of 2.15x10-8 mm Hg and a molecular weight of 391.3. In agreement with the GRAM, the inhalation exposure during sleeping under a permethrin-treated long-lasting net is considered negligible because of the low vapor pressure (WHO, 2012; 2018). Thus, for permethrin, 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 From 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 dermal absorption factor of 3.3 % established by the USEPA. Table 4 reflects the systemic doses for all populations due to dermal exposures from sleeping under treated nets.

$$\text{Systemic TWA dose} = \frac{\text{Absorption (dermal) x Transl x ESA x SF x TC}}{\text{BW}} \text{ x } 1000$$

Table 4. Permethrin: estimated TWA systemic dose for all populations due to dermal exposure 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	3.3	6	0.408	10	1000	60.0	1.34
Children	3.3	6	0.225	10	1000	23.9	1.86
Toddlers	3.3	6	0.115	10	1000	10.0	2.28
Infants	3.3	6	0.100	10	1000	8.0	2.46

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

2.2.1.3 From 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.

From hand-to-mouth transfer

It is assumed that hand-to-mouth transfer is significant only for toddlers and infants. The estimated daily systemic doses from hand-to-mouth transfer is calculated as indicated in Table 5.

$$\text{Systemic dose} = \frac{\text{Absorption (oral)} \times \text{SE} \times \text{Transl} \times \text{EHA} \times \text{FHM} \times \text{SF} \times \text{TC}}{\text{BW}} \times 1000$$

Table 5. Permethrin: estimated systemic dose due to 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	10	1000	10.0	0.4486
Infants	100	57	6	0.007	0.164	10	1000	8.0	0.4907

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

From direct mouth contact

Direct mouth contact is only relevant for toddlers and infants. The estimated systemic dose from direct mouth contact is indicated in Table 6.

$$\text{Systemic dose} = \frac{\text{Absorption (oral)} \times \text{SE} \times \text{NM} \times \text{SF} \times \text{TC}}{\text{BW}} \times 1000$$

Table 6. Permethrin: 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	10	1000	10.0	7.98
Infants	100	57	0.0014	10	1000	8.0	9.97

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

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

A total daily systemic exposure to permethrin while sleeping under a treated net was calculated in Table 7 as the summation of the values for inhalation, dermal and oral routes of exposure given above.

Table 7. Permethrin: estimated total systemic dose (µg/kg bw/day) due to sleeping under treated nets

Population	Inhalation exposure	Dermal exposure	Oral indirect exposure (hand to mouth)	Oral direct exposure	Total exposure (µg/kg bw/day)
Adults	Negligible	1.34	N/A	N/A	1.34
Children	Negligible	1.86	N/A	N/A	1.86
Toddlers	Negligible	2.28	0.4486	7.98	10.71
Infants	Negligible	2.46	0.4907	9.97	12.92

2.2.2 Estimation of systemic dose during washing of 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 adults and children only.

2.2.2.1 Dermal exposure during net washing

The estimated systemic dose (maximum) from acute dermal exposure from washing of nets depicted in Table 8.

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

Table 8. Permethrin: estimated systemic dose (maximum) from acute dermal exposure due to washing treated 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	3.3	5	36.7	10	1000	25	4000	60.0	63.08
Children	3.3	5	17.6	10	1000	25	4000	23.9	75.94

NoN = default = 5
VLS = default = 36.7 ml/adult and 17.6 ml/child
SF = 100 – wash resistance index % = 10%
TC = 1000 mg/m²
SN = default = 25 m²
VolW = default = 4000 ml
BW = default values
1000 = conversion of mg to µg

From repeated (TWA) exposure

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

Table 9. Permethrin: 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	3.3	20/3 years	5	36.7	10	1000	25	4000	60.0	365	1.15
Children	3.3	20/3 years	5	17.6	10	1000	25	4000	23.9	365	1.39

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 = 1000 mg/m²
SN = default = 25 m²
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

Estimated systemic dose from acute (maximum) exposure is shown in Table 10.

