Generic risk assessment – Human Health

DELTAMETHRIN
(CAS No. 52918-63-5)

An active ingredient in insecticide-treated nets

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

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Contents

Acronym list

Abs	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 deltamethrin-treated nets (factory-coated or incorporated). It is intended to be used by applicants, regulatory authorities and other interested parties as an example of the implementation of the *Generic risk assessment model for insecticide-treated nets, 2nd edition* (GRAM) (World Health Organization [WHO], 2018).

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

The assessment was conducted based on a uniformly treated deltamethrin ITN (coated or incorporated) with the following product characteristic values:

- fabric weight: 40 g/m^2
- concentration by weight of net: 3 g deltamethrin/kg net
- concentration by net area: 120 mg deltamethrin/m^2
- wash resistance index: 90%.[1]

Note: The selected values are not intended to put a limit on the possible concentration of deltamethrin in an ITN. The selected values do not represent the maximum concentration of deltamethrin at which the assessed risks may become unacceptable.

In support of new product applications or change applications submitted to the 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 deltamethrin 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.

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).

- **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 deltamethrin is based on the proposed uses of the ITN products, i.e., net used over sleeping areas.

2.1 Hazard assessment

The complete deltamethrin 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

Deltamethrin is rapidly absorbed following an oral dose, and effects are typically observed within two to five hours after dosing. The combination of rapid absorption, metabolism and elimination precludes accumulation and increased toxicity following repeated dosing. Due to the lack of increased hazard from repeated exposure to deltamethrin, the risk estimates derived from acute exposure are protective of risk from repeated exposures. Therefore, it is not necessary to assess chronic risk for deltamethrin due to a lack of increased toxicity with increased duration of exposure.

Dermal exposure

Systemic toxicity via the dermal route of exposure is not anticipated. No treatment-related systemic findings were observed at the limit dose of 1,000 mg/kg/day in the 21-day dermal study.

An in-vitro human skin dermal absorption study with deltamethrin showed 1% of the dose diffused into the receptor fluid (Hughes and Edwards, 2010). The 1% dermal absorption is also mentioned in a risk assessment for the use of deltamethrin on bednets for the prevention of malaria (Barlow et al., 2001). Therefore, a dermal absorption default value of 1% is used for the purpose of this 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 5 mg/kg/day (NOAEL) from an acute neurotoxicity study in rats (JMPR, 2000). The USEPA (2015, 2018) considered the acute neurotoxicity study in rats (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 as the POD 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 POD established from Wolansky's acute study with NOAELs obtained from repeated dosing studies, it is apparent that repeat exposures do not result in lower PODs. This observation is consistent with the general kinetic profile for pyrethroids. As a result, the oral $BMDL_{1SD}$ of 1.49 mg/kg/day is chosen as the acute POD for acute risk assessment in this document.

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

Chronic oral exposure

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

Deltamethrin is rapidly absorbed 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, 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)

Deltamethrin was evaluated by the Food and Agriculture Organization (FAO)/WHO JMPR in 2000, at which time an aRfD of 0.05 mg/kg bw was established based on a POD of 5 mg/kg/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities (see Table 1).

aRfD = 0.05 mg/kg bw/day (JMPR, 2000)

Table 1. JMPR aRfD – Oral

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

The USEPA (2015, 2018) used the $BMDL_{1SD}$ of 1.49 mg/kg/day from the Wolansky study (2006) and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities to establish an aRfD of 0.015 mg/kg bw (USEPA, 2015; USEPA, 2018) (see Table 2).

aRfD = 1.49 mg/kg/day ÷ 100 = 0.015 mg/kg

Table 2. USEPA aRfD – Oral

Population of concern	POD = NOAEL (mg/kg/day)	Uncertainty factor	aRfD (mg/kg)	Toxicological endpoint of concern	Study selected	Reference
Acute dietary	$BMDL_{1SD}$ = 1.49 mg/kg	100	0.015	Decreased motor activity. BMD_{1SD} value = 2.48 mg/kg	Wolansky et al., 2006	USEPA, 2015, 2018

Chronic reference dose (cRfD)

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

Deltamethrin was evaluated by the FAO/WHO JMPR in 2000, at which time an ADI of 0.01 mg/kg bw/day was established based on a NOAEL of 1.0 mg/kg bw/day from the 1-year dog study and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities (see Table 3)

Table 3. ADI

NOAEL (mg/kg/day)	Uncertainty factor	ADI (mg/kg/day)	Toxicological endpoint of concern	Study selected	Reference
1.0	100	0.01	Clinical signs of neurotoxicity	one-year dog study	JMPR, 2000

2.1.3 Selection of Tolerable Systemic Dose (TSD)

The PQT/VCP selected the aRfD of 0.015 mg/kg bw/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 deltamethrin exposure and risk.

The PQT/VCP selected the ADI of 0.01 mg/kg bw/day established by JMPR (2000) as the TSD for long term risk assessment and the ADI is appropriate for assessing the toxicity of deltamethrin 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 (EPA, 2012b, 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 GRAM (WHO, 2018) specification of the net (default variability of the concentration being +/- 25%).

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

Using the selected product design attributes of 3.0 g deltamethrin/kg net and 40 g/m^2 fabric weight, the TC is calculated as follows:

$$TC = 125\% \times 3.0 \text{ g deltamethrin/kg net} \times 40 \text{ g/m}^2 = 150 \text{ mg/m}^2$$

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

Abs = Dermal absorption from net surface (1% is used as default)
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 = 0.57 [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) = 150 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
Deltamethrin Molecular Mass = 505.21 g/mol
Deltamethrin Vapor Pressure = 1.5 x 10 e-8 mm Hg at 250 Celsius

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

Deltamethrin incorporated in ITN has a low vapor pressure (15 x 10e-8 mmHg at 25°C); therefore, inhalation exposure is negligible. It is expected that inhalation of deltamethrin would not exceed 0.07–2.0% of the exposure which occurs via oral and dermal routes (USEPA, 2012b; WHO, 2018). Thus, for deltamethrin, 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 1% default dermal absorption factor (Barlow et al., 2001; Hughes and Edwards, 2010). Table 4 reflects the systemic doses for all populations due to dermal exposures from sleeping under treated nets.

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

Table 4. Deltamethrin: estimated TWA systemic dose for all populations due to dermal exposure from sleeping under the treated nets

Population	Absorption (%)	Transl (%)	ESA (m^2)	SF (%)	TC (mg/m^2)	BW (kg)	Systemic dose (µg/kg bw/day)
Adults	1	6	0.408	10	150	60.0	0.061
Children	1	6	0.225	10	150	23.9	0.085
Toddlers	1	6	0.115	10	150	10.0	0.104
Infants	1	6	0.100	10	150	8.0	0.113

Translodgeable default = 6%
ESA = Exposed skin area values
SF = 100 – wash resistance index % = 10%
TC = 150 mg/m^2
BW = 60 kg/adult; 23.9 kg/child; 10 kg/toddler; 8 kg/infant
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 toddlers and infants.

From hand-to-mouth transfer

It is assumed that hand-to-mouth transfer is significant only for toddlers and infants. The estimated daily systemic dose from hand-to-mouth transfer is calculated as indicated in Table 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. Deltamethrin: estimated systemic dose due to hand-to-mouth transfer sleeping under treated nets

Population	Absorption (%)	SE (%)	Transl (%)	EHA (m^2)	FHM	SF (%)	TC (mg/m^2)	BW (kg)	Systemic dose (µg/kg bw/day)
Toddlers	100	57	6	0.008	0.164	10	150	10	0.067
Infants	100	57	6	0.007	0.164	10	150	8	0.073

SE = Salivary extraction = 57% default value in the absence of actual value
Translodgeable default = 6%
EHA = Exposed hand area values
FHM = Fraction transfer hand to mouth (default = 0.164)
SF = 100 – wash resistance index % = 10%
TC = 150 mg/m^2
BW = 10 kg/toddler; 8 kg/infant
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. Deltamethrin: estimated systemic dose due to direct mouth contact sleeping under treated nets

Population	Absorption (%)	SE (%)	NM (m^2)	SF (%)	TC (mg/m^2)	BW (kg)	Systemic dose (µg/kg bw/day)
Toddlers	100	57	0.0014	10	150	10	1.197
Infants	100	57	0.0014	10	150	8	1.496

SE = Salivary extraction factor = 57% default value used in the absence of actual value NM = Area of net mouth (default = 0.0014 m^2)
SF = 100 – wash resistance index % = 10%
TC = Target concentration = 150 mg/m^2
BW = 10 kg/toddler; 8 kg/infant
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 deltamethrin 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. Deltamethrin: estimated total systemic dose (µg/kg bw/day) due to sleeping under treated nets

Population	Inhalation exposure	Dermal exposure	Oral (indirect) exposure	Oral (direct) exposure	Total systemic dose (µg/kg bw/day)
Adults	Negligible	0.061	N/A	N/A	0.061
Children	Negligible	0.085	N/A	N/A	0.085
Toddlers	Negligible	0.104	0.067	1.197	1.368
Infants	Negligible	0.113	0.074	1.469	1.682

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 is 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. Deltamethrin: estimated systemic dose (maximum) from acute dermal exposure due to washing treated nets

Population	Absorption (%)	NoN (Nets)	VLS (ml)	SF (%)	TC mg/m²	SN (m²)	VolW (ml)	BW (kg)	Systemic dose (µg/kg bw/day)
Adults	1	5	36.7	10	150	15	4000	60	1.720
Children	1	5	17.6	10	150	15	4000	23.9	2.071

Dermal absorption = 1%
NoN = Number of nets washed per day (default = 5)
VLS = Volume liquid on skin = 36.7 ml/adult and 17.6 ml/child
SF = 100 – wash resistance index % = 10%
TC = Target concentration = 150 mg/m²
SN = Surface of net (15 m²)
VolW = Volume of washing water (4000 ml)
BW = 60 kg/adult; 23.9 kg/child
1000 = Conversion of mg to µg

From repeated (TWA) exposure:

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

Table 9. Deltamethrin: estimated systemic dose (TWA) from repeated dermal exposure due to washing treated nets

Population	Absorption (%)	NoW (washes)	NoN (Nets)	VLS (ml)	SF (%)	TC (mg/m²)	SN (m²)	VolW (ml)	BW (kg)	AT (days)	Systemic dose (µg/kg bw/day)
Adults	1	20/3 years	5	36.7	10	150	15	4000	60.0	365	0.031
Children	1	20/3 years	5	17.6	10	150	15	4000	23.9	365	0.038

Dermal absorption = 1%
NoW = Number of washes per net (20/3 years)
NoN = Number of nets washed per day (default = 5)
VLS = Volume liquid on skin = 36.7 ml/adult and 17.6 ml/child
SF = 100 – wash resistance index % = 10%
TC = Target concentration = 150 mg/m²
SN = Surface of net (15 m²)
VolW = Volume of washing water (4000 ml)
BW = 60 kg/adult; 23.9 kg/child
Averaging Time = 365 days
1000 = Conversion of mg to µg

2.2.2.2 Oral exposure during net washing

Estimated systemic dose from acute oral (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. Deltamethrin: estimated systemic dose from acute oral (maximum) exposure due to washing treated nets

Population	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	150	0.164	15	4000	60	6.303
Children	100	5	4.3	10	150	0.164	15	4000	23.9	8.298

NoN = Number of nets washed per day (default = 5)
VLH = Volume liquid on hand = 8.2 ml/adult and 4.3 ml/child
SF = 100 – wash resistance index % = 10%
TC = Target concentration in the net (150 mg/m²)
FHM = Fraction transfer hand to mouth (default = 0.164)
SN = Surface of net (15 m²)
Vol W = Volume of washing water (4000 ml)
BW = 60 kg/adult; 23.9 kg/child
1000 = Conversion of mg to µg

From repeated (TWA) exposure:

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

Table 11. Deltamethrin: estimated systemic dose from repeated oral exposure due to washing treated nets

Population	Absorption (%)	NoW (washes)	NoN (Nets)	VLH (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	150	0.164	15	4000	60.0	365	0.115
Children	100	20/3 years	5	4.3	10	150	0.164	15	4000	23.9	365	0.151

NoN = Number of nets washed per day (default = 5)
NoW = Number of washes (default = 20 washes/3 years)
VLH = Volume liquid on hand = 8.2 ml/adult and 4.3 ml/child
SF = 100 – wash resistance index % = 10%
TC = Target concentration in the net (150 mg/m²)
FHM = Fraction transfer hand to mouth (default = 0.164)
SN = Surface of net (15 m²)
Vol W = Volume of washing water (4000 ml)
BW = 60 kg/adult; 23.9 kg/child
AT = Averaging time = 365 days
1000 = Conversion of mg to µg

2.2.2.3 Total systemic exposure due to washing of treated nets

Table 12 depicts the estimated total systemic dose from washing of nets.

Table 12. Deltamethrin: estimated maximum 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	1.720	6.304	8.024
Children	2.071	8.298	10.369
Repeated exposure (TWA)			
Adults	0.031	0.115	0.146
Children	0.038	0.151	0.189

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:

$$\text{Systemic dose TWA} = \frac{\text{Absorption (100\%) x SolC} \times \text{dose (mother)} \times T_{½} \times \text{IR}}{\text{BW}} \text{ x } 1000$$

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

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

Mother dose Maximum = 0.039 + 15.274 µg/kg bw/day = 15.313 µg/kg bw/day

Mother dose (TWA) = 0.039 + 0.279 µg/kg bw/day = 0.318 µg/kg bw/day

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

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

Subpopulation	Absorption (%)	SolC	Dose (µg/kg/day)	$T_{1/2}$ (days)	IR (kg/day)	BW (kg)	Systemic dose (µg/kg bw/day)
Infants	100	0.361	15.313	2	0.66	8	0.912
Newborns	100	0.361	15.313	2	0.66	4.2	1.737

SolC = Solubility constant = 0.361
Dose = Daily dose to the mother = Sleeping under a net + Total from net washing
$T_{½}$ = First-order kinetics half-life of deltamethrin in days, 38.5 hours (NPIP, 2011); round off to 2 days
IR = Ingestion rate of milks (default = 0.66 kg/day)
BW = 8 kg/infant; 4.2 kg/newborn

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

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

Subpopulation	Absorption (%)	SolC	Dose (µg/kg/day)	$T_{1/2}$ (days)	IR (kg/day)	BW (kg)	Systemic dose (µg/kg bw/day)
Infants	100	0.361	0.318	2	0.66	8	0.02
Newborns	100	0.361	0.318	2	0.66	4.2	0.04

SolC = Solubility constant = 0.361
Dose = Daily dose to the mother = Sleeping under a net + Total from net washing (TWA)
$T_{½}$ = First-order kinetics half-life of deltamethrin in days, 38.5 hours (NPIP, 2011); round off to 2 days
IR = Ingestion rate of milks (default = 0.66 kg/day)
BW = 8 kg/infant; 4.2 kg/newborn

2.3 Risk characterization

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

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

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

$$\text{Ratio} = \frac{\text{Estimated maximal daily systemic dose}}{TSD_{AC}}$$

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 deltamethrin are presented in Tables 15–18.

2.3.1 Exposure estimates and risk ratios for sleeping under treated nets

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

Table 15. Exposure estimates and risk ratios for all populations sleeping under deltamethrin-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	0.061	N/A	N/A	0.061	10	0.01
Children	0.085	N/A	N/A	0.085	10	0.01
Toddlers	0.104	0.067	1.197	1.368	10	0.14
Infants	0.113	0.074	1.496	1.682	10	0.17

TSD = 10 µg/kg bw/day (JMPR, 2000)
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 deltamethrin-treated nets

Subpopulation	Dermal exposure (µg/kg bw/day)	Oral exposure (µg/kg bw/day)	Total exposure (µg/kg bw/day)	TSD_{AC} (µg/kg bw/day)	TSD (µg/kg bw/day)	Risk ratio
Acute exposure (maximum)						
Adults	1.720	6.304	8.024	15	N/A	0.54
Children	2.071	8.298	10.369	15	N/A	0.69
Repeated exposure (TWA)						
Adults	0.031	0.115	0.146	N/A	10	0.01
Children	0.038	0.151	0.189	N/A	10	0.02

TSD = 10 µg/kg bw/day (JMPR, 2000)
TSD_{AC} = aRfD = 15 µg/kg bw/day (USEPA, 2018)
Risk ratio = Total Exposure – Acute/TSD_{AC} 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 of treated nets are depicted in Table 17.

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

Subpopulation	Sleeping under nets (combined) (µg/kg bw/day)	Washing of nets (combined) (µg/kg bw/day)	Total exposure (µg/kg bw/day)	TSD_{AC} (µg/kg bw/day)	TSD (µg/kg bw/day)	Risk ratio
Acute exposure (maximum)						
Adults	0.061	8.024	8.085	15	N/A	0.54
Children	0.085	10.369	10.454	15	N/A	0.70
Repeated exposure (TWA)						
Adults	0.061	0.146	0.207	N/A	10	0.02
Children	0.085	0.189	0.274	N/A	10	0.03

TSD = 10 µg/kg bw/day (JMPR, 2000)
TSD_{AC} = aRfD = 15 µg/kg bw/day (USEPA, 2018)
Risk ratio = Total Exposure – Acute/TSD_{AC} 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 deltamethrin-treated nets and consuming breast milk

Subpopulation	Total exposure sleeping under nets (dermal + oral indirect + oral direct) (µg/kg bw/day)	Breast milk exposure (µg/kg bw/day)	Total exposure (µg/kg bw/day)	TSD_{AC} (µg/kg bw/day)	TSD (µg/kg bw/day)	Risk ratio
Acute exposure (maximum)						
Infants	1.682	0.912	2.594	15	N/A	0.17
Newborns	N/A	1.737	1.737	15	N/A	0.12
Repeated exposure (TWA)						
Infants	1.682	0.02	1.702	N/A	10	0.17
Newborns	N/A	0.04	0.04	N/A	10	0.01

TSD = 10 µg/kg bw/day (JMPR, 2000)
TSD_{AC} = aRfD = 15 µg/kg bw/day (USEPA, 2018)
Risk ratio = Total Exposure – Acute/TSD_{AC} or Total Exposure – TWA/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:

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

Table 19. Summary of risk characterization for deltamethrin as ITN (up to 3 g/kg or 120 mg/m^2)

Activity/population	Risk acceptable/not acceptable
Sleeping under net – repeated exposure	
Adults	Acceptable
Children	Acceptable
Toddlers	Acceptable
Infants	Acceptable
Washing of nets – acute exposure	
Adults	Acceptable
Children	Acceptable
Washing of nets – repeated exposure	
Adults	Acceptable
Children	Acceptable
Sleeping under and washing of nets – acute exposure	
Adults	Acceptable
Children	Acceptable
Sleeping under and washing of nets – repeated exposure	
Adults	Acceptable
Children	Acceptable
Exposure via breast milk from mothers exposed to deltamethrin	
Infants (acute and chronic)	Acceptable
Newborns (acute and chronic)	Acceptable
Sleeping under net and exposed via breast milk from mothers exposed to deltamethrin	
Infants (acute and chronic)	Acceptable
Newborns (acute and chronic)	Acceptable

3 Conclusion

The assessment of the available information on safety indicates that a deltamethrin-treated ITN, coated or incorporated, with a concentration of 120 mg a.i./m^2 (fabric weight 40 g/m^2 and 3 g a.i./kg net) and a wash resistance index of 90%, can be used safely for its intended use as a vector control product.

Appendix: Deltamethrin health hazard assessment

Product Name: DELTAMETHRIN
Empirical formula: C22H19Br2NO3
Chemical Abstract Number: 52918-63-5

1 Background information

Deltamethrin (1R,3R)-R-cyano (3-phenoxyphenyl) methyl 3-(2,2-dibromoethenyl)-2,2-dimethylcyclo-propanecarboxylate) is a broad-spectrum pyrethroid insecticide that is approved for direct application to a wide variety of food/feed crops, for use on stored grains, for use in food/feed handling establishments and for as a wide-area mosquito adulticide. Several formulations of deltamethrin are also approved for use in commercial and residential outdoor and indoor sites as well as in treated nets. Pyrethroids act through disruption of the voltage-gated sodium channels in the nervous system, resulting in neurotoxicity. The pyrethroids have historically been classified into two groups, Type I and Type II, based on chemical structure and toxicological effects. Deltamethrin contains an alpha-cyano moiety and is classified as a Type II pyrethroid. Clinical signs characteristic of Type II pyrethroids (such as increased salivation, altered mobility/gait and tremors) were observed throughout the health hazard database.

2 Relevant toxicity information on deltamethrin

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

Deltamethrin has either moderate or minimal toxicity (GHS Category 3 to 5; depending on vehicle used) via the oral route of exposure in acute oral studies, moderate acute toxicity (GHS Category 3) via the inhalation route of exposure and minimal toxicity (GHS Category 4) via the dermal route of exposure. It is minimally irritating to the eye (GHS Category 2B) and non-irritating to the skin (GHS Category: Not classified). It is not a skin sensitizer (GHS Category: Not classified). A summary of acute toxicity information is shown in Table A1.

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

Table A1. Summary of deltamethrin acute toxicity data

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

Source: FAO, 2016; EC, 2018; GHS, 2017; USEPA 2018

Table A2. Summary of deltamethrin repeated exposure and special studies

Deltamethrin – toxicity profile: sub-chronic, chronic and other special studies		
Study type	**Test material; purity; dose levels; design**	**Results**
Sub-chronic toxicity		
21-day dermal, rats	Technical (99.6%) dissolved in PEG 400; 0, 100, 300 and 1000 mg/kg bw/day	NOAEL dermal = 1000 mg/kg bw/day NOAEL systemic = 1000 mg/kg bw/day
13-week dietary, Crl:CD (SD) BR rats	Technical (98.9%) mixed in diet at 0, 30, 300, 3000 and 6000 ppm. Each group consisted of 20 rats/sex.	NOAEL = 300 ppm (corresponding to 24 and 30 mg/kg bw/day for males and females, respectively) LOAEL = 1000 ppm (supplemental study) corresponding to 72 and 84 mg/kg bw/day for males and females, respectively
13-week oral gavage, Sprague Dawley rats	Doses at 0, 0.1, 1.0, 2.5 and 10 mg/kg bw/d. Each group consisted of 20 rats/sex.	NOAEL = 1 mg/kg bw/day LOAEL = 2.5 mg/kg bw/day
12-week dietary, CD-1 mice	Technical (99.7%) mixed in diet at 0, 30, 300, 3000, and 6000 ppm. Each group consisted of 10 mice/sex.	NOAEL = 300 ppm (corresponding to 62 and 77 mg/kg bw/d for males and females, respectively). LOAEL = 3000 ppm (decreased food consumption and body weight.
13-week oral (capsule), beagle dogs	Technical dissolved in PEG 200. Gelatin capsule with 0, 0.1, 1.0, 2.5 and 10 mg/kg bw/day. Each group consisted of five dogs/sex except control and low dose groups had three dogs/sex.	A recovery group with two males and three females from the three highest dosage groups for an additional 20 weeks. Neurological examinations conducted at five and 12 weeks after dosing. NOAEL = 1 mg/kg bw/day LOAEL = 2.5 mg/kg bw/day (abnormal electroencephalogram-gram patterns) Unsteadiness, body tremors, jerking movements and neurological effects at 10 mg/kg bw/day.
13-week oral (capsule), beagle dogs	Technical (98.9%) given in capsule at 0, 2, 10, and 50 mg/kg bw/day. Control and highest dose groups had 6 dogs/sex. Other groups had only three dogs/sex.	NOAEL = 10 mg/kg bw/day LOAEL = 50 mg/kg bw/day (reduced body weight gains). No treatment-related findings at neurological examinations.
Reproductive and developmental toxicity		
Developmental toxicity, Sprague Dawley rats	Dose levels: 0, 0.1, 1 or 10 mg/kg bw/day given by gavage on gestational days (GD) 6–15.	Dev. Tox NOAEL = > 10 mg/kg bw/day (highest dose tested) Dev. Tox LOAEL = not established
Developmental toxicity, rats	Dose levels: 0, 1.25, 2.5 or 5.0 mg/kg bw/day dissolved in corn oil given by gavage on GD 7–20	Maternal NOAEL = 2.5 mg/kg bw/day Maternal LOAEL = 5 mg/kg bw/day (reduced BW) Dev. Tox NOAEL = 5 mg/kg bw/day (highest dose tested) Dev. Tox LOAEL = not established
Developmental toxicity, New Zealand rabbits	Dose levels: 0, 1, 4 or 16 mg/kg bw/day dissolved in sesame oil given by gavage on GD 6–19	Dev. Tox NOAEL = 16 mg/kg bw/day (highest dose tested) Dev. Tox LOAEL = not established
Developmental toxicity, KBL New Zealand rabbits	Dose levels: 0, 3, 10 or 32 mg/kg bw/day dissolved in corn oil given by gavage on GD 6–28 post-coitum	Maternal NOAEL = 10 mg/kg bw/day Maternal LOAEL = 32 mg/kg bw/day (decreased BW) Dev. Tox NOAEL = 32 mg/kg bw/day (highest dose tested) Dev. Tox LOAEL = not established
Study type	**Test material; purity; dose levels; design**	**Results**

Reproductive and developmental toxicity (continued)		
Post-natal developmental toxicity, Sprague Dawley rats	Dose levels: 0, 2.5 or 5.0 mg/kg bw/day dissolved in corn oil given by gavage	Test material given from gestation day 7 to lactation day 15. Dams were allowed to deliver and rear the young. Post-natal measurements on pups (body weight, eye-opening, startle reflex, air righting, etc.). No effects on parturition, litter size, pup viability and behavioral parameters.
Developmental neurotoxicity, Wistar rats	Dose levels: 0, 20, 80 or 200 ppm (corresponding to 0, 1.64, 6.78 or 16.1 mg/kg bw/day)	Test material given in the diet from GD 6 through to lactation day 21. Reproductive parameters were not affected. Maternal NOAEL = 80 ppm Maternal LOAEL = 200 ppm (reduced body weight gain) Dev Neurotox NOAEL = 200 ppm (16.1 mg/kg bw/day) Dev Neurotox LOAEL = not established
Multigeneration reproduction, Charles River rats	Dose levels: 0, 2, 20 or 50 mg/kg bw in the diet	3-generation reproduction study (3 litters/1st generation; 2 litters/2nd and 3rd generation). Parental systemic NOAEL = 20 mg/kg bw/day Parental systemic LOAEL = 50 mg/kg bw/day (decreased body weight and food consumption) Parental reproductive NOAEL = 50 mg/kg bw/day Offspring NOAEL = 50 mg/kg bw/day (highest dose tested)
2-generation reproduction, Charles River rats	Dose levels: 0, 5, 20, 80 or 320 ppm in diet	Parental systemic NOAEL = 80 ppm (4.2 mg/kg bw/day) Parental systemic LOAEL = 320 ppm (18 mg/kg bw/day; reduced body weight gain and feed consumption) Offspring NOAEL = 80 ppm (11 mg/kg bw/day) Offspring LOAEL = 320 ppm (reduced BW, increased mortality, clinical signs) Reproductive NOAEL = 320 ppm (18 mg/kg bw/day)
Neurotoxicity		
Acute neurotoxicity, Sprague Dawley rats	Dose level: 0, 5, 15 or 50 mg/kg bw/day dissolved in corn oil given by gavage as a single dose	Neuropathy NOAEL = 50 mg/kg bw/day (highest dose tested) Neuropathy LOAEL = not established
Acute neurotoxicity, Long Evans rats (Non-guideline but acceptable study; Wolansky et al., 2006)	Dose level: single oral dose of deltamethrin in corn oil at 0, 0.03, 0.1, 0.3, 1, 3, and 10 mg/kg – Groups of eight rats/dose	Motor activity measured two hours after dosing BMD = 2.48 BMDL = 1.49 Results used to derive PODs
13-week neurotoxicity study, rats	Dose levels: 0, 50, 200 or 800 ppm in the diet (corresponding to 0, 4, 16, and 58 mg/kg bw/day)	Systemic NOAEL = 50 ppm Systemic LOAEL = 200 ppm (hypersensitivity to noise) Neuropathy NOAEL = 800 ppm (54-58 mg/kg bw/day) Neuropathy LOAEL = not established

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

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

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