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A read-across justification to address the repeated-dose neurotoxicity endpoint that is currently insufficiently investigated for pyrethrins

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Table of Contents

Summary 3
Introduction 3
1. Read-across hypothesis and justification 3
2. Pesticidal mode of action of pyrethrins and pyrethroids 4
3. Overview of (geno)toxicity data for pyrethrins and pyrethroids 9
3.1 Acute toxicity, irritation and sensitisation data 9
3.2 Genotoxicity, reproductive and developmental toxicity 9
3.3 Carcinogenicity 9
3.4 Repeat dose toxicity 9
3.5 Neurotoxicity data 9
3.6 ToxCast data 16
4. Selection of (a) read across substance(s) 20
Conclusion 21

Summary

During the EFSA peer review process of pyrethrins, the sub-chronic neurotoxicity endpoint for pyrethrins has been identified as insufficiently investigated. Therefore, in line with EFSA request for additional data a read-across approach to similar substances (pyrethroids) for which repeated dose neurotoxicity data exist has been developed to support the already available data and to address the data requirement according to Regulation (EU) No 283/2013. The read across approach was based on the common insecticidal mode of action (MoA) for pyrethrins and pyrethroids and the insecticides bifenthrin, deltamethrin, alpha-cypermethrin, esfenvalerate, etofenprox, lambda-cyhalothrin and tefluthrin were identified as potential source substances to read across data to pyrethrins. Subsequently, their toxicity profiles were compared to that of pyrethrins to select the most appropriate source substance with available sub-chronic neurotoxicity data.

Reading across sub-chronic neurotoxicity data from deltamethrin and tefluthrin is considered to be appropriate because of to the common MoA and the comparable toxicity profiles, but yet conservative approach due to their more potent neurotoxic properties as demonstrated by the lower dose levels at which clinical signs indicative of neurotoxicity are seen when compared to those for pyrethrins. In addition, deltamethrin and tefluthrin represent pyrethroid substances with and without the α-cyano phenoxybenzyl moiety, thus, addressing the potential of this moiety to contribute to overall neurotoxic potential.

Introduction

According to Regulation (EU) No 283/2013 neurotoxicity studies "*shall be performed for active substances with structures that are similar or related to those capable of inducing neurotoxicity, and for active substances which induce specific indications of potential neurotoxicity, neurological signs or neuropathological lesions in toxicity studies at dose levels not associated with marked general toxicity. Performance of such studies shall also be considered for substances with a neurotoxic mode of pesticidal action.*"

The data package for pyrethrins includes a guideline acute neurotoxicity study, but no sub-chronic neurotoxicity study. However, the there is no evidence in the overall data that the transient neurotoxic effects observed following a single administration of pyrethrins progress to more severe effects during repeat administration at the same dose level, in fact repeat dose studies show that neurotoxicity decreases with repeated dosing; therefore, a repeat dose neurotoxicity in rodents was not triggered.

Nevertheless, it has been requested by EFSA during the peer review to address this endpoint by read across from similar substances such as pyrethroids. Therefore, based on the common insecticidal mode of action the following pyrethroid molecules have been considered for read across: bifenthrin, deltamethrin, alpha-cypermethrin, esfenvalerate, etofenprox, lambda-cyhalothrin, tefluthrin. Their toxicity profile was compared to that of pyrethrins in order to identify the most suitable active molecule with available sub-chronic neurotoxicity data.

1. Read-across hypothesis and justification

It has been requested by EFSA during the peer review process to provide a scientifically substantiated justification using a read-across approach to similar substances (pyrethroids) for which repeated dose neurotoxicity exist to support the already available data and to address the data requirement according to Regulation (EU) No 283/2013. Therefore, it is considered appropriate to justify this read across approach based on the common insecticidal mode of action (MoA) for pyrethrins and pyrethroids. Therefore, the

insecticides bifenthrin, deltamethrin, alpha-cypermethrin, esfenvalerate, etofenprox, lambda-cyhalothrin and tefluthrin have been identified as potential candidates to read across data to pyrethrins.

