World Health Organization

WHO Prequalification Programme / Vector Control Product Assessment

WHO Public Assessment Report: WHOPAR Part 4

Sylando 240 SC (BASF Agro B.V. Arnhem (NL) Freienbach Branch)

P-00136

Safety Assessment

Contents

1 Risk assessment summary

1.1 Introduction

The applicant, BASF Agro B.V. Arnhem (NL) Freienbach Branch, (Switzerland), submitted a product dossier to the WHO PQT/VCP containing supporting data for the proposed product Sylando 240 SC for use as an Indoor Residual Spray (IRS). Sylando 240 SC is intended to be used for malaria control. In response to the identification of a need to review and update the hazard assessment for chlorfenapyr, the WHO PQT/VCP has assessed the IRS product Sylando 240 SC in the present document.

This human health risk assessment has been completed based on the "*Generic Risk Assessment Model for Indoor Residual Spraying of Insecticides, 2nd Edition*" (GRAM) (WHO, 2018).

1.2 Product identification

Applicant:	BASF Agro B.V. Arnhem (NL) Freienbach Branch (Switzerland)
Product name:	Sylando 240 SC
Active ingredient:	Chlorfenapyr (240 mg/ml)
CAS no.:	122453-73-0
Product type:	Indoor Residual Spray
Formulation type:	Suspension Concentrate (SC)
Application rate:	250 mg a.i./m^2
Spray concentration:	6.25 - 12.48 mg a.i./mL*
Volume applied:	20 - 40 ml/m^2 spraying rate**

*Maximum labelled application rate and spray concentrations used as representative values to assess worst-case exposure scenarios in risk assessment
** Volume applied depended upon surface type, therefore, dilution is adjusted accordingly

1.3 Active ingredient statement

Chlorfenapyr (CAS No. 122453-73-0) is an N-substituted halogenated pyrrole. It is a pro-insecticide that is converted to its active metabolite by P450 monooxygenases mechanisms.

1.4 Discussion and conclusion

In this human health risk assessment, the estimated risk ratios for Sylando 240 SC are based on the target application rate of chlorfenapyr (250 mg a.i./m^2).

The assessment supports the following conclusions:

- The existing toxicology database for Sylando 240 SC and chlorfenapyr technical is adequate for risk assessment and supports the labelled use of Sylando 240 SC up to a target application rate of 250 mg a.i./m^2.
- The use of Sylando 240 SC formulated as an aqueous suspension and diluted to 6.25 mg ai/mL (porous surfaces) and 12.48 mg ai/mL (non-porous surfaces) for malaria control as an IRS result in risk ratios of ≤1, hence, do not exceed the level of concern for all operator and residential exposure scenarios. Given risk ratios did not exceed 1 with a spray concentration of 12.48 mg ai/mL (maximum application rate for non-porous surfaces), further assessment at the lower rate for porous surfaces (6.25 mg ai/mL) were not performed.
- The safety assessment of the submitted information supports prequalification of Sylando 240 SC.

2 Human health risk assessment

This human health risk assessment for Sylando 240 SC is conducted according to the "*A Generic Risk Assessment Model for Indoor Residual Spraying of Insecticides, 2nd edition"* (GRAM) (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 occur, and the dose/exposure levels below which no adverse effects are observed. Authoritative evaluations are used as starting points for the risk assessment of insecticides. Examples of authoritative evaluations are: Joint Meeting on Pesticide Residues (JMPR), International Programme on Chemical Safety (IPCS), International Agency for Research and Cancer (IARC), United States Environmental Protection Agency (USEPA), European Food Safety Authority (EFSA).
Exposure assessment 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-end point estimates of the default distributions are used as defaults. No account is taken of intended misuse. All relevant routes of exposure are covered.
In **risk characterization,** estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situation.

2.1 Hazard assessment

2.1.1 Acute Product Toxicity Data

BASF Agro B.V. Arnhem (NL) Freienbach Branch, Switzerland, submitted acute toxicity studies conducted with the formulated product AC 303,630 2SC (22.09% w/w, Chlorfenapyr). The content of Chlorfenapyr (22.09%) in this product is suitably comparable to the Chlorfenapyr content (21.4% w/w) in the Sylando 240 SC formulation. Therefore, these studies were deemed relevant for determining the acute toxicity of Sylando 240 SC formulation). All acute studies were conducted at Toxicology Department, American Cyanamid Company, New Jersey, U.S.A. according to the US FIFRA guidelines and followed all GLP regulations. The results are summarized as below:

Table 1. Acute toxicity of AC 303, 630 (Similar product to Sylando 240 SC)

Route of exposure	Toxicity	GHS category	Reference
Oral LD_{50} – Rat	LD_{50} = 560 mg/kg (males) LD_{50} = 567 mg/kg (females)	4	Bradley, 1994a
Dermal LD_{50} – Rat and Rabbit, respectively	LD_{50} = >2000 mg/kg	5	Bradley, 1994b
Inhalation LC_{50} – Rat	LC_{50} = 0.571 mg/L (males) LC_{50} = > 2.43 mg/L (females)	3	Hoffman, 1998
Primary Dermal Irritation – Rabbit	Non-irritant	Not classified	Boczon, 1994b
Primary Eye Irritation – Rabbit	Mild irritant	2	Boczon, 1994a
Skin Sensitization – Guinea pig	Non-sensitizer	Not applicable	Blanset, 1996

2.1.2 Chlorfenapyr Toxicity Data

Sylando 240 SC is composed of the active ingredient, chlorfenapyr. This risk assessment relies heavily on toxicity studies conducted on the AI itself as the AI is the biologically active substance that produces a target pesticidal effect but can also have the potential to product toxic biological effects.

Chlorfenapyr is an active ingredient in the pyrroles chemical class and toxicology studies have been evaluated by the USEPA (2020), JMPR (2012), and EFSA (2005, 2012). Furthermore, human health hazard assessments and summary reports were completed by these regulatory bodies. The toxicity profile of chlorfenapyr is presented in Appendix A and the complete Hazard Assessment of chlorfenapyr is presented in Appendix B.

Chlorfenapyr targets the central nervous system (CNS), inducing neurophysiological changes following subchronic and chronic dietary administration to mice and rats. Rats exhibited neurobehavioral changes on the day of dosing and decreased motor activity in adults as well as in offspring following repeated exposure. Several rat studies also noted effects in the liver (increased organ weights and tumours) at doses similar to or above those where CNS effects were seen. There is no evidence for developmental, reproductive, or immunogenic or genotoxic potential. USEPA has classified Chlorfenapyr as showing "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" (USEPA, 2020). **The toxicity profile of chlorfenapyr is presented in Appendix 1**.

Points of Departures (PODs) based on the most sensitive endpoints in the toxicity database are available for chlorfenapyr. The PODs and toxicological endpoints of concern selected for risk assessment are considered protective of any potential adverse effects, including neuro-, developmental, reproductive, immune, and systemic toxicity as well as carcinogenicity for all populations including infants and children.

2.1.2.2 Oral absorption

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

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

In another study, groups of four male and four female Sprague-Dawley rats were treated as follows: low dose: 1.85 MBq/2 mg at a dosing volume of 4 ml/kg bw, single oral administration; high dose: 1.85 MBq/20 mg at a dosing volume of 4 ml/kg bw, single oral administration. The radiolabeled test substance was administered orally by gavage as an aqueous solution in 1% sodium carboxymethylcellulose plus 1%

Tween 80. Urine was sampled at 12, 24, 48- and 72-hours post-dosing. Feces were collected at 24, 48- and 72-hours post-dosing. In bile duct–cannulated animals, bile was collected at 3, 6, 12 and 24 hours; urine was collected at 6, 12 and 24 hours; and feces was collected at 24 hours post-dosing.

Almost all ^{14}C detected in feces was unchanged chlorfenapyr. There was no unchanged chlorfenapyr in bile. This finding indicated that the unchanged chlorfenapyr in the feces did not come from the bile, but consisted of chlorfenapyr that was not absorbed from the gastrointestinal tract and was directly excreted into the feces. It follows, therefore, that the per cent absorption of chlorfenapyr from the gastrointestinal tract can be obtained by subtracting the percentage of fecal excretion of chlorfenapyr from the administered dose: male rats (2 mg/kg bw): 100% − 17.0% = 83.0% ; female rats (2 mg/kg bw): 100% − 23.1% = 76.9%; male rats (20 mg/kg bw): 100% − 35.2% = 64.8% ; and female rats (20 mg/kg bw): 100% − 33.0% = 67.0% . In summary, the per cent absorption of chlorfenapyr from the gastrointestinal tract was approximately 80% and 65% in the 2 mg/kg bw and 20 mg/kg bw groups, respectively, with an apparent decrease in absorption with increasing dose. Chlorfenapyr was absorbed unchanged; there was no evidence that degradation occurred in the digestive tract.

Based on these data, the oral absorption of chlorfenapyr was determined to be 65% (JMPR, 2012; BASF, 2018).

A goat metabolism study was conducted using 14C labeled chlorfenapyr. The study was conducted at a low dose and high dose using chlorfenapyr with a 14C label in either the phenyl ring or pyrrole ring. The goats were dosed for 7 consecutive days and residues in milk were measured each day prior to sacrifice. The total radioactive residues in the milk are highest in the low dose for each label. The 14C residues in the phenyl labeled study were 4.3% of total applied radioactivity and the 14C residues in the pyrrole labeled study were 4.4% of the total applied radioactivity. A value of 4.4% was used in the risk assessment for the fraction of the dose excreted in milk (Fr_{MILK}) to calculate the breast milk exposure for newborn and infant. The 4.4% represents a worst-case value because this is total radioactive residues which would include all metabolites and chlorfenapyr (BASF, 2018).

2.1.2.3 Dermal absorption

In the *in vivo* study, rats received dermal application of a formulation concentrate (BAS 306 02) at 2.4 mg/cm^2 and 0.0217 mg/cm^2. At 8, 24, and 120 hours, dermal absorption (tissues, excreta, surrounding skin, and application site) for the 2.4 mg/cm2 dose was 6.4%, 3.9%, and 3.6%, respectively. At 8, 24, and 120 hours, dermal absorption (tissues, excreta, surrounding skin, and application site) for the 0.0217 mg/cm2 dose was 13.1%, 10.7%, and 15.1%, respectively. A dermal absorption factor (Abs-D) of 13% after 8 hours of exposure was calculated at the lowest dose tested (approximately 25 µg/cm2) based on excreta, cage wash, blood, plasma, carcass, application site, and the surrounding skin (USEPA, 2020).

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

Abs-D = rat *in vivo* (13%) x human *in vitro* (1.4%) = 1.2%

rat *in vitro* (15.8%)

Based on these results, a dermal absorption value of 1.2% is used in this risk assessment for the formulation concentrate.

Dermal absorption was determined using ^{14}C-BAS 306 I in BAS 306 02 I formulation. The BAS 306 02 I formulation is the same as Sylando 240 SC. The study was assessed by a single topical application at target doses of 250 ug/cm2, 100 ug/cm2, and 25 ug/cm2 to split thickness human skin preparations. The mean absorbed doses were 0.37, 0.11, and 1.2% of the dose for skin treated with the high, mid, and low dose, respectively.

A dermal absorption factor of 0.4% was selected for risk assessment of concentrated product (BASF, 2018).

2.1.2.4 Inhalation absorption

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

2.1.3 Points of departure

Points of departure (PODs) (no observed adverse effect level [NOAEL]; Benchmark dose) are determined from the toxicological database based on the most sensitive endpoints. The PODs and toxicological endpoints of concern selected for risk assessment are considered protective of any potential adverse effects, including neuro-, developmental, reproductive, immune, and systemic toxicity as well as carcinogenicity for all populations including infants and children. According to the risk assessment model, authoritative sources may be used as starting points for the risk assessment of insecticides used in long-lasting mosquito nets.

2.1.3.1 Acute oral exposure

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

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

Acute oral POD = 5 mg/kg bw/day

2.1.3.2 Chronic oral exposure

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

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

Chronic oral POD = 5 mg/kg bw/day

Although the POD established by the USEPA is slightly higher than that established by JMPR, the higher POD is chosen for both acute and chronic risk assessments due to the toxicological significance of the adverse effects observed in the most sensitive population subgroup (pups) in a study that examined developmental neurobehavior and neuropathology. Consequently, this endpoint is the most appropriate to assess health risk to infants and children in the current exposure scenarios (e.g., sleeping under and washing treated nets). Furthermore, the chosen POD will adequately be protective of the adverse effects observed in other studies in the database.

2.1.4 Reference doses (RfD)

Once PODs are developed, safety factors and uncertainty factors (UF) are used in conjunction with the PODs to derive a safe exposure level, generally referred to as reference dose (RfD), acceptable daily intake (ADI) or a safe margin of exposure (MOE).

2.1.4.1 Acute reference dose (aRfD)

JMPR established an **aRfD of 0.03 mg/kg bw** based on a POD of 3 mg/kg/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities as shown below in Table 2.

Table 2. Chlorfenapyr: Acute reference dose (aRfD) established by JMPR

POD (mg/kg/day)	Uncertainty factor	aRfD (mg/kg)	Toxicological endpoint of concern	Study selected	Reference
3	100	0.03	Decreased spontaneous motor activity at 10 mg/kg.	Pharmacology - Mouse	JMPR, 2012

USEPA established an **aRfD of 0.05 mg/kg bw** based on a POD of 5 mg/kg/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities as shown below in Table 3.

Table 3. Chlorfenapyr: Acute reference dose (aRfD) established by USEPA

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

2.1.4.2 Chronic reference dose (cRfD)

USEPA established an **cRfD of 0.05 mg/kg bw** based on a POD of 5 mg/kg/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities as shown below in Table 4.

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

2.1.4.3 Acceptable daily intake (ADI)

JMPR established an ADI of 0.03 mg/kg bw/day based on a NOAEL of 2.8 mg/kg bw/day and an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variabilities as shown in Table 5.

Table 5. Chlorfenapyr: Acceptable daily dose (ADI) established by JMPR					
POD (mg/kg/day)	**Uncertainty factor**	**ADI (mg/kg/day)**	**Toxicological endpoint of concern**	**Study selected**	**Reference**
2.8	100	0.03	Decreases in body weight gain and vacuolation of the white matter of the brain	Carcinogenicity - Mouse	JMPR, 2012

2.1.5 Selection of tolerable systemic dose

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

2.2 Exposure assessment

The second step in performing a risk assessment is to estimate exposure to the insecticide in the various groups of people potentially at risk. Exposure must take various parameters into consideration, including the route of exposure, the actual amounts of material involved, the duration of exposure in terms of both daily and annual exposure and seasonality and whether this exposure is intermittent or continuous.

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) is assessed according to the WHO-GRAM (second edition): "*Generic Risk Assessment Model for Indoor Residual Spraying of Insecticides" 2nd Edition (2018)*" and chemical-specific data. Exposure assessment includes operators mixing and loading, application of the insecticide product by spraying and washing and maintenance of the equipment, dermal exposure through contaminated surfaces, ingestion exposure from foodstuffs on surfaces, and exposure via breast milk. In the total exposure assessments, all relevant routes and different scenarios were summed up to

derive the total systemic dose. Exposure is also assessed in a "lax standard scenario" (Appendix C), which increases the anticipated exposure based on the removal of a safety factor associated with the use of personal protective equipment. This is presented for informational purposes based on its inclusion in the GRAM. WHO does not recommend the application of IRS without PPE.

The Sylando 240 SC nominal concentration (240mg ai/mL 300 g/L) and the application rate (250 mg a.i./m^2) were selected as input values for assessing the IRS use pattern based on the highest labelled application rate.

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

Abs-D = Dermal absorption (0.4% and 1.2%, data derived)
Abs-P = Respiratory absorption (default = 100%)
Abs-O = Oral absorption (65%, data derived)
AT = Average time (default = 365 days)
AV= Average proportion of spray residue on the wall during 6 months of first-order kinetics' decay with a half-time of 60 d (0.42)
BV = Breathing volume = 1.25 m^3/hour
BW = Body weight (default = 60 kg/adult, 23.9 kg/children, 10 kg/toddlers)
C_{spray}= Concentration of the a.i in the spray in mg/ml (12.48 mg a.i./ml)
CF= Concentration of formulation mg/ml (product label): 240 mg a.i./ml
$Dose_M$=Daily dose to the mother (µg/kg bw/day): est. dose mg/kg bw x body weight of the mother kg
ED = Exposure duration = 4 hours spraying per 8 hours working day
EF= Exposure frequency (6 days/week, 6 weeks per treatment round, 2 rounds/year=72 days/year)
ESA = Exposed skin areas (default= 0.308 m^2/adults; 0.153 m^2/child; 0.133 m^2 /toddlers and 0.394 m^2/infants).
F_{HM} = fraction of hand area mouthed (default = 0.164 – 75th percentile)
F_{EXS} = Fraction extracted in saliva (default = 0.57)
$Fr_{Mother's\ Dose}$ = Fraction of mother's do se excreted in breast milk (default =3.98)
Fr_{MILK} = Fraction of the dose excreted in milk in an experimental animal (4.4%, data derived)
ML= Amount of insecticide (a.i.) handled per day; default 12 loads per day, 10 L tank, concentration of the a.i. in the spray from the product label and dilution for spraying
NOD= Number of mixing operations per day (default=12)
PPE= Personal protective equipment.
Guideline scenario = 0.1 (90% protection); Lax standard scenario = 1 (no protection)
RPE = Respiratory protection = 0.1 for guideline scenario and 1.0 for lax standard scenario
SAF = Surface area of food in contact with the shelf (0.0169, 0.0126, 0.0124 and 0.0105 m^2 for adults, children, toddlers, and infants, respectively). Half of food items are in contact with contaminated surfaces
$SysD_{TWA}$= TWA systemic dose (µg/kg bw/day)
$SysD_{MAX}$ = Maximal systemic dose (µg/kg bw/day)
TC_{WALL}= Target amount of the a.i. on the wall, 250 mg ai/m^2
Transl= Fraction translodged onto skin; default 8% of the amount on the surface
UE_{LIQ} = Unit exposure for a liquid formulation (no gloves) mL/operation, 0.01 mL/operation
VS_{dermal}= volume of spray on hands = 8.2 ml

2.2.1 Occupational exposure

Exposure to operators occurs during mixing and loading and application of the insecticide product by spraying and washing and maintenance of the equipment. Operator exposure assessments for these scenarios are presented below.

2.2.1.1 Operator exposure during mixing and loading of SYLANDO 240SC

Inhalation Exposure

Sylando 240 SC is a liquid suspension concentrate formulation, so inhalation exposure is insignificant and not included.

Dermal exposure

The estimated time weighted average (TWA) systemic dose from chlorfenapyr to operators due to potential dermal exposure from mixing and loading is calculated as follows:

$$SysD_{TWA} = \frac{UE_{LIQ} \times PPE \times CF \times NOD \times Abs\text{-}D \times EF \times 1000}{BW \times AT}$$

Table 6. Estimated long term systemic dose (TWA) to operator from dermal exposure during mixing and loading

UE_{LIQ} (mL)	PPE	CF (mg/mL)	NOD	Abs-D (%)	EF (days)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
0.01	0.1	240	12	0.4	72	60.0	365	0.04

The estimated maximal daily systemic dose to operators due to potential dermal exposure from mixing and loading is calculated as follows:

$$SysD_{MAX} = \frac{UE_{LIQ} \times PPE \times CF \times NOD \times Abs\text{-}D \times 1000}{BW}$$

Table 7. Estimated maximal daily systemic dose to operator from dermal exposure during mixing and loading

UE_{LIQ} (mL)	PPE	CF (mg/mL)	NOD	Abs-D (%)	BW (kg)	Systemic dose (µg/kg/day)
0.01	0.1	240	12	0.4	60.0	0.19

2.2.1.2 Operator exposure during application, washing, and maintenance

Dermal exposure

The estimated TWA systemic dose of chlorfenapyr to operators due to potential dermal exposure during application, washing and maintenance is calculated as follows:

$$\text{Systemic TWA dose} = \frac{VS_{dermal} \times C_{spray} \times PPE \times EF \times Abs\text{-}D \times 1000}{BW \times AT}$$

Table 8. Estimated long-term (TWA) systemic dose to operator from dermal exposure during application, washing, and maintenance							
VS $_{dermal}$ (ml)	C $_{Spray}$ (mg/ml)	PPE	EF (days)	Abs-D (%)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
8.2	12.48	0.1	72	1.2	60	365	0.40

The estimated maximal systemic dose of chlorfenapyr to operators due to potential dermal exposure during application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{VS_{dermal} \times C_{spray} \times PPE \times Abs_D \times 1000}{BW}$$

Table 9. Estimated maximal systemic dose to operator from dermal exposure during application, washing, and maintenance					
VS $_{dermal}$ (ml)	C$_{Spray}$ (mg/ml)	PPE	Abs-D (%)	BW (kg)	Systemic dose (µg/kg/day)
8.2	12.48	0.1	1.2	60	2.05

Inhalation exposure

The estimated TWA systemic dose of chlorfenapyr to operators due to potential inhalation exposure during application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{10^{-3} \times TC_{WALL} \times RPE \times BV \times ED \times Abs\text{-}P \times EF \times 1000}{BW \times AT}$$

Table 10. Estimated long-term (TWA) systemic dose to operator from inhalation exposure during application, washing and maintenance								
TC_{WALL} (mg/m^2)	RPE	BV (m^3/hr)	ED (hours)	Abs-P (%)	EF (days)	BW (kg)	AT (days)	Systemic dose (µg/kg/day)
Guideline scenario								
250	0.1	1.25	4	100	72	60	365	0.41

The estimated maximal systemic dose of chlorfenapyr to operators due to potential inhalation exposure during application, washing and maintenance is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{10^{-3} \times TC_{WALL} \times RPE \times BV \times ED \times Abs\text{-}P \times 1000}{BW}$$

Table 11. Estimated maximal systemic dose to operator from inhalation exposure during application, washing and maintenance						
TC_{WALL} (mg/m2)	RPE	BV (m^3/hr)	ED (hours)	Abs-P (%)	BW (kg)	Systemic dose (µg/kg/day)
Guideline scenario						
250	0.1	1.25	4	100	60	2.08

2.2.1.3 Total operator exposure

Estimated total systemic exposure from dermal exposure from mixing and loading and from dermal and inhalation exposure from application, washing and maintenance.

Table 12. Estimated total operator exposure from dermal and inhalation exposure

Scenario	Dermal exposure		Inhalation exposure	Estimated systemic dose (µg/kg/day)
	Mixing/Loading (µg/kg/day)	Application/Washing/ Maintenance (µg/kg/day)	Application/Washing/ Maintenance (µg/kg/day)	
Estimated TWA				
Guideline	0.04	0.40	0.41	0.85
Estimated maximal				
Guideline	0.19	2.05	2.08	4.32

2.2.2 Residential exposure

Residential exposure is presumed to be the result of dermal exposure to directly sprayed walls and sometimes from furniture, shelves and floors sprayed inadvertently. Oral exposure to toddlers can occur from ingestion of contaminated foodstuff (via contact with contaminated shelves) and house dust (insecticides loosen from walls) as well as from hand-to-mouth activity (put contaminated objects in their mouth). Operator exposure assessments for these scenarios are presented below.

2.2.2.1 Dermal exposure due to touching of contaminated surfaces

The estimated TWA dermal exposure due to touching of contaminated surfaces is calculated as follows:

$$\text{Sys-D}_{TWA} = \frac{0.15 \times TC_{WALL} \times AV \times Transl \times ESA \times Abs\text{-}D \times 1000}{BW}$$

The estimated maximal dermal exposure due to touching of contaminated surfaces is calculated as follows:

$$\text{Sys-D}_{MAX} = \frac{0.15 \times TC_{WALL} \times Transl \times ESA \times Abs\text{-}D \times 1000}{BW}$$

Table 13. Estimated systemic dose from dermal exposure due to touching of contaminated surfaces

Population	TC_{WALL} (mg/m²)	Transl (%)	AV	ESA (m²)	Dermal absorption (%)	BW (kg)	Systemic dose (µg /kg/day)
TWA scenario							
Adults	250	8	0.42	0.308	1.2	60	0.08
Children	250	8	0.42	0.153	1.2	23.9	0.10
Toddlers	250	8	0.42	0.153	1.2	10	0.20
Infant	250	8	0.42	0.394	1.2	8	0.75
Maximal scenario							
Adults	250	8	N/A	0.133	1.2	60	0.18
Children	250	8	N/A	0.153	1.2	23.9	0.23
Toddlers	250	8	N/A	0.308	1.2	10	0.48
Infant	250	8	N/A	0.394	1.2	8	1.77

2.2.2.2 Ingestion exposure from contaminated foodstuffs

The estimated TWA exposure due to ingestion of contaminated foodstuffs from surfaces is calculated as follows:

$$\text{Sys-}D_{TWA} = \frac{0.30 \times 0.5 \times AV \times TC_{WALL} \times Transl \times SAF \times Abs\text{-}O \times 1000}{BW}$$

The estimated maximal exposure due to ingestion of contaminated foodstuffs from surfaces is calculated as follows:

$$\text{Sys-}D_{MAX} = \frac{0.30 \times 0.5 \times TC_{WALL} \times Transl \times SAF \times Abs\text{-}O \times 1000}{BW}$$

Table 14. Estimated ingestion exposure of contaminated foodstuffs from surfaces

Population	TC_{WALL} (mg/m²)	AV	Transl (%)	SAF (m²)	Abs-O (%)	BW (kg)	Systemic dose (µg /kg/day)
TWA scenario							
Adults	250	0.42	8	0.0169	100	60	0.23
Children	250	0.42	8	0.0126	100	23.9	0.43
Toddlers	250	0.42	8	0.0124	100	10	1.02
Infants	250	0.42	8	0.0105	100	8	1.07
Maximal scenario							
Adults	250	N/A	8	0.0169	100	60	0.55
Children	250	N/A	8	0.0126	100	23.9	1.03
Toddlers	250	N/A	8	0.0124	100	10	2.42
Infants	250	N/A	8	0.0105	100	8	2.56

2.2.2.3 Ingestion exposure of toddlers via hand-to-mouth behaviour

The estimated TWA ingestion exposure of toddlers via hand to mouth behaviour is calculated as follows:

$$\text{SysD-}_{TWA} = \frac{0.15 \times AV \times TC_{WALL} \times Transl \times ESA \times F_{HM} \times F_{EXS} \times Abs\text{-}O \times 1000}{BW}$$

The estimated maximal ingestion exposure of toddlers via hand to mouth behaviour is calculated as follows:

$$SysD\text{-}_{MAX} = \frac{0.15 \times TC_{WALL} \times Transl \times ESA \times F_{HM} \times F_{EXS} \times Abs\text{-}O \times 1000}{BW}$$

Table 15. Estimated ingestion exposure of toddlers via hand-to-mouth behaviour

Conc. on surface to wall target conc.	TC_{WALL} (mg/m^2)	AV	Transl (%)	ESA (m^2)	F_{HM}	F_{EXS}	Abs-O (%)	BW	Systemic dose (µg /kg/day)
TWA scenario									
0.15	250	0.42	8	0.023	0.164	0.57	65	10	0.18
Maximal scenario									
0.15	250	N/A	8	0.023	0.164	0.57	65	10	0.42

2.2.2.4 Total residential exposure

Table 16. Estimated total residential systemic dose from dermal, ingestion, and hand-to-mouth exposure

Population	Dermal exposure (Contaminated Surfaces) (µg/kg/day)	Ingestion contaminated foods (from surfaces) (µg/kg/day)	Hand to mouth (µg/kg/day)	Estimated systemic dose (ug/kg bw/day)
TWA scenario				
Adults	0.08	0.23	-	0.31
Children	0.10	0.43	-	0.53
Toddlers	0.20	1.02	0.18	1.40
Infants	0.75	1.07	-	1.82
Maximal scenario				
Adults	0.18	0.55	-	0.73
Children	0.23	1.03	-	1.26
Toddlers	0.48	2.42	0.42	3.32
Infants	1.77	2.56	-	4.33

2.2.3 Combined exposure for resident operator

This represents the worst-case scenario for a resident who also works as operator.

Combined Exposure = Total Operator Exposure + Total Residential exposure

Table 17. Combined exposure for resident operator

Population	Total operator exposure (µg/kg/day)	Total residential exposure (µg/kg/day)	Total combined exposure (µg/kg/day)
TWA exposure – guideline			
Adult	0.85	0.31	1.16
Maximal daily dose - guideline			
Adult	4.32	0.78	5.10

2.2.4 Exposure via breast milk

Newborns might be exposed to chlorfenapyr through breast milk of lactating mother. The estimated systemic dose to the newborn is calculated using the maximum dose of 0.00853 mg ai/kg bw/per day. This dose represents the highest aggregate exposure value where residents also work as spray operators. WHO does not approve nor recognize a scenario where a nursing or lactating mother is working as an operator. The values provided demonstrate worst-case exposure scenario.

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

$$\text{Systemic dose TWA} = \frac{3.98 \times Fr_{MILK} \times Abs\text{-}O \times \text{Dose}_{M}}{BW}$$

Table 18. Estimated systemic dose from exposure to breast milk (residential exposure)

Population	$Fr_{Mother's\ Dose}$	Fr_{MILK}	Abs-O (%)	Dose $_M$ (µg /bw)	BW (kg)	Systemic dose (µg/kg/day))
TWA – Guideline Scenario						
Newborns	3.98	4.4	65	8.53x60	4.2	13.86
Infant	3.98	4.4	65	8.53x60	8	7.28

2.3 Risk characterization

The purpose of risk characterization is to examine the probability of adverse effects occurring 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 a.i.s (WHO, 2018).

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

When the ratios are less than 1, the health risk is deemed acceptable. Ratios greater than 1 may indicate possible health risks, in which case steps may be taken to reduce the risk, such as changing the recommended operational conditions or the amount of a.i. 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).

Table 19. Risk characterization for all populations and exposure scenarios

Population	Operator exposure (dermal and inhalation) (µg/kg bw/day)	TSD (µg/kg bw/day)	Risk ratio
Total operator exposure – TWA scenario			
Adult	0.85	50	0.017
Total operator exposure – maximal exposure			
Adult	4.32	50	0.0864
Total operator/resident exposure – TWA scenario			
Adult	1.16	50	0.0232
Total oprator/resident exposure – maximal scenario			
Adult	5.10	50	0.102
Population	**Residential exposure (dermal and foodstuffs) (µg/kg bw/day)**	**TSD (µg/kg bw/day)**	**Risk ratio**
Total exposure – TWA scenario			
Adult	0.31	50	0.0062
Children	0.53	50	0.0106
Toddler	1.40	50	0.0278
Infant	1.82	50	0.0364
Total exposure – maximal scenario			
Adult	0.73	50	0.0146
Children	1.26	50	0.0252
Toddler	3.32	50	0.0664
Infant	4.33	50	0.0866
TWA Total exposure – breast milk - residential			
Newborn	13.86	50	0.2772
Infant	7.28	50	0.1456

For operators (mixing/loading/applying/maintenance), the risk ratios are all below 1.

For adult resident scenario (dermal exposure through surfaces and ingestion of foodstuffs), the risk ratios are below 1 for all populations of concern.

For resident operator, the risk ratios are all below 1.

For the potential exposure via breast milk or mother as a resident operator (WHO does not approve nor recognize a scenario where a nursing or lactating mother is working as an operator, these figures are provided to demonstrate a worst-case exposure and risk scenario), the risk ratio is below 1.

2.4 Conclusions

PQT-VCP concludes that the human health risk of Sylando 240 SC (240 mg a.i./mL) for malaria control at 250 mg/m^2 chlorfenapyr as an IRS insecticide does not present any unacceptable risk for operators, residents, residents working as operators, or to children, toddlers, infants, or newborns exposed through breastmilk.

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4 Appendices

Appendix A. Toxicity Profile: Chlorfenapyr Technical

A.1. Acute toxicity of chlorfenapyr technical

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

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

Chlorfenapyr – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Dose levels; design**	**Results**
Subchronic- toxicity		
90-Day Oral – Rat	0, 150, 300, 600, 900, 1200 Ppm. Equivalent to 0, 11.7, 24.1, 48.4, 72.5, 94.5 mg/kg/day	NOAEL =24.1 mg/kg/day. LOAEL = 48.4 mg/kg/day based on spongiform myelopathy in the brain and spinal cord of male rats, and increased liver weight in males and females, increased absolute liver weight in females and decreased hemoglobin in females.
90-Day Oral – Mouse	0, 40, 80, 160, 320 ppm Equivalent to 0, 7.1, 14.8, 27.6, 62.6 mg/kg/day in males and 0, 9.2, 19.3, 40, 78 mg/kg/day in females.	NOAEL = 14.8/19.3 mg/kg/day (M/F). LOAEL = 27.6/40.0 mg/kg/day (M/F) based on increased spleen weights (absolute and relative). Spongiform encephalopathy and significant changes in blood chemistry observed in both sexes at the HDT.
90-Day Oral – Dog	0, 60, 120, ~247 ppm Equivalent to 0, 2.1, 3.9, 6.7 mg/kg/day in males and 0, 2.2, 4.5, 6.8 mg/kg/day in females.	NOAEL = 6.7/6.8 mg/kg/day (M/F). LOAEL not established.

Table A2. Subchronic, chronic, carcinogenicity, and other toxicity studies with Chlorfenapyr		
Chlorfenapyr – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Dose levels; design**	**Results**
28-Day Dermal Toxicity (rat)	0, 100, 300, 1000 ppm. Equivalent to 0, 72.1, 205.5, 835 mg/kg/day	NOAEL = 205.5 mg/kg/day. LOAEL = 835 mg/kg/day based on clinical signs consisting of slight to moderate urine smearing of the anogenital region for several days in female rats and liver weight increases (absolute and relative) in both sexes.
90-day inhalation – Rat	0, 5, 20, 40, 80 mg/m^3	NOAEL = 20 mg/m^3. LOAEL = 40 mg/m^3 based on visually accelerated respiration, increased white blood cell and lymphocyte counts, and changes in clinical parameters in both sexes. Mortality observed in males at 80 mg/m^3.
Developmental and reproductive toxicity		
Developmental – Rat	0, 25, 75, 225 mg/kg/day	Maternal NOAEL = 225 mg/kg/day. Maternal LOAEL not established. Developmental NOAEL = 225 mg/kg/day. Developmental LOAEL not established.
Developmental – Rabbit	0, 5, 15, 30 mg/kg/day	Maternal NOAEL = 30 mg/kg/day. Maternal LOAEL not established. Developmental NOAEL = 30 mg/kg/day. Developmental LOAEL not established.
Reproduction and fertility effects – Rat	0, 60, 300, 600 ppm Equivalent to 0, 4.5, 22.2, 44.0 mg/kg/day in males and 0, 5.0, 24.5, 48.3 mg/kg/day in females	Parental NOAEL = 22.2/24.5 mg/kg/day (M/F). Parental LOAEL = 44.0/48.3 mg/kg/day (M/F) based on decreased body weight. Offspring NOAEL = 4.5/5.0 mg/kg/day (M/F). Offspring LOAEL = 22.2/24.5 mg/kg/day (M/F) based on decreased pup weights. Pup deaths were considered adverse at the high-dose in the F_2 generation. Reproductive NOAEL = 44.0/48.3 mg/kg/day (M/F). Reproductive LOAEL not established.
Neurotoxicity		
Acute neurotoxicity screening battery – Rat	0, 45, 90, 180 mg/kg	NOAEL = not established. LOAEL = 45 mg/kg/day based on decreased motor activity on day of dosing.
Chronic neurotoxicity screening battery – Rat	0, 60, 300, 600 ppm Equivalent to 0, 2.6, 13.6, 28.2 mg/kg/day in males and 0, 3.4, 18.0, 37.4 mg/kg/day in females	NOAEL = 2.6/3.4 mg/kg/day (M/F). LOAEL = 13.6/18.0 mg/kg/day (M/F) based on the presence of alterations in the myelin of the CNS in male rats, decreased body-weight, food efficiency, absolute food consumption (females) and water consumption (males).

Table A2. Subchronic, chronic, carcinogenicity, and other toxicity studies with Chlorfenapyr		
Chlorfenapyr – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Dose levels; design**	**Results**
Developmental neurotoxicity – Rat	0, 5, 10, 15 mg/kg/day	Maternal NOAEL = 15 mg/kg/day. Maternal LOAEL not established. Developmental NOAEL = 5 mg/kg/day. Developmental LOAEL = 10 mg/kg/day based on increased pup deaths and decreased motor activity.
Chronic toxicity/carcinogenicity		
Chronic – Dog	0, 60, 120, 240 ppm Equivalent to 0, 2.1, 4.0, 8.7 mg/kg/day in males and 0, 2.3, 4.5, 10.1 mg/kg/day in females	NOAEL = 4.0/4.5 mg/kg/day (M/F). LOAEL = 8.7/10.1 mg/kg/day (M/F) based on decreased body-weight.
Carcinogenicity – Mouse	0, 20, 120, 240 ppm Equivalent to 0, 2.8, 16.6, 34.5 mg/kg/day in males and 0, 3.7, 21.9, 44.5 mg/kg/day in females	NOAEL = 2.8/3.7 mg/kg/day (M/F). LOAEL = 16.6/21.9 mg/kg/day (M/F) based on brain vacuolation and scabbing of the skin). No evidence of carcinogenicity.
Combined chronic toxicity/ carcinogenicity – Rat	0, 60, 300, 600 ppm Equivalent to 0, 2.9, 15.0, 30.8 mg/kg/day in males and 0, 3.6, 18.6, 37.0 mg/kg/day in females	NOAEL = 15 mg/kg/day (males). LOAEL = 30.8 mg/kg/day based on anemia. NOAEL = 3.6 mg/kg/day (females). LOAEL = 18.6 mg/kg/day based on decreased body-weight in females. "Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential" based on significant trends in liver tumours (adenomas and combined adenomas/carcinomas), malignant histiocytic sarcomas, and testicular cell tumours in male rats and uterine polyps in female rats seen at the highest dose.
Genotoxicity		
Bacterial reverse mutation	S. typhimurium strains TA 98, TA 100, TA 1535, TA 1537, TA 1538, and E. coli strain WP2 uvrA – exposed up to cytotoxicity (50 µg/plate, +/- S9).	Negative
In vitro mammalian cell gene mutation	(500 µg/mL) in the presence of S9 activation or the solubility limit (250 µg/mL) without S9 activation	Negative
In vitro mammalian chromosome aberration	100 µg/mL –S9 or 25 µg/mL +S9; higher doses with or without S9 Activation.	Negative

Table A2. Subchronic, chronic, carcinogenicity, and other toxicity studies with Chlorfenapyr		
Chlorfenapyr – toxicity profile: sub-chronic, chronic, and other special studies		
Study type	**Dose levels; design**	**Results**
In vitro chromosome aberration assay in Chinese hamster lung cells	Up to a precipitating level without S9 activation (225 µg/mL) or a concentration range of 3.5-14.1 µg/mL +S9. Higher S9-activated doses (≥28 µg/mL) were cytotoxic.	Negative
Mammalian micronucleus (mouse)	Mice administered single oral gavage doses of 7.5-30 mg/kg (males) or 5-20 mg/kg (females).	Negative
Unscheduled DNA synthesis	Primary rat hepatocyte cultures exposed up to severely toxic concentrations (≥30 µg/mL).	Negative
Metabolism and dermal absorption		
Metabolism and pharmacokinetics – Rat	20, 200 mg/kg/day	Low recoveries of the radioactive dose in urine and tissues indicated limited absorption. More than 80% of the doses were eliminated in the feces. Most of the radioactivity was eliminated in the feces and urine within 48 hours of dosing. After 7 days, 89-121% of the dosed radioactivity was recovered. At sacrifice, female rats had greater recovery (about twice) in the carcass, blood, and fat at all doses than did males. The highest recovery of radioactivity from a single organ was from the liver (0.15-0.48% of dose). Parent compound was the major component found in excreta (40-70% of administered doses). Based on the metabolites identified, the major deposition route of orally administered chlorfenapyr is fecal excretion of unaltered parent compound. Metabolites are minimally accumulated in tissue and excreted primarily in urine.
In vivo dermal-penetration – Rat	Formulation concentrate (BAS 306 02 I) at 2.4 mg/cm^2 and 0.0217 mg/cm^2	At 8, 24, and 120 hours, dermal absorption (tissues, excreta, surrounding skin, and application site) for the 2.4 mg/cm^2 dose was 6.4%, 3.9%, and 3.6%, respectively. At 8, 24, and 120 hours, dermal absorption (tissues, excreta, surrounding skin, and application site) for the 0.0217 mg/cm^2 dose was 13.1%, 10.7%, and 15.1%, respectively.
Pharmacological Study - Mouse	Vehicle control, 0.3, 1, 3, 10, 30, 100 mg/kg bw	NOAEL = 3 mg/kg bw LOAEL = 10 mg/kg bw depression of grooming behavior and reactivity, increased frequency of prone position and slight diarrhea.

(USEPA, 2020; JMPR, 2012)

Appendix B. Hazard Assessment of Chlorfenapyr

WHO Prequalification Programme / Vector Control Product Assessment

WHO

Hazard Assessment:

Chlorfenapyr

(CAS No. 122453-73-0)

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Prequalification Vector Control Team
World Health Organization
May 2024

Introduction to Chlorfenapyr

The use of vector control products (VCPs) is critical in the protection of global human health by combatting and preventing the transmission of major vector-borne diseases. Through the procedures of Prequalification Unit Vector Control Product Assessment Team (PQT/VCP), VCPs and public health pesticide active ingredients are assessed to determine that they can be used safely and effectively and are manufactured to a high-quality standard. The intent of the hazard assessment of each active ingredient (AI) is to consolidate the relevant toxicological information and authoritative evaluations from national and/or international organizations and characterize the chemical as it relates to uses of VCPs. PQT/VCP relies on these authoritative evaluations, focusing on the studies and endpoints applicable to the risk assessment of the use patterns of VCPs. As such, this hazard assessment is not exhaustive in its summary or assessment of publicly available information characterizing the hazard of the AI.

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

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

Hazard Characterization

Only studies relevant to the hazard evaluation are discussed, for a full description of all toxicology studies related to the active ingredient, the reader is referred to the references cited. There is sufficient information on the toxicity of the active ingredient, chlorfenapyr technical, to conduct a human health hazard assessment. Chlorfenapyr targets the central nervous system (CNS). The most common effects from subchronic and chronic administration were neurohistological changes including spongiform myelinopathy of the brain and spinal cord and vacuolization of the brain, spinal cord, and optic nerve. Neurobehavorial effects such as decreased motor activity was observed in the acute neurotoxicity study and the developmental neurotoxicity study. Increased liver organ weights and tumors were also notes in the mammalian studies. There is no evidence to suggest that chlorfenapyr is mutagenic. It is classified as “suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential” (USEPA, 2020).

Acute Toxicity

Chlorfenapyr has low toxicity via the oral and dermal routes of exposure and mild to moderate toxicity via the inhalation route of exposure. Acute oral resulted in Category 4 as per the Globally Harmonized System of Classification (GHS). Acute dermal was classified as Category 5 and acute inhalation toxicity was

classified as GHS Category 3. It is neither a skin irritant nor a dermal sensitizer (not classifiable) but did result in mild eye irritant and classified in Category 2B (USEPA, 2020) (Appendix 5.1).

Subchronic Toxicity

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

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

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

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

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

Chronic Toxicity and Carcinogenicity

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

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

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

Developmental

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

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

Reproduction Toxicity

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

Genotoxicity

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

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

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

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

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

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

Neurotoxicity

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

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

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

Special Study

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

Absorption, Distribution, Metabolism, and Excretion (ADME)

Absorption, distribution, metabolism and elimination (ADME) studies on the product are not required by PQT/VCP, however ADME on the AI are considered and integrated into the hazard assessment.

Oral route studies

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

Dermal route studies

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

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

Dermal absorption was determined using ^{14}C-BAS 306 I in BAS 306 02 I formulation. The BAS 306 02 I formulation is the product that is used in Sylando 240 SC Mosquito Adulticide. The study was assessed by a single topical application at target doses of 250 ug/cm2, 100 ug/cm2, and 25 ug/cm2 to split thickness human skin preparations. The mean absorbed doses were 0.37, 0.11, and 1.2% of the dose for skin treated with the high, mid, and low dose, respectively. A dermal absorption factor of 0.4% was selected for risk assessment of concentrated product (BASF, 2018).

Inhalation route studies

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

Points of Departure (POD), Reference Doses (RfD), and Cancer Classification

Points of Departure

Points of departure (PODs) (No Observed Adverse Effect Level [NOAEL]; Benchmark Dose [BMD]) are determined from the toxicological database based on the most sensitive endpoints. Once PODs are developed, safety factors (SF) and uncertainty factors (UF) are used in conjunction with the PODs to derive a safe exposure level, generally referred to as reference dose (RfD) or acceptable daily intake (ADI).

Reference Doses

Acute Reference Dose (aRfD)

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

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

Acute oral POD = 5 mg/kg bw

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

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

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

Chronic Reference Dose (aRfD)

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

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

Chronic oral POD = 5 mg/kg bw/day

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

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

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

Acceptable Daily Intake (ADI)

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

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

Cancer Classification

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

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Appendix C. Exposure lax scenarios and risk characterization

In the guideline scenario, 0.1 is used for the personal protective equipment (PPE) coefficient. In the lax scenario, 1.0 is used for the PPE coefficient. The results for the lax scenario of the GRAM are provided for information only. WHO does not recommend any application of IRS without appropriate PPE.

Table C.1 - Exposure Estimates for Operators – TWA Long Term Systemic Dose – Guideline and Lax Scenario

Exposure scenario	Routes of exposure	$SysD_{TWA}$ – Guideline Scenario (µg/kg bw/day)	$SysD_{TWA}$ – Lax Scenario (µg/kg bw/day)
Mixing/loading	Dermal	0.04	0.38
Application/Washing/Maintenance	Dermal	0.4	4.04
Application	Inhalation	0.41	4.11
Operator's combined exposure		**0.85**	**8.53**

Table C.2 - Exposure Estimates for Operators – Maximal Systemic Dose – Guideline and Lax Scenario

Exposure scenario	Routes of exposure	$SysD_{MAX}$ – Guideline Scenario (µg/kg bw)	$SysD_{MAX}$ – Lax Scenario (µg/kg bw)
Mixing/loading	Dermal	0.19	1.92
Application/Washing/Maintenance	Dermal	2.05	20.47
Application	Inhalation	2.08	20.83
Operator's combined exposure		**4.32**	**43.22**

($SysD_{MAX}$ = maximal systemic dose in µg/kg bw)

Risk characterization for operators, residents, and operator residents under the guideline and Lax scenarios are depicted in Table C.3 – C.7. Note that Lax scenarios are not applicable to resident exposure scenarios.

Table C.3 - Risk Characterization for Operators Guideline Scenarios

Exposure scenario	Routes of exposure	$SysD_{TWA}$ – Guideline Scenario (µg/kg bw/day)	Risk Ratios $SysD_{TWA}$ Guideline [1]	$SysD_{MAX}$ – Guideline Scenario (µg /kg bw)	Risk Ratios $SysD_{MAX}$ Guideline [2]
Mixing/loading	Dermal	0.04	0.0008	0.19	0.004
Application Washing/ Maintenance	Dermal	0.4	0.0082	2.05	0.041
Application	Inhalation	0.41	0.0080	2.08	0.042
Total Exposure	**All routes**	**0.85**	**0.017**	**4.32**	**0.087**

TSD = 50 µg/kg bw/day
Risk Ratio = Exposure/TSD

Table C.4 - Risk Characterization for Operators Lax scenarios					
Exposure scenario	**Routes of exposure**	**$SysD_{TWA}$ – Lax Scenario (µg /kg/bw/day)**	**Risk Ratios $SysD_{TWA}$ Lax [1]**	**$SysD_{MAX}$ – Lax Scenario (µg/kg bw)**	**Risk Ratios $SysD_{MAX}$ – Lax Scenario[2]**
Mixing/loading	Dermal	0.38	0.0076	1.92	0.038
Application Washing/ Maintenance	Dermal	4.04	0.0808	20.47	0.409
Application	Inhalation	4.11	0.0822	20.83	0.417
Total Exposure	**All routes**	**8.53**	**0.17**	**43.22**	**0.864**

TSD = 50 µg/kg bw/day
Risk Ratio = Exposure/TSD

Residential exposure risk ratios for residents (all age groups) are presented in table C.6.

Table C.6 - Risk Characterization for Residents (all groups) Guideline Scenario					
Exposure scenario	**Routes of exposure**	**$SysD_{TWA}$ – Guideline Scenario (µg /kg bw/day)**	**Risk Ratios $SysD_{TWA}$ – Guideline[1]**	**$SysD_{MAX}$ – Guideline Scenario (µg /kg bw)**	**Risk Ratios $SysD_{MAX}$ – Guideline [2]**
Adult	Dermal	0.08	0.0016	0.18	0.0036
	Ingestion	0.23	0.0046	0.55	0.011
	All routes	0.31	0.0062	0.73	0.0146
Children	Dermal	0.10	0.002	0.23	0.0046
	Ingestion	0.43	0.0086	1.03	0.0206
	All routes	0.53	0.0106	1.26	0.0252
Toddler	Dermal	0.20	0.004	0.48	0.0096
	Ingestion	1.02	0.0204	2.42	0.0484
	Hand to mouth	0.18	0.0036	0.42	0.0084
	All routes	1.40	0.0278	3.32	0.0664
Infant	Dermal	0.75	0.015	1.77	0.0354
	Ingestion	1.07	0.0214	2.56	0.0512
	Breast milk	7.28	0.1456	N/A	N/A

	All routes	9.1	0.182	4.33	0.0866
Newborn	Breast milk	13.86	0.2772	N/A	N/A

TSD = 50 µg/kg bw/day
Risk Ratio = Exposure/TSD

Risk characterization for the resident operator, is depicted in Table C.7.

Table C.7 - Risk Characterization for Operator-Resident – All Routes of Exposure

Exposure scenario	$SysD_{TWA}$ – (µg /kg bw/day)	Risk Ratios $SysD_{TWA}$	$SysD_{MAX}$ – (µg/kg bw)	Risk Ratios $SysD_{MAX}$
Guideline	1.16	0.0232	5.10	0.102
Lax	11.6	0.232	51.0	1.02

TSD = 50 µg/kg bw/day
Risk Ratio = Exposure/TSD