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

Table 10. Permethrin: estimated systemic dose (maximum) from acute oral exposure due to washing treated nets

Population	Oral absorption (%)	NoN (nets)	VLH (ml)	SF (%)	TC (mg/m²)	FHM	SN (m²)	VolW (ml)	BW (kg)	Systemic dose (µg/kg bw/day)
Adults	100	5	8.2	10	1000	0.164	25	4000	60.0	70.04
Children	100	5	4.3	10	1000	0.164	25	4000	23.9	92.21

NoN = default = 5
VLH = default = 8.2 ml/adult and 4.3 ml/child
SF = 100 – wash resistance index % = 10%
TC = 1000 mg/m²
FHM = default = 0.164
SN = default 25 m²
Vol W = default 4000 ml
BW = default values
1000 = conversion of mg to µg

From repeated (TWA) exposure

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

Table 11. Permethrin: estimated systemic dose (TWA) from repeated oral exposure due to washing treated 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	8.2	10	1000	0.164	25	4000	60.0	365	1.28
Children	100	20/3 years	5	4.3	10	1000	0.164	25	4000	23.9	365	1.68

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 = 1000 mg/m²
FHM = default = 0.164
SN = default = 25 m²
Vol W = default = 4000 ml
BW = default values
AT = default = 365 days
1000 = conversion of mg to µg

2.2.3 Total systemic exposure due to washing of treated nets

Table 12. Permethrin estimated total systemic doses 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)			
Adults	63.08	70.04	133.84
Children	75.34	92.21	167.55
Repeated exposure (TWA)			
Adults	1.15	1.28	2.43
Children	1.39	1.68	3.07

2.2.4 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:

$$\text{Systemic dose} = \frac{\text{Absorption x Sol C} \times \text{dose (mother)} \times T_{½} \times \text{IR}}{\text{BW}}$$

SolC = Solubility constant = 0.361 for lipid soluble insecticide
Dose = Daily dose to the mother = Sleeping under a net + Total from net washing

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.

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

Mother dose Maximum = 1.34 + 133.84 = 135.18 µg/kg bw/day

Mother dose (TWA) = 1.34 + 2.43 = 3.77 µg/kg bw/day

The estimated maximum systemic dose from exposure via breast milk is shown in Table 13.

Table 13. Permethrin: estimated maximum systemic dose from exposure via breast milk

Population	Oral absorption (%)	Sol C	Dose (µg/kg/day)	$T_{1/2}$ (days)	IR (kg/day)	BW (kg)	Systemic dose (µg/kg bw/day)
Newborns	100	0.361	135.18	0.5	0.66	4.2	3.83
Infants	100	0.361	135.18	0.5	0.66	8.0	2.01

$T_{1/2}$ = First-order kinetics half time of permethrin in days, 1.5 days
IR = default = 0.66 kg/day
BW = default values

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

Table 14. Permethrin: estimated TWA systemic dose from exposure via breast milk

Population	Oral absorption (%)	Sol C	Dose (µg/kg/day)	$T_{1/2}$ (days)	IR (kg/day)	BW (kg)	Systemic dose (µg/kg bw/day)
Newborn	100	0.361	3.77	0.5	0.66	4.2	0.11
Infants	100	0.361	3.77	0.5	0.66	8.0	0.06

$T_{1/2}$ = First-order kinetics half time of permethrin in days, 1.5 days
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 tolerable systemic dose (TSD) established in the hazard assessment. The TSD is the same as the ADI or the cRfD established for the active ingredients (WHO, 2018).

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

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).

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

When the ratios are less than one, the health risk is deemed acceptable. Ratios greater than one 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 permethrin are presented in Tables 15–18.

2.3.1 Exposure estimates and risk ratios for sleeping under the treated nets

The risk ratios for all populations sleeping under treated nets are depicted in Table 15.

Table 15. Exposure estimates and risk ratios for all populations sleeping under permethrin-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
Adults	1.34	N/A	N/A	1.34	50	0.02
Children	1.86	N/A	N/A	1.86	50	0.03
Toddlers	2.28	0.4486	7.98	10.71	50	0.21
Infants	2.46	0.4907	9.97	12.92	50	0.26

TSD = 50 µg/kg bw/day (JMPR, 1999)
Risk ratio = Total exposure/aRfD or 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 16.

Table 16. Exposure estimates and risk ratios for populations washing permethrin-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	63.08	70.04	133.84	440	N/A	0.304
Children	75.34	92.21	167.55	440	N/A	0.381
Repeated exposure (TWA)						
Adult	1.15	1.28	2.43	N/A	50	0.049
Children	1.39	1.68	3.07	N/A	50	0.061

aRfD = 440 µg/kg bw/day (EPA, 2017)
TSD = 50 µg/kg bw/day (JMPR, 1999)
Risk ratio = total exposure/aRfD or total exposure

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 permethrin-treated nets.

Table 17. Exposure estimates and risk ratios for populations sleeping under and washing permethrin-treated nets

Subpopulation	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	1.34	133.84	135.18	440	N/A	0.307
Children	1.86	167.55	169.41	440	N/A	0.385
Repeated exposure (TWA)						
Adults	1.34	2.43	3.77	N/A	50	0.075
Children	1.86	3.07	4.93	N/A	50	0.099

aRfD = 440 µg/kg bw/day (EPA, 2017)
TSD = 50 µg/kg bw/day (JMPR, 1999)
Risk ratio = total exposure/aRfD or 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 18.

Table 18. Exposure estimates and risk ratios for populations sleeping under permethrin-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)	Acute (µg/kg/day)	TSD (µg/kg/day)	Risk ratio
Acute exposure (maximum)						
Newborns	12.92	2.01	14.93	440	N/A	0.034
Infants	N/A	3.83	3.83	440	N/A	0.009
Repeated exposure (TWA)						
Newborns	12.92	0.06	12.98	N/A	50	0.260
Infants	N/A	0.11	0.11	N/A	50	0.002

aRfD = 440 µg/kg bw/day (EPA, 2017)
TSD = 50 µg/kg bw/day (JMPR, 1999)
Risk ratio = total exposure/aRfD or total exposure/TSD

2.4 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.

Table 19. Summary of risk characterization for permethrin as ITN (up to 20 g/kg or 800 mg/m^2)

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

3 Conclusion

The assessment of the available information on safety indicates that a permethrin-treated ITN, coated or incorporated, with a concentration of 800 mg ai/m^2 (fabric weight 40 g/m^2 and 20 g ai/kg net) and a wash resistance index of 90% can be used safely for its intended use as a vector control product.

Appendix: Permethrin health hazard assessment

Product Name: PERMETHRIN
Empirical formula: C21H20CL2O3
Chemical Abstract Number: 52645-53-1

1 Background information

Permethrin [(3-phenoxyphenyl) methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate] is a broad spectrum, non-systemic, synthetic pyrethroid insecticide and is registered for use in/on numerous food/feed crops, livestock and livestock housing, mosquito abatement programmes, indoor and outdoor residential spaces, pets, clothing and treated nets. Pyrethroids disrupt the voltage-gated sodium channels in the nervous system resulting in neurotoxicity and have historically been classified into two groups based on chemical structure and toxicological effects: Type I and Type II. Permethrin lacks an alpha-cyano moiety and is classified as a Type I pyrethroid. Clinical signs characteristic of Type I involves the nervous system characterized by tremors, hyperactivity, elevated body temperature and altered functional observational battery (FOB) observations. The term T-syndrome (from tremor) has been applied to Type I responses.

Technical permethrin is a racemic mixture of the 1R-diastereomers (cis and trans) and 1 S-diastereomers (cis and trans). Only 1R-diastereomers are neurotoxic in mammals, and the insecticidal potency of permethrin is dependent on the proportion of the 1R-diastereomers in the product (WHO, 2015). The 1R-cis isomer has the most insecticidal activity among all isomers, followed by the 1R-trans isomer. 1R-trans permethrin has lower toxicity to mammals, including humans, in part due to its rapid hydrolysis. No clear-cut difference seems to exist between the nonracemic and racemic permethrin.

2 Relevant toxicity information on permethrin

Note: Only information relevant to hazard assessment is discussed in this document. Additional information can be found in the references cited.

Permethrin is classified as United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Category 5 for acute oral, dermal, and inhalation toxicity and as GHS Category 3 for eye irritation and dermal irritation. Permethrin is not considered a skin sensitizer based on a weight-of-evidence evaluation of available data.

The toxicity profile of permethrin is presented in Tables A1 and A2 below.

Table A1. Acute toxicity of permethrin

Permethrin – toxicity profile: acute toxicity		
Study type	**Results**	**GHS Category**
Acute oral toxicity in rats	LD50 = 3580 mg/kg (M) LD50 = 2280 mg/kg (F)	5
Acute dermal toxicity in rabbits	LD50 > 2000 mg/kg	5
Acute inhalation toxicity in rats	LC50 > 4.638–23.5 mg/L2	4–5
Primary eye irritation in rabbits	Irritation 24–48 hours. All cleared by 72 hours.	2B
Primary dermal irritation in rabbits	All irritation cleared by 48 hours.	3
Skin sensitization in guinea pigs	Non-sensitizer	Not applicable

Table A2. Subchronic, chronic/carcinogenicity, developmental, reproductive and other toxicity studies with permethrin (JMPR, 2002; USEPA, 2012, 2017)

Study type	Species/strain/sex: Dose levels tested	Results
Sub-chronic toxicity		
21-day dermal, rat	Male/Female Wistar Rat 0, 50, 150 or 500 mg/kg bw/day for 6 hours/day for 21 consecutive days	NOAEL = 500 mg/kg/day No systemic effects were reported at the highest dose tested.
15-day inhalation, rat	Male/Five Female Charles River Rat 0, 6.1, 42.4 or 583 mg/m^3 or 0, 0.0061, 0.042 or 0.583 mg/L for 15 consecutive days	NOAEL = 0.042 mg/L LOAEL = 0.583 mg/L based on based on body tremors and hypersensitivity to noise
90-day oral – dietary, rat	Male/Female Sprague-Dawley Rat 0, 22.5, 46.0, 92.9 or 185 mg/kg bw/day for males and 0, 27.5, 52.3, 110 or 221 mg/kg bw/day for females	NOAEL = 110 mg/kg/day LOAEL = 221 mg/kg/day based on tremors and hypersensitivity
90-day oral – dietary, rat	Male/Female Wistar Rat 0, 200, 600, 2000 or 4000 ppm. Equivalent to doses of 0, 17, 49.9, 179.6 or 357.4 mg/kg bw/day for males and 0, 18.5, 56.2, 176.5 or 356.7 mg/kg bw/day for females, respectively	NOAEL = 175 mg/kg/day LOAEL = 355 mg/kg/day
6-month oral – dietary, rat	Male/Female Sprague-Dawley Rat 0, 375, 750, 1500 or 3000 mg/kg /day for 6 months	NOAEL = 1500 mg/kg/day LOAEL = 3000 mg/kg/day based on signs of hyperexcitability and tremor
90-day oral – capsule, dog	Male/Female Beagle Dog 0, 5, 50 or 500 mg/kg/day for 3 months	NOAEL = 50 mg/kg/day LOAEL = 500 mg/kg/day based on liver weights and liver-to-body weight ratios
90-day oral – capsule, dog	Male/Female Beagle Dog 0, 10, 100 and 2000 mg/kg/day for 13 weeks	NOAEL = 100 mg/kg/day LOAEL = 2000 mg/kg/day based on clinical signs of toxicity
6-month oral – capsule, dog	Male/Female Beagle Dog (25:75 cis/trans) at 0, 10, 50 or 250 mg/kg/day for 6 months	NOAEL = 10 mg/kg/day LOAEL = 50 mg/kg/day based on increased liver weight

Study type	Species/strain/sex: Dose levels tested	Results
Chronic toxicity/carcinogenicity		
1-year oral – capsule, dog	Male/Female Beagle Dog (40/60 cis/trans) by capsule at 0, 5, 100 or 1000 mg/kg bw/day for one year	NOAEL = 100 mg/kg/day LOAEL = 1000 mg/kg/day based on clinical signs, decreased body weight and increased liver weight
Combined chronic toxicity/ carcinogenicity – oral – dietary, rat	Male/Female Rat (strain not specified) 0, 500, 1000 or 2500 ppm for a period of 104 weeks. Equivalent to dose levels of 0, 19.4, 36.9 or 91.5 mg/kg bw/day, respectively, for males and 0, 19.1, 40.2 or 104 mg/kg bw/day, respectively, for females	Systemic NOAEL = 36.9 mg/kg/day Systemic LOAEL = 104 mg/kg/day based on tremor and hypersensitivity
Carcinogenicity – oral –dietary, mouse	Male/Female CD-1 Mouse 0, 20, 500 or 2000 ppm for males and 0, 20, 2500 or 5000 ppm for 24 months. Equivalent to dose levels of 0, 3, 71 or 286 mg/kg bw per day, respectively, for males and to 0, 3, 357 or 714 mg/kg bw/day, respectively for females	Statistically significant increases in liver adenomas at all doses for males and at mid and high doses for females with a significant dose-related trend in both sexes
Carcinogenicity – oral –dietary, mouse	Male/Female Alderly Mouse of 0, 250, 1000 or 2500 ppm for 98 weeks. Equivalent to dose levels of 0, 26.9, 110.5 or 287.2 mg/kg bw per day, respectively, for males and 0, 29.8, 124.2 or 316.1 mg/kg bw per day, respectively, for females	NOAEL = 110.5 mg/kg/day (M) and 124.2 mg/kg/day (F) LOAEL = 316 mg/kg /day (F) and based on tremor and hypersensitivity No evidence of carcinogenicity
Carcinogenicity – oral –dietary	Female Mouse 0 or 5000 ppm (corresponding to 780–807 mg/kg bw per day) for 39, 52, 65 or 78 weeks.	Significant increases in the incidences of lung bronchioloalveolar adenomas in mice Increased incidences of basophilic hepatocellular adenoma did not show a relationship to the treatment duration No progression to carcinoma was observed in the lung or liver
Developmental Toxicity		
Oral – gavage, rat, permethrin	Pregnant Sprague-Dawley 0, 15, 50 or 150 mg/kg/day given by gavage on gestation days 6-15	Maternal toxicity NOAEL = 50 mg/kg/day Maternal LOAEL = 150 mg/kg/day based on clinical signs of toxicity Developmental toxicity NOAEL = 600 mg/kg/day Developmental toxicity LOAEL = 150 mg/kg/day based on decrease in fetal body weights and an increase in the incidence rate of short length extra ribs
Oral – gavage, rabbit	Pregnant New Zealand White Rabbit 0, 600, 1200 or 1800 mg/kg/day	Maternal NOAEL = Not established Maternal LOAEL = 600 mg/kg/day based on decreased body weight gain Developmental toxicity NOAEL = 600 mg/kg/day Developmental toxicity LOAEL = 1200 mg/kg/day based on increased post implantation loss, greater numbers of early and late resorptions and decreased ossification
Reproductive Toxicity		
Oral – dietary, rat	Male/Female Rat 0, 25, 50 or 125 mg/kg/day for 2-generation	Parental/systemic NOAEL = 50 mg/kg/day Parental/systemic LOAEL = 125 mg/kg/day based on tremors Reproductive NOAEL = 125 mg/kg/day Reproductive LOAEL = Not established Offspring NOAEL = 125 mg/kg/day Parental LOAEL = Not established

Study type	Species/strain/sex: Dose levels tested	Results
Neurotoxicity		
Acute oral – gavage, rat	Male/Female Sprague-Dawley Rat A single gavage dose at 0, 25, 75 or 150 mg/kg in corn oil	NOAEL = 25 mg/kg LOAEL = 75 mg/kg based on observations of clinical signs (i.e., aggression, abnormal and/or decreased movement) and increased body temperature
Acute oral – gavage, rat	Male/Female Sprague-Dawley Rat A single gavage dose at 0, 10, 150 or 300 mg/kg bw in corn oil	NOAEL = 150 mg/kg LOAEL = 300 mg/kg based on tremors, gait impairment and decreased forelimb grip strength
Acute oral – gavage, rat (Wolansky et al. 2006)	Male Long Evans Rat A single oral dose of 0, 0.1, 1.0, 40.0, 60.0, 80.0, 100.0, 120.0, 160.0, 200.0 permethrin mg/kg bw in corn oil Motor activity was measured at 1-4 hours after dosing utilizing a figure eight maze with motion photodetectors (time of peak effect for each pyrethroid)	$BMDL_{1SD}$ = 44.4 mg/kg BMD = 63.10 mg/kg
Acute oral toxicity – FOB	McDaniel and Moser 1993	At >20 mg/kg/day, clinical sign (gait abnormalities, ataxia, tip toe walking, limb dragging) decreased grip strength and decreased motor activity
Immunotoxicity		
Oral – dietary	0, 4, 12 or 34 mg/kg/day	NOAEL = 34 mg/kg/day LOAEL = Not established
Oral – dietary	Male/Female Rat (strain not specified) 0, 100, 200 or 400 mg/kg/day for 13 weeks	NOAEL = 100 mg/kg/day LOAEL = 200 mg/kg/day based on tremors and irritability
Oral – dietary	Male/Female Sprague-Dawley Rat 0, 250, 1500 or 2500 ppm for 13 weeks Equivalent to respective time weighted average doses of 0, 15.5, 91.5 or 150.4 mg/kg/day for males and 0, 18.7, 111.4 or 189.7 mg/kg/day for females	NOAEL = 15.5 mg/kg/day LOAEL = 91.5 mg/kg/day based on clinical signs of neurotoxicity
Mutagenicity		
Bacterial reverse mutation assay (Ames assay)	Salmonella typhymurium	There was no evidence of increased reverent colonies above controls in 5 strains up to 5000 µg/plate in the presence and absence of metabolic activation.
Unscheduled DNA synthesis	*In vitro*	There was no evidence of unscheduled DNA synthesis above control up to 10^{-4} molar.
Mouse bone marrow micronucleus	*In vivo*	There was no evidence of clasotenicity.

Study type	Species/strain/sex: Dose levels tested	Results
Metabolism		
Oral – gavage, permethrin		Following a single oral dose of 6.5 mg/kg, most radioactivity (58-65%) from a single dose of the [^{14}C-alcohol] permethrin was eliminated via the urine over a 7-day period with much of the remainder (29–43%) being excreted in the faeces. Urinary excretion of radioactivity following a single dose of [^{14}C-acid] permethrin was slightly less and faecal excretion correspondingly greater. Results of tissue distribution and autoradiographic experiments showed that most radioactivity was associated with adipose tissue and, initially, with the gastrointestinal tract and organs/tissue associated with excretory function. Following multiple doses, radioactivity in adipose tissue appears to be greater for [^{14}C-alcohol] permethrin than for [^{14}C-acid] permethrin. This is also consistent with blood kinetics data showing lower radioactivity (Cmax) in the blood of rats receiving [^{14}C-acid] permethrin.

Study type	Species/strain/sex: Dose levels tested	Results
Dermal absorption		
In vivo dermal absorption	Male Wistar Rat Dermal application at 0.004, 0.08, 0.86 or 9.1 mg ^{14}C-Permethrin/rat applied in concentrated 2EC formulation or water diluted formulation. Rats were sacrificed at 0.5, 1, 2 4, 10 and 24 hours after treatment.	Following 10 hours of exposure, a total of 21.7% permethrin was absorbed.
In vivo/*in vitro* dermal absorptions	In *in vivo* and *in vitro* dermal penetration studies permethrin was applied to the dermal surface of groups of nine human skin samples/group, six rat skin samples/group or the dorsal surface of 12 Sprague-Dawley rats/group at concentrations of 2.25, 20 or 200 pg/cm° for 24 hours. For the *in vivo* study, half the rats in each group were sacrificed 24 hours after dermal application with the remainder sacrificed 120 hours after application. For quality control purpose, piperonyl butoxide (100 qg/cm$^{2'}$ was included to both studies because results of dermal penetration on piperonyl butoxide are well documented in rat and human skin models.	The overall recovery of the radiolabeled permethrin was good to excellent in both studies; being >96% for the *in vitro* rat and human studies and 85% for the *in vivo* rat study. Dermal penetration and absorption of radiolabeled permethrin were consistent between the two types of experiments with rats being 21% for the *in vitro* and *in vivo* studies. For the *in vitro* study, the absorption of permethrin applied at three concentrations was relatively consistent within species (1–3% in humans and 18–24% in rats); indicating that absorption was not saturated at any of the applied concentrations in either species. In addition, absorption of permethrin was linearly distributed (r2 = 0.999) for both species and was approximately 11-fold greater through rat skin than human. For the *in vivo* study, permethrin absorption was relatively consistent at the three concentrations after 24 (22–28%) or 120 (30–38%) hours, again indicating that absorption was not saturated at the highest dose. However, the slight increase in absorption at 120 hours is indicative that radiolabel remaining in the skin after washing at 24 hours was bioavailable. This is supported by the decrease in radiolabel at the application site from 24 (13–22%) to 120 hours (1.9–2.3%) hours after application of the dose with a concomitant increase in the excreta from 24 hours (2.8–4.2%) to 120 hours (23–30%). Although permethrin is highly lipophilic (LogP = 6.50), no significant accumulation was found in the residual carcass. Permethrin was readily excreted with most occurring within 48 hours of application. The amount excreted in the urine was approximately threefold greater than that found in the faeces at 24 and 120 hours after application. The comparative *in vitro* dermal penetration study using human and rat skin showed that 18% of an applied dose was absorbed through rat skin and 2.3% through human skin, which indicates that *in vitro* rat skin is 6.6 times more permeable than *in vitro* human skin. Therefore, a dermal absorption factor of 21.7/6.6 = 3.3% is considered appropriate for risk assessment.

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