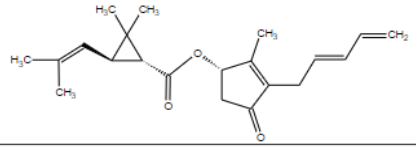
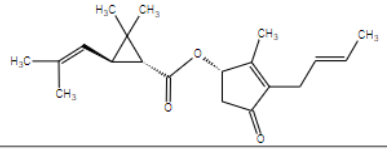
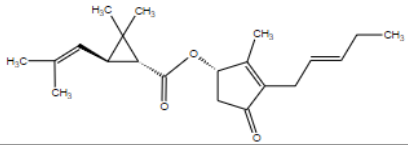
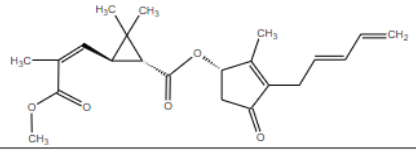
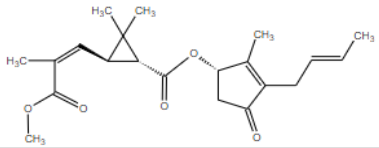
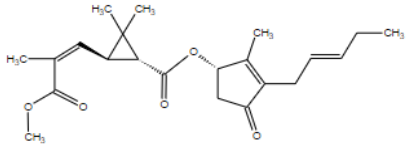
2. Pesticidal mode of action of pyrethrins and pyrethroids

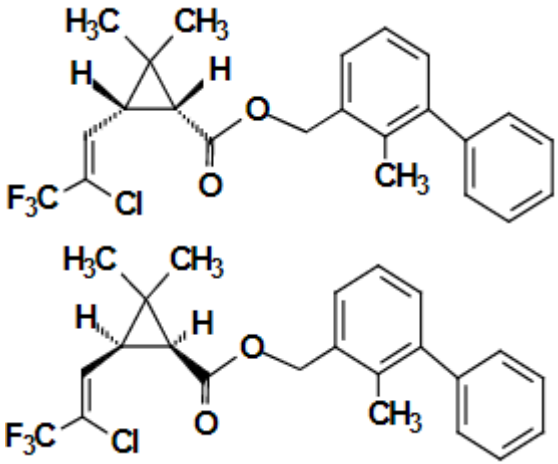
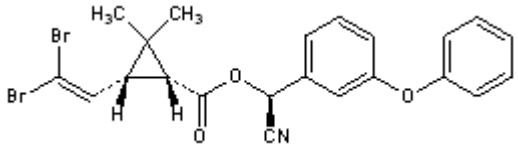
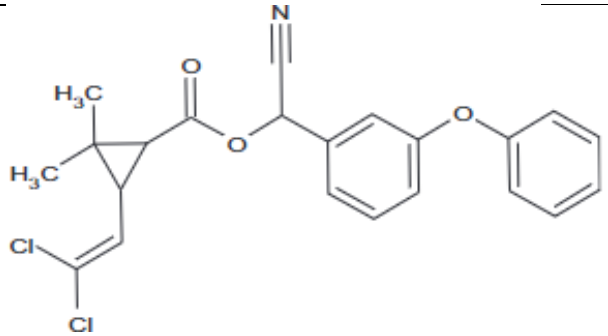
The insecticidal MoA of pyrethrins and pyrethroids involves the altering of the sodium ion channels activity in nerves resulting in repetitive nerve firing and death. The voltage-gated sodium channels present on neuronal axons are the primary molecular target of pyrethroid insecticides. They selectively bind open sodium channels, allowing continuous entry of sodium ions into the cell. This hyperdepolarization of the nerve membrane results in a prolonged tail current, uncontrolled firing, and neurotransmitter release resulting in clinical signs such as ataxia, paralysis and eventually death.

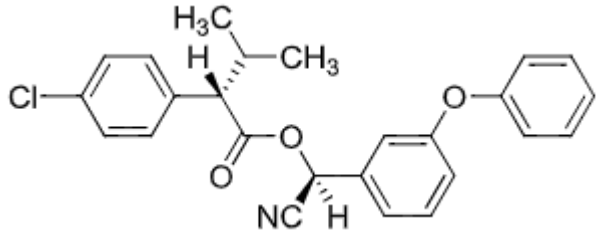
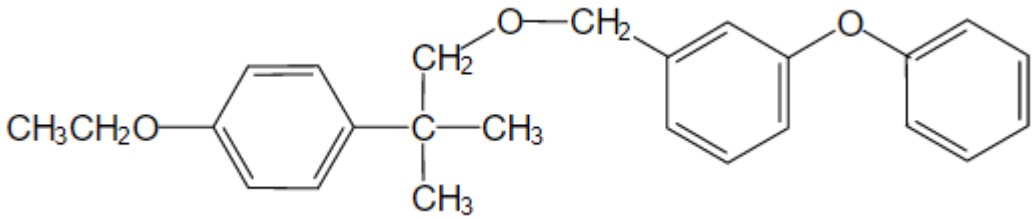
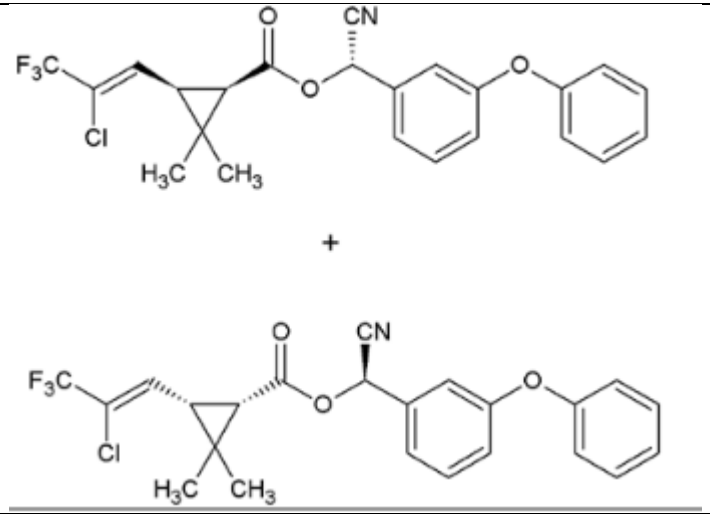
Pyrethroids are divided in two groups based on their chemical structures. Type II pyrethroids have cyano moiety at the alpha-position, while type I lack such moiety. The candidates for read across represent type I and II pyrethroids. Type II pyrethroids are deltamethrin, alpha-cypermethrin, esfenvalerate and lambda-cyhalothrin, molecules with α-cyano phenoxybenzyl moiety, while bifenthrin, etofenprox and tefluthrin lack this moiety, i.e. they are type I pyrethroids. α-Cyano phenoxybenzyl moiety is not present in the target molecule pyrethrins. In order to identify the most suitable candidate, molecules with and without α-cyano phenoxybenzyl moiety have been considered for read-across.

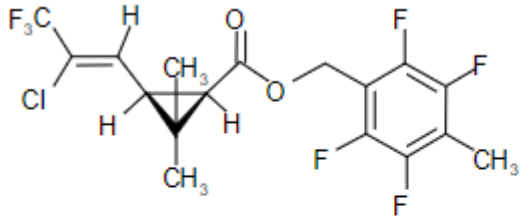
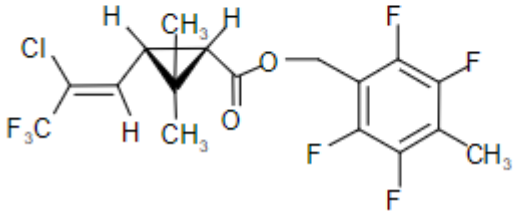
The names and structural formula of pyrethrins and pyrethroid substances are presented in the Table 2.1.

Table 2.1: Name and structural formula of pyrethrins and pyrethroids

Name	Molecular formula	Structural formula	
Pyrethrins (target substance)	pyrethrin 1: $C_{21}H_{28}O_3$ cinerin 1: $C_{20}H_{28}O_3$ jasmolin 1: $C_{21}H_{30}O_3$ pyrethrin 2: $C_{22}H_{28}O_5$ cinerin 2: $C_{21}H_{28}O_5$ jasmolin 2: $C_{22}H_{30}O_5$	pyrethrin 1	
		cinerin 1	
		jasmolin 1	
		pyrethrin 2	
		cinerin 2	
		jasmolin 2	

Name	Molecular formula	Structural formula
Bifenthrin	$C_{23}H_{22}ClF_3O_2$	
Deltamethrin	$C_{22}H_{19}Br_2NO_3$	
alpha-cypermethrin	$C_{22}H_{19}Cl_2NO_3$	

Name	Molecular formula	Structural formula
Esfenvalerate	$C_{25}H_{22}ClNO_3$	
Etofenprox	$C_{25}H_{28}O_3$	
Lambda-cyhalothrin	$C_{23}H_{19}ClF_3NO_3$	

Name	Molecular formula	Structural formula
Tefluthrin	$C_{17}H_{14}ClFO_2$	 *Z*-(1*R*, 3*R*)  *Z*-(1*S*, 3*S*)

3. Overview of (geno)toxicity data for pyrethrins and pyrethroids

A summary of the available toxicity data for these potential source substances is presented in Table 3.1. The toxicity profile of pyrethrins is also presented for comparison.

3.1 Acute toxicity, irritation and sensitisation data

All of the active substances except for etofenprox are acutely toxic by the oral and inhalation route of exposure. The majority of the substances are not acutely toxic by the dermal route with the exception of lambda-cyhalothrin and tefluthrin. Neither of the insecticides are irritating to skin or eyes. Pyrethrins, bifenthrin, esfenvalerate and lambda-cyhalothrin are the only ones that have been identified as skin sensitisers.

3.2 Genotoxicity, reproductive and developmental toxicity

Neither of the substances are genotoxic, reprotoxic or teratogens.

3.3 Carcinogenicity

Only bifenthrin has been identified as potential carcinogen, while Leydig cell tumours in rat testes were reported for esfenvalerate but no classification for carcinogenicity was triggered. All the other pyrethroids have been concluded to not have any carcinogenic potential relevant to humans.

3.4 Repeat dose toxicity

In repeat dose studies with pyrethrins no signs of neurotoxicity were observed in rodents and dogs at well-tolerated doses and no lesions were observed in nerve tissue that could be directly attributed to pyrethrins administration. The target organs appeared to be the liver consistently in all short-term oral studies. Clinical signs of neurotoxicity were reported in the repeated dose toxicity data for deltamethrin, which were either transient in nature or observed at lethal doses. Clinical signs of neurotoxicity were consistently observed across the data package for tefluthrin, which were mainly of transient nature and indicative of acute toxicity. No lesions indicative of neurotoxicity were noted during histopathology for deltamethrin and tefluthrin. No effects indicative of neurotoxicity were reported in the repeated dose toxicity studies with etofenprox, for which the liver and thyroid were identified as the target organ. The main effect seen in the repeat dose toxicity data for bifenthrin was neurotoxicity that was not transient in nature. The short-term studies with alpha-cypermethrin demonstrated neurotoxicity in rats, mice and dogs as well as axonal degeneration in rats. Clinical signs of neurotoxicity were reported in the short-term studies for lambda-cyhalothrin and esfenvalerate which were considered to be the critical finding in these studies.

3.5 Neurotoxicity data

Acute neurotoxicity data are available for all the substances including pyrethrins, while repeat dose neurotoxicity data are available for all except for lambda-cyhalothrin and the target pyrethrins. Developmental neurotoxicity (DNT) data are available for deltamethrin, alpha-cypermethrin, etofenprox and lambda-cyhalothrin.

In the acute neurotoxicity study with pyrethrins, only transient clinical signs of neurotoxicity on the day of administration were observed. The histomorphological changes within the peripheral nerve sections indicated the presence of scattered degenerating nerve fibres or myelin sheaths, mainly graded as minimal. There was insufficient evidence to definitively link the pyrethrin extract treatment to this minimal neuropathy. The NOAEL was concluded to be 20 mg/kg bw/day. There is no sub-chronic or DNT data available for pyrethrins. However, the available short-term repeat dose toxicity data in rats, mice and dogs indicate that clinical signs indicative of neurotoxicity are only seen at the highest test doses, which were also associated with mortality. There were no signs indicative of neurotoxicity seen in the chronic studies

with rats and dogs, while some neurotoxic sings were seen during the first week of treatment in mice at the top dose at which mortality was also observed.

The NOAEL for acute neurotoxicity for bifenthrin was 35 mg/kg bw based on mortality and a variety of changes to nervous system function including clinical signs, functional observations seen at 75 mg/kg bw. The NOAEL from a sub-chronic neurotoxicity study was 2.9 mg/kg bw/day in males and 3.7 mg/kg bw/day in females based on clinical signs of neurotoxicity and effects on functional observations at higher doses. Bifenthrin was classified STOT RE 1 (H372 – nervous system) based on persistent clinical sings of neurotoxicity seen in repeated dose studies at low doses. There is no DNT data for bifenthrin.

The NOAEL for acute neurotoxicity for deltamethrin was 5 mg/kg bw based on functional changes in animals given a dose level of 15 mg/kg bw. The NOAEL from a sub-chronic neurotoxicity study was 4 mg/kg bw/day based on clinical signs (hypersensitivity to noise and gait alterations) noted in animals that received deltamethrin at >14 mg/kg bw/day. There were no effects indicative of developmental neurotoxicity in the available DNT study with deltamethrin and the NOAEL was the highest dose tested 16.1 mg/kg bw/day. Deltamethrin is not classified as STOT SE or RE for nervous system as the mode of action of the nervous system findings seen in repeat dose studies appears to be the same as that producing the lethality in acute studies.

The neurotoxicity of alpha-cypermethrin has been investigated in an acute, sub-chronic and developmental neurotoxicity study. The acute NOAEL was 4 mg/kg bw based on the increased neurologic reactivity and fibre degeneration in sciatic nerves at 20 mg/kg bw, while the 90-day NOAEL was 36.1 mg/kg bw/day, the highest dose tested. In the DNT, the maternal NOAEL was 2 mg/kg bw/day based on decreased body weight gain, and the developmental NOAEL was <0.25 mg/kg bw/day based on clinical signs in pups (tremor and hindlimb twitching). On the basis of the observed neurotoxic effects in repeat dose studies and DNT rat study, alpha-cypermethrin was classified STOT RE 1 (H372 – nervous system).

An acute neurotoxicity study and a sub-chronic neurotoxicity study are available for esfenvalerate. In the acute neurotoxicity study in rats, the NOAEL of 1.75 mg/kg bw was concluded on the basis of clinical signs of neurotoxicity. Similar effects were observed in the 90-day study with a NOAEL of 3.2 mg/kg bw/day based on reductions in forelimb grip strength at 6.4/7.3 mg/kg bw/day. There is no DNT data for esfenvalerate. As neurotoxicity was seen at non-lethal doses in acute studies, esfenvalerate was classified as STOT SE 1 (H370 – nervous system), while no STOT RE classification was triggered for nervous system as the same target organ toxicity of similar severity was affected in acute and repeat dose studies.

There was no evidence of neurotoxic effects in the acute and sub-chronic neurotoxicity studies with etofenprox, therefore the acute NOAEL was >2000 mg/kg bw and the sub-chronic NOAEL was 604 mg/kg bw/day, the highest dose tested. The rat developmental neurotoxicity study showed no selective developmental neurotoxicity at dose levels with slight maternal toxicity, the maternal and developmental NOAEL were both 28.4 mg/kg bw/day. Etofenprox was concluded to be of no concern for neurotoxicity.

The available neurotoxicity data for lambda-cyhalothrin demonstrated that increased breathing rate was the critical effect observed in the acute neurotoxicity study, for which the NOAEL was 2.5 mg/kg bw. No sub-chronic neurotoxicity study is available, but brain morphological changes were identified as the critical effects in the DNT study for which the NOAEL was 4.9 mg/kg bw/day. Lambda-cyhalothrin has not been classified for STOT SE or RE for effects on nervous system, however, there is some indication of potential developmental neurotoxicity as indicated in the DNT assay.

In the acute neurotoxicity study with tefluthrin the NOAEL was 2.5 mg/kg bw based on neurotoxic effects (decreased landing food splay, increased breathing rate). Similarly, the NOAEL of 11.6 mg/kg bw/day from

the sub-chronic neurotoxicity study was also based on neurotoxic effects (increased breathing rate). There is no DNT data for tefluthrin. No classification STOT SE or RE for nervous system was triggered for tefluthrin as there was no clear evidence in the data that neurotoxicological effects were due to repeated exposure, but they were rather indicative of acute toxicity.

Table 3.1: (Geno)toxicity data for pyrethrins and pyrethroids

Endpoint		Target molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule
		Pyrethrins	**Bifenthrin**	**Deltamethrin**	**Alpha-cypermethrin**	**Esfenvalerate**	**Etofenprox**	**Lambda-cyhalothrin**	**Tefluthrin**
Acute toxicity	Oral LD_{50} (mg/kg bw)	402	54.5	87	40-80	88.5	>2000	56	21.8
	Inhalation LC_{50} (mg/L)	3.9	1.01	0.6	1.33	0.48	>5.88	0.066	0.037
	Dermal LD_{50} (mg/kg bw)	>1151	>2000	>2000	>2000	>5000	>2000	632	177
	Skin irritation	Non-irritant	Non-irritant	Non-irritant	Non-irritant	Non-irritant	Non-irritant	Non-irritant	Non-irritant
	Eye irritation	Non-irritant	Non-irritant	Non-irritant	Non-irritant	Non-irritant	Non-irritant	Non-irritant	Non-irritant
	Skin sensitisation	Sensitiser	Sensitiser	Not sensitising	Not sensitising	Sensitiser	Not sensitising	Sensitiser (based on read-across data)	Not sensitising
Short-term repeat dose toxicity data	Critical effect	Changes in liver	Neurotoxic effect	Clinical signs of neurotoxicity	Clinical signs of neurotoxicity ; liver changes	Clinical signs of neurotoxicity	Changes in liver and thyroid	Clinical signs of neurotoxicity, changes in liver	Clinical signs of neurotoxicity
Genotoxicity	Mutagenicity	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Clastogenicity/aneugenicity	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Carcinogenicity	Rat	Benign liver tumours thyroid tumours Concluded to be not carcinogenic	Not carcinogenic	Not carcinogenic	Not carcinogenic	Leydig cell tumours in testes Concluded to be not carcinogenic	Not carcinogenic	Not carcinogenic	Not carcinogenic
	Mouse	Not carcinogenic	Bladder tumours	Not carcinogenic	Not carcinogenic	Not carcinogenic	Not carcinogenic	Not carcinogenic	Not carcinogenic
Reproductive toxicity	Rat	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects
Developmental toxicity	Rat	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects
	Rabbit	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects	No adverse effects
Neurotoxicity	Acute neurotoxicity data	**NOAEL = 20 mg/kg bw per day in females and**	**NOAEL = 35 mg/kg bw** (clinical signs;	**NOAEL = 5 mg/kg bw** (Salivation; soiled fur;	**NOAEL = 4 mg/kg bw** (proximal or distal fibre	**NOAEL = 1.75 mg/kg bw**	**NOAEL > 2000 mg/kg bw** (highