Generic risk assessment – Human Health

ALPHA-CYPERMETHRIN
(CAS No. 67375-30-80)

A long-lasting mosquito net treated with alpha-cypermethrin

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

16 JUNE 2021

World Health Organization

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
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 Purpose

The purpose of this document is to present a human health hazard and risk assessment for alpha-cypermethrin-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* (GRAM) (WHO, 2018).

The product characteristics, including the fabric weight (g/m^2) concentration of alpha-cypermethrin- (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 alpha-cypermethrin ITN (coated or incorporated) with the following product characteristic values:

- fabric weight: 35 g/m^2
- concentration by weight of the net: 5.8 g alpha-cypermethrin
- concentration by net area: 203 mg/m^2 alpha-cypermethrin/m^2
- wash resistance index: 90%

Note: The selected values are not intended to put a limit on the possible concentration of alpha-cypermethrin in an ITN. The selected values do not represent the maximum concentration of alpha-cypermethrin 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 alpha-cypermethrin was conducted according to the *Generic risk assessment model for insecticide-treated nets, 2nd edition* (WHO, 2018). Risk assessment involves three steps: hazard assessment, exposure assessment and risk characterization.

- **Hazard assessment** is the identification of the possible toxic effects of a substance, the dose/exposure levels at which those effects may occur and the dose/exposure levels below which no adverse effects are observed. Authoritative evaluations may be used as starting points for the risk assessment. Examples of authoritative evaluations are: Joint Meeting on Pesticide Residues (JMPR) – Monographs and Evaluations; International Programme on Chemical Safety (IPCS): Concise International Chemical Assessment Documents, Environmental Health Criteria Documents; International Agency for Research and Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans: United States Environmental Protection Agency (USEPA) – Pesticide Evaluations; European Food Safety Authority (EFSA) – Pesticide Risk Assessments; European Chemicals Agency – Information on Chemicals. JMPR assessments, if available, are used by WHO for risk assessment unless a more recent authoritative evaluation exists.
- **Exposure assessment** may concern insecticide operators, applicators, residents of treated 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 alpha-cypermethrin is based on the proposed uses of the ITN products, i.e., net used over sleeping areas.

2.1 Hazard assessment

The complete alpha-cypermethrin hazard assessment conducted to support this risk assessment is included in the appendix. This assessment was conducted based on information available at the time of publication. It is necessary for manufacturers who may rely on this assessment to ensure that points of departure and/or reference doses are still appropriate in the preparation of their product dossier.

Oral exposure

Several studies with rats, dogs and mice are available to describe the metabolism in mammals. Some of these studies assess individual *cis* and *trans* radio labeled isomers, and other studies assess the metabolism of alpha-cypermethrin with the label in the cyclopropyl of the phenoxy benzyl ring. In general, the following has been demonstrated from these studies: alpha-cypermethrin is readily absorbed from the gastrointestinal tract and extensively metabolized. It is mostly excreted in the urine that contains several characterized metabolites derived from conjugation of the hydrolysis products of the parent compound following cleavage of the esteratic linkage site (USEPA, 2012, 2017).

Dermal exposure

Following dermal application, a portion of the applied dose (0.76–0.78%) remained in the skin at the application site and surrounding skin at 120 hours post-application, with the low dose providing a conservative estimate of dermal absorption factor (DAF) of 13.4% (USEPA, 2012).

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 [BMD]) 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.

In 2002, JMPR established a NOAEL of 4 mg/kg/day and a lowest observed adverse effect level (LOAEL) of 20 mg/kg/day was based on gait abnormalities, prostration, thrashing, vocalization, piloerection, unkept appearance, limb abnormalities and increased reactivity in rats in an acute neurotoxicity study (JMPR, 2006).

The USEPA (2015, 2018) considered the acute neurotoxicity study in rats (Wolansky et al., 2006) as the most robust data set for assessing alpha-cypermethrin 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 7.1 mg/kg bw is chosen as the acute POD for risk assessment in this document (USEPA, 2012a,b, 2016, 2017).

Acute oral POD = BMDL of 7.1 mg/kg bw

Chronic oral exposure

Alpha-cypermethrin is rapidly absorbed from the gastrointestinal tract and extensively metabolized following an oral dose, and effects are typically observed within two to five 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, 2012 a,b, 2017).

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)

Alpha-cypermethrin was evaluated by the Food and Agriculture Organization/WHO JMPR (2002), at which time an aRfD of 0.04 mg/kg/day based on the POD of 4 mg/kg/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variation (see Table 1).

aRfD = 5 mg/kg bw/day

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	4	100	0.04	Gait abnormalities, prostration, thrashing, vocalization, piloerection, unkept appearance, limb abnormalities and increased reactivity at 20 mg/kg (LOAEL)	Acute neurotoxicity – rat	JMPR, 2006

The USEPA (2012) used the $BMDL_{1SD}$ of 7.6 mg/kg/day from the Wolansky study (2006) and an uncertainty factor of 100 to account for interspecies extrapolation and for intraspecies variation to establish aRfD of 0.07 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 =7.6	100	0.07	Decreased motor activity	Wolansky et al., 2006	USEPA, 2012a,b, 2017

Chronic reference dose (cRfD)

The USEPA did not establish a cRfD since the single-dose and repeated-dose studies with alpha-cypermethrin 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, 2012a,b, 2017).

cRfD = Not established

Acceptable daily intake (ADI)

Alpha-cypermethrin was evaluated by FAO/WHO JMPR in 2006, at which time an ADI of 0.02 mg/kg bw/day was established based on a POD of 2.25 mg/kg bw/day from the subchronic study in rats and a chronic study in dogs, and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variation (see Table 3, JMPR, 2006).

ADI = 0.02 mg/kg bw/day

Table 3. ADI

NOAEL (mg/kg/day)	Uncertainty factor	ADI (mg/kg/day)	Toxicological endpoint of concern	Study selected	Reference
2.25	100	0.02	Significant clinical signs characterized by tremors, gait abnormalities, ataxia, agitation, head nodding and lip licking in both sexes of dogs at 6.75 mg/kg/day (LOAEL) Supported by alopecia and abdominal skin reddening in dogs at 3 mg/kg/day.	Subchronic rat study And 1-year dog	JMPR, 2006

2.1.3. Selection of tolerable systemic dose (TSD)

The PQT/VCP selected the aRfD of 0.07 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 alpha-cypermethrin exposure and risk.

The PQT/VCP selected the ADI of 0.02 mg/kg/day established by the JMPR (2006) as the TSD for long-term risk assessment, and the ADI is appropriate for assessing repeated toxicity of alpha-cypermethrin 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 5.8 g alpha-cypermethrin/kg net and 35 g/m^2 fabric weight, the TC is calculated as follows:

$$TC = 125\% \times 5.8 \text{ g/kg net} \times 0.035 \text{ kg/m}^2 \times 1000 = 253.75 \text{ mg/m}^2$$

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

Abs = Dermal from net surface (data driven = 13.4%)
Abs-o = Oral absorption (default) = 100%
AT = Average time (default = 365 days)
BW = Body weight (default = adult = 60 kg adult; 23.9 kg/child; 10 kg/toddler; 8 kg infant [less than 12 months]; 4.2 kg/newborn [birth to 1 month]
ESA = Exposed skin area (m^2)
EHA = Exposed hand area (default = 0.008 m^2/toddler; 0.007 m^2/infant)
FHM = Fraction transferred from hand to mouth (default = 0.164 [75th percentile])
NM = Net mouthed (default = 0.0014 m^2)
NoN = Number of nets washed per day (default = 5)
NoW = Number of washes per year (default = 20 washes/3 years)
RSW = Release rate (analytical data)
SE = Salivary extraction factor (default = 57%)
SN = Maximal actual size of the net (default = 15 m^2)
SF = Surface fraction (100 – wash resistance index %) = 10%
Transl = Translodgeable fraction (default = 6%)
TC = Total concentration of active ingredient on net surface (derived value)
VLH = Volume liquid on hand (default = 8.2 ml/adult; 4.3 ml/child)
VLS = Volume of liquid on skin (default = 36.7 ml/adult; 17.6 ml/child)
VolW = Volume of washing water (default = 4 litres)
WRI = Wash resistance index = 90%
1000 = conversion of mg to µg
Alpha-cypermethrin molecular mass = 416.3 g/mol
Alpha-cypermethrin vapor pressure = 2.55 X10^{-9} mm Hg @ 25° C

2.2.1 Exposure from sleeping under treated nets

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

2.2.1.1 From inhalation exposure

Alpha-cypermethrin has a vapor pressure of 2.55 X10^{-9} and a molecular weight of 416.3. In agreement with the GRAM, the inhalation exposure during sleeping under an alpha-cypermethrin-treated long-lasting net is considered negligible because of the low vapor pressure (WHO, 2012; 2018). Thus, for alpha-cypermethrin, 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 DAF of 13.4 % 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. Alpha-cypermethrin: 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)
Adults	13.4	6	0.408	10	253.75	60.0	1.39
Children	13.4	6	0.225	10	253.75	23.9	1.92
Toddlers	13.4	6	0.115	10	253.75	10.0	2.35
Infants	13.4	6	0.100	10	253.75	8.0	2.55

Translodgeable = default = 6%
ESA = default value
SF= 100 – wash resistance index % = 10%
TC = 253.75 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.

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

Table 5. Alpha-cypermethrin: 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	253.75	10.0	0.114
Infants	100	57	6	0.007	0.164	10	253.75	8.0	0.125

SE = default value = 57%
Transl = default value = 6%
EHA = default values
FHM = default value = 0.164
SF= 100 – wash resistance index % = 10%
TC = 253.75 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.

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

Table 6. Alpha-cypermethrin: 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	253.75	10.0	2.02
Infants	100	57	0.0014	10	253.75	8.0	2.53

SE = default value = 57%
NM = default = 0.0014 m^2
SF= 100 – wash resistance index % = 10%
TC = 253.75 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 alpha-cypermethrin 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. Alpha-cypermethrin: estimated total systemic dose (µg/kg bw/day) 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 exposure (µg/kg bw/day)
Adults	Negligible	1.39	N/A	N/A	1.39
Children	Negligible	1.92	N/A	N/A	1.92
Toddlers	Negligible	2.35	0.114	2.02	4.48
Infants	Negligible	2.55	0.125	2.53	5.21

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 adult and child 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. Alpha-cypermethrin: estimated systemic dose (maximum) from acute dermal exposure due to washing treated nets

Population	Dermal absorption (%)	NoN (nets)	VLS (ml)	SF (%)	TC (mg/m^2)	SN (m^2)	VolW (ml)	BW (kg)	Systemic dose (µg/kg bw/day)
Adults	13.4	5	36.7	10	253.75	15	4000	60.0	38.99
Children	13.4	5	17.6	10	253.75	15	4000	23.9	46.95

NoN = default = 5
VLS = default = 36.7 ml/adult and 17.6 ml/child)
SF= 100 – wash resistance index % = 10%
TC = 253.75 mg/m^2
SN = default = 25 m^2
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. WW Alpha-cypermethrin: 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	13.4	20/3 years	5	36.7	10	253.75	15	4000	60.0	365	0.713
Children	13.4	20/3 years	5	17.6	10	253.75	15	4000	23.9	365	0.858

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 = 253.75 mg/m²
SN = default =15 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. Alpha-cypermethrin: 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	253.75	0.164	15	4000	60.0	10.66
Children	100	5	4.3	10	253.75	0.164	15	4000	23.9	14.04

NoN = default = 5
VLH = default = 8.2 ml/adult and 4.3 ml/child
SF= 100 – wash resistance index % = 10%
TC = 253.75 mg/m²
FHM = default = 0.164
VolW = default = 4000 ml
BW = default values
1000 = conversion of mg to µg

From repeated (TWA) exposure

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

Table 11. Alpha-cypermethrin: estimated systemic dose (TWA) from repeated oral exposure due to washing treated nets

Population	Dermal 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	253.75	0.164	15	4000	60.0	365	0.195
Children	100	20/3 years	5	4.3	10	253.75	0.164	15	4000	23.9	365	0.256

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 = 253.75 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

2.2.2.3 Total systemic exposure due to washing of treated nets

The estimated total systemic dose from washing of nets is shown in Table 12.

Table 12. Alpha-cypermethrin: 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)			
Adults	38.99	10.66	49.65
Children	46.95	14.04	60.99
Repeated exposure (TWA)			
Adults	0.713	0.195	0.908
Children	0.858	0.256	1.11

2.2.3 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:

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

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 = 1.39 + 49.65 µg/kg bw/day = 51.04µg/kg bw/day

Mother dose (TWA) = 1.39 + 0.908 = µg/kg bw/day = 2.30 µg/kg bw/day

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

Table 13. Alpha-cypermethrin: estimated maximum systemic dose from exposure via breast milk

Subpopulation	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	51.04	2.5	0.66	4.2	7.2
Infants	100	0.361	51.04	2.5	0.66	8.0	3.8

$T_{1/2}$ = First-order kinetics half time of alpha-cypermethrin in days, 2.5 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. Alpha-cypermethrin: estimated TWA systemic dose from exposure via breast milk

Subpopulation	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	2.30	2.5	0.66	4.2	0.326
Infants	100	0.361	2.30	2.5	0.66	8.0	0.171

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

2.3 Risk characterization

The purpose of risk characterization is to examine the probability of adverse effects occurring resulting from the use of the insecticide under defined exposure conditions. Risk characterization consists of comparing the estimate of total exposure (i.e., estimated systemic dose) with the TSD established in the hazard assessment. The TSD is the same as the ADI or the cRfD established for the active ingredients (WHO, 2018).

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

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 alpha-cypermethrin 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 alpha-cypermethrin-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	1.39	N/A	N/A	1.39	20	0.070
Children	1.92	N/A	N/A	1.92	20	0.096
Toddlers	2.35	0.114	2.02	4.48	20	0.224
Infants	2.55	0.125	2.53	5.21	20	0.261

TSD = 20 µg/kg bw/day (JMPR, 2006)
Risk ratio = Total exposure/TSD

2.3.2 Exposure estimates and risk ratios for washing treated nets

The risk ratios for all populations washing treated nets are depicted in Table 16.

Table 16. Exposure estimates and risk ratios for populations washing of alpha-cypermethrin-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	38.99	10.66	49.65	70	N/A	0.709
Children	46.95	14.04	60.99	70	N/A	0.871
Repeated exposure (TWA)						
Adult	0.713	0.195	0.908	N/A	20	0.045
Children	0.858	0.256	1.11	N/A	20	0.056

aRfD = 70 µg/kg bw/day (EPA, 2017)
TSD = 20 µg/kg bw/day (JMPR, 2006)
Risk ratio = Total Exposure/aRfD or Total Exposure (TWA)/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 alpha-cypermethrin-treated nets are depicted in Table 17.

Table 17. Exposure estimates and risk ratios for populations sleeping under and washing alpha-cypermethrin-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	1.39	49.65	51.04	70	N/A	0.729
Children	1.92	60.99	62.91	70	N/A	0.899
Repeated exposure (TWA)						
Adults	1.39	0.908	2.30	N/A	20	0.115
Children	1.92	1.11	3.03	N/A	20	0.152

aRfD = 70 µg/kg bw/day (EPA, 2017)
TSD = 20 µg/kg bw/day (JMPR, 2006)
Risk ratio = Total Exposure/aRfD or Total Exposure (TWA)/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 Alpha-cypermethrin-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 RfD (µg/kg/day)	TSD (µg/kg/day)	Risk ratio
Acute exposure (maximum)						
Newborns	N/A	7.2	7.2	70	N/A	0.103
Infants	5.21	3.8	9.01	70	N/A	0.129
Repeated exposure (TWA)						
Newborns	N/A	0.326	0.326	N/A	20	0.016
Infants	5.21	0.171	5.38	N/A	20	0.269

aRfD = 70 µg/kg bw/day (EPA, 2017)
TSD = 20 µg/kg bw/day (JMPR, 2006)
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 alpha-cypermethrin as ITN (up to 5.8 g/kg or 203 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 an alpha-cypermethrin-treated ITN, coated or incorporated, with a concentration of 203 mg ai/m^2 (Fabric weight 35 g/m^2 and 5.8 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: Alpha-cypermethrin health hazard assessment

Product Name: ALPHA-CYPERMETHRIN
Empirical formula: C22H19Cl2NO3
Chemical Abstract Number: 67375-30-80

1 Background information

Alpha-cypermethrin is a broad-spectrum insecticide, effective against target pests through contact and ingestion.

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. Alpha-cypermethrin is a Type II pyrethroid. 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. In repeated-dose studies with rodents, the main toxicological findings were reduced body weight gain, reduced food consumption and at higher doses, signs of neurotoxicity (convulsions, tremors, hypersensitivity to touch and sound). Dogs appeared to be the most sensitive species, with clinical signs of neurotoxicity (tremors, gait abnormalities, ataxia, agitation, head nodding, and lip licking) being observed in the absence of body weight loss. There is no evidence for genotoxic, developmental, reproductive, immunotoxic or carcinogenic potential.

It should be noted that toxicology studies on cypermethrin, alpha-cypermethrin and zeta-cypermethrin were included in the referenced reviews to evaluate the hazard potentials and inform the selection of PODs for alpha-cypermethrin.

2 Relevant toxicity information on alpha-cypermethrin

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

The toxicity profile for alpha-cypermethrin, which includes studies on cypermethrin and zeta-cypermethrin, is presented in Tables A1 and A2 in the appendix.

Alpha-cypermethrin has either moderate or minimal toxicity (GHS Category 3 to 5 depending on the vehicle used) via the oral route of exposure in acute oral toxicity studies and has moderate acute toxicity via the inhalation route (GHS Category 3). It is minimal toxicity via the dermal route (GHS Category 5). It is a mild eye and skin irritant (GHS Category 3) and is a non-skin sensitizer.

A summary of the subchronic, chronic, developmental, reproductive, neurotoxicity, chronic toxicity/carcinogenicity genotoxicity studies is presented in Table A.2.

Table A1. Acute toxicity of alpha-cypermethrin

Alpha-cypermethrin – toxicity profile: acute toxicity		
Study type	**Results**	**GHS Category**
Acute oral toxicity in rats	>2000 mg/kg	5
	>5000 mg/kg bw (Aqueous suspension) >57 mg/kg bw (Corn oil)	3
Acute dermal toxicity in rabbits	>2000 mg/kg	5
Acute inhalation toxicity in rats	>2.79 mg/L	3
Primary eye irritation in rabbits	Mild irritant	3
Primary dermal irritation in rabbits	Mild irritant	3
Skin sensitization in guinea pigs	Non-sensitizer	Not applicable

Table A2. Subchronic, chronic/carcinogenicity, developmental, reproductive and other toxicity studies with alpha-cypermethrin (USEPA, 2012a, 2017)

Study type	Species/strain/sex: Dose levels tested	Results
Sub-chronic toxicity		
21-day dermal, zeta-cypermethrin, rats	Male/Female Rat (strain not specified) 0, 100, 500 or 1000 mg/kg/day, 6 hours/day, 5 days/week for 3 weeks	Systemic NOAEL = 1000 mg/kg/day Systemic LOAEL = Not established Dermal NOAEL = Not established Dermal LOAEL = 100 mg/kg/day based on erythema and/or eschar
21-day inhalation, cypermethrin, rats	Male/Female Rat 0, 0.01, 0.05 or 0.25 mg/L	NOAEL = 0.01 mg/L LOAEL = 0.05 mg/L based on increased salivation
90-day oral – dietary, alpha-cypermethrin, rats	Male/Female Wistar Rat 0, 20, 60, 180 or 540 ppm for 90 days Equivalent to doses of 0, 1.02, 1.74, 9.3 or 29.6 mg/kg/day, respectively, in males and 0,1.2, 3.8, 11.3 or 35 mg/kg/day, respectively, in females	NOAEL = 9.3 mg/kg/day LOAEL = 29.6 mg/kg/day based on decreased body weight, body weight gain, decreased food consumption and gait changes
90-day oral – dietary, alpha-cypermethrin, dogs	Male/Female Beagle Dog 0, 30, 90 or 270 ppm for 90 days Equivalent to doses of 0, 0.75, 2.25 or 6.75 mg/kg/day	NOAEL = 2.25mg/kg/day LOAEL = 6.75 mg/kg/day based on clinical signs (tremors, gait abnormalities, ataxia, agitation, head bobbling and lip licking)
Chronic toxicity/carcinogenicity		
1-year oral – dietary, alpha-cypermethrin, dogs	Male/Female Dog 0, 60, 120 or 240 ppm Equivalent to doses of 0, 2.02, 4.11 or 7.90 mg/kg/day respectively, in males and 0, 2.18, 4.29 or 8.45 mg/kg/day respectively, in females	NOAEL = 4.1 mg/kg/day (M) and 4.29 mg/kg/day (F) LOAEL = 7.9 mg/kg/day (M) and 8.45 mg/kg/day (F) based on clinical signs (skin reddening, hair loss and tail irritation)
Combined chronic toxicity/carcinogenicity – oral – dietary, cypermethrin, rats	Male/Female Rat 0, 20, 150 or 1500 ppm Equivalent to 0, 0.1, 1 or 75 mg/kg/day	NOAEL = 75 mg/kg/day LOAEL = Not established No evidence of carcinogenicity
Carcinogenicity – oral –dietary, alpha-cypermethrin, mice	Male/Female CD-1 Mouse 0, 30, 100 or 300 ppm for 78 weeks Equivalent to doses of 0, 3, 10.6 or 35.2 mg/kg/day, respectively in males and 0, 3.5, 11.5 or 37.7 mg/kg/day, respectively, in females	Male NOAEL = 10.6 mg/kg/day LOAEL = 35.2 mg/kg/day based on decreased body weight, body weight gains, and clinical signs No evidence of carcinogenicity
Developmental Toxicity		
Oral – gavage alpha-cypermethrin, rats	Pregnant Sprague-Dawley Rat 0, 3, 9 or 15 mg/kg/day dissolved in corn oil given by gavage during gestation Days 6–15, inclusive	Maternal Toxicity NOAEL = 9 mg/kg/day Maternal Toxicity LOAEL = 15 mg/kg/day based on decreases in body weight and clinical signs (unsteady gait, piloerection, limb splay and hypersensitivity to sound and touch) Developmental Toxicity NOAEL= 9 mg/kg/day Developmental Toxicity LOAEL = 15 mg/kg/day based on decreased fetal body weight
Oral – gavage alpha-cypermethrin, rabbits	Pregnant New Zealand White Rabbit 0, 3, 15 or 30 mg/kg/day dissolved in corn oil given by gavage during gestation Days 7–19, inclusive	Maternal Toxicity NOAEL = 15 mg/kg/day Maternal Toxicity LOAEL =30 mg/kg/day based on decreases in body weight and food consumption Developmental Toxicity NOAEL= 30 mg/kg/day Developmental Toxicity LOAEL = Not established

Study type	Species/strain/sex: Dose levels tested	Results
Reproductive Toxicity		
One generation reproduction study, oral – dietary zeta-cypermethrin, rats	Male/Female Rat 0, 7.5, 258, 100, 375 or 750 ppm Equivalent to doses of 0, 0.5, 1.8, 7, 27 or 45 mg/kg/day for 1-generation	Parental systemic NOAEL = 7 mg/kg/day Parental systemic LOAEL = 27 mg/kg/day based on decreased body weight gain and increased relative brain weights Reproductive NOAEL = 27 mg/kg/day Offspring NOAEL = 7 mg/kg/day Parental LOAEL = 27 mg/kg/day based on decreased body weight gain during lactation
Neurotoxicity		
Acute oral – dietary, rats	Male/Female CD Rat A single gavage dose at 0, 4, 20 or 40 mg/kg in corn oil	NOAEL = 4 mg/kg LOAEL = 20 mg/kg based on clinical signs, FOB changes and mortality
Acute oral – motor activity, rats (Wolansky et al., 2006)	Male Long Evans Rat A single oral dose of cypermethrin at 0, 0.1, 0.5, 1.0, 10.0, 40.0, 120.0 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).	$BMDL_{1SD}$= 7.16 mg/kg BMD= 11.20 mg/kg
Acute oral toxicity, rats – 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
Acute oral, rat – FOB	Nemec 2006	$BMDL_{20}$= 55.9 mg/kg BMD_{20}= 76.3 mg/kg
Immunotoxicity		
Oral – dietary, rat	0, 4, 12 or 34 mg/kg/day	NOAEL = 34 mg/kg/day LOAEL = Not established
Mutagenicity		
Bacterial reverse mutation assay (Ames assay), zeta-cypermethrin	*Salmonella typhimurium & S. cerevisiae* 0, 100, 333, 1000, 3333, 5000, 10 000 µg/plate	Negative in both presence and absence of metabolic activation
In vitro gene mutation, Zeta-cypermethrin	0, 14, 45, 140, 450, 1400 and 4500 ug/ml	Negative in both presence and absence of metabolic activation
In vivo cytogenetics, rats	Rat bone marrow 0, 20 or 40 mg/kg	No evidence of structural chromosomal aberrations
Unscheduled DNA synthesis-mammalian cell, zeta-cypermethrin	0, 1, 10, 25, 50, 100 (estimated limit of solubility), 400, 700 and 1000 ug/ml	Negative
Dominant lethal assay, mice	CD-1 Mouse 0, 2.5, 5, 7.5, 10 mg/kg/day for 5 days	Negative

Study type	Species/strain/sex: Dose levels tested	Results
Metabolism		
Oral – gavage, cypermethrin, rats	In a series of rat oral metabolism studies Wistar rats were treated with a single gavage dose of [^{14}C-benzyl] or [^{14}C-cyclopropyl] cypermethrin (radiochemical purity >99%) at 2 or 200 mg/kg in Mazola corn oil (2 mL/kg dosing volume). The following studies were performed. (1) Metabolism: An experiment was performed in 5 rats/sex receiving 2 mg kg [^{14}C-benzyl] cypermethrin that evaluated the excretion and tissue distribution of radioactivity at up to 4 days post-dose. (2) Tissue distribution: Was assayed in 8 subgroups of 3 female rats/time point sacrificed at 8 intervals up to 42 days after the administration of 2 mg/kg [^{14}C-benzyl] cypermethrin. (3) Blood kinetics and plasma metabolism: In a whole blood kinetics experiment, both doses and radiolabeled compounds were evaluated in 6 rats/sex/dose/radiolabel, and blood samples were collected up to 1 day after administration of the low dose or 3 days after administration of the high dose.	In the 2 mg/kg groups evaluated for blood kinetics, absorption and excretion were rapid; maximum concentrations were observed in the blood within 3–4 hours (≤1.75 µg equiv./mL) and negligible amounts were observed at 16 hours post-dose. No sex differences were noted in maximum concentrations or times to maximum concentration. The concentrations in the [^{14}C-benzyl] cypermethrin groups were approximately 3-fold higher than observed in the [^{14}C-cyclopropyl] cypermethrin groups, but the radiolabel position did not affect the times at which the maximum concentrations were observed. In the 200 mg/kg groups evaluated for blood kinetics, maximum concentrations of radioactivity in the blood were as follows: in the [^{14}C-benzyl] cypermethrin groups (males – 39.7 µg equiv./mL at 23 hours; females – 41.9 µg equiv./mL at 16 hours) and in the [^{14}C-cyclopropyl] cypermethrin groups (males – 10.3 µg equiv./mL at 24 hours; females – 6.65 µg equiv./mL at 8 hours). No significant sex differences were noted in maximum concentrations, but concentrations reached maximum sooner in the plasma of females than in males, regardless of the radiolabel position. The concentrations in the [^{14}C-benzyl] cypermethrin groups were higher by approximately 4-fold in males and 6-fold in females compared to the [^{14}C-cyclopropyl] cypermethrin groups, but the radiolabel position did not have an appreciable effect on the times at which the highest concentrations were observed. The concentrations were <5 µg equiv/mL in all high dose groups by 48 hours post dose. An increase in dose of 100-fold led to an increase in blood of 12- to 28-fold, suggesting absorption may have been saturated at the high dose.

Study type	Species/strain/sex: Dose levels tested	Results
Dermal absorption		
In vivo dermal absorptions, rats	Male Crl:WI (Han) Rat Actual doses of 1.5 or 333 µg/cm^2 skin were applied to the skin of each rat in volumes of 10 µl/cm^2 skin in a vehicle consisting of the blank formulation BAS 308 4 I or a 1/200 aqueous dilution of the blank formulation plus test material, respectively. Four rats/dose/time point were tested using an exposure duration of 6 hours and termination times of 6, 24 or 120 hours post-application. Urine and faeces samples were collected at 6 hours (end of dosing), 24 hours and then at 24-hour intervals until study termination.	Only 0.76–0.78% AD remained in the skin at the application site and surrounding skin at 120 hours post-application, indicating absorption was essentially complete at that time. The low dose (1.5 µg/cm^2) at 120 hours post-dosing provided the most conservative estimate of total absorbed at 13.4% from Days 1 to 8 were 1.6–2.7 days in skin and fat. The half-lives based on data obtained from Days 14 to 42 were 40 days in skin, 26 days in perovarian fat, 19 days in peri-renal fat, and 17 days in subcutaneous fat. In contrast, elimination of radioactivity in other tissues was rapid: in the liver and kidney the half-lives were 2.3 and 2.0 days, respectively, and levels of radioactivity at 2 weeks post-dosing were below the limit of detection. A total of 6 compounds were tentatively identified in the excreta (identified using thin layer chromatography separation with standards for identification: further analytical methods were not employed). There was only one major metabolite that was isolated: 3-(4-hydroxyphenoxybenzoic acid Osulfate ester was isolated from the urine (34–40% AD). In the faeces of the combined sexes, the parent was the predominant compound (22% AD). Metabolism of cypermethrin occurs by estercleavage followed by hydroxylation and sulfation of the 3-phenoxybenzoic acid portion of the compound. The cyclopropanecarboxylic acid portion of the insecticide is rapidly eliminated as the glucuronide conjugate. Hydroxylation of the intact ester also occurs to a small degree. The proportion of the radioactive residues isolated in the hexane extract of peri-renal and parovarian fat (as opposed to the acetonitrile phase) increased steadily with time from 28% of the total radioactive residue at Day 3 to 48% at Day 22. As cypermethrin partitions almost exclusively into the acetonitrile fraction, this suggests that lipophilic metabolites are present in the fat at increasing levels over time. The lipophilic metabolites were not further analyzed in this study. In the [^{14}C-benzyl] cypermethrin treated animals, a steady increase with time in the % total radioactive residue in the plasma attributable to cypermethrin was observed at both doses; however, no obvious effect on this percentage was noted in animals treated with [^{14}C-cyclopropyl] cypermethrin. Concentrations of cypermethrin in the plasma were an order of magnitude higher in the [^{14}C-benzyl] cypermethrin groups compared to the [^{14}C-cyclopropyl] cypermethrin groups.

References

Joint Meeting on Pesticide Residues (2006). Joint FAO/WHO Meeting of Pesticide Residue (JMPR). Pesticide Residues in Food-2006. Toxicological Evaluations. Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group, Rome, Italy 3–12. October 2006.

McDaniel, K.L. and Moser, V.C. (1993). Utility of a neurobehavioral screening battery for differentiating the effects of two pyrethroids, permethrin and cypermethrin. Neurotoxicol Teratol 15(2) 71–83.

Nemec, M. (2006). An Acute Functional Observational Battery Comparison Study in Rats. WIL Research Laboratories, LLC, 1407 George Road, Ashland, OH 44805-9281. Laboratory report numbers

United States Environmental Protection Agency (2012). Benchmark dose technical guidance. Risk Assessment Forum, June 2012.

United States Environmental Protection Agency (2012a). Alpha-Cypermethrin – Human Health Risk Assessment for New Active Ingredient. DP Barcode D376098. Office of Pesticides Program. (https://www.regulations.gov/document?D=EPA-HQ-OPP-2012-0185-0005, accessed 21 December 2017).

United States Environmental Protection Agency (2012b). Standard Operating Procedures for Residential Pesticide Exposure Assessment. Office of Chemical Safety and Pollution Prevention, Washington DC, October 2012.

United States Environmental Protection Agency (2016). U.S. Environmental Protection Agency. DER for M.J. Wolansky et al 2006. Relative potencies for acute effects of pyrethroids on motor function in rats. DP Barcode D422817. TXR No.0057059. MRID No.47885701. April 28, 2016. Health Effects Division, Office of Pesticides Program. (https://www.regulations.gov/document/EPA-HQ-OPP-2008-0331-0064, accessed 10 May 2021).

USEPA (2017). U.S. Environmental Protection Agency. Cypermethrin, Zeta-cypermethrin, and Alpha-cypermethrin, Draft Human Health Risk Assessment for Registration Review. DP Barcode: D424964. Office of Pesticides Program. (https://www.regulations.gov/document?D=EPA-HQ-OPP-2014-0601-0011, accessed 21 December 2017).

Wolansky, M.J., Gennings, C. and Crofton, K.M. (2006). Relative potencies for acute effects of pyrethroids on motor function in rats. Toxicological Sciences, 89(1), 271–277.

World Health Organization (2018). Generic risk assessment model for insecticide-treated nets. 2edn. United Nations.

World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

WHO Prequalification of Vector Control Products:
https://extranet.who.int/pqweb/vector-control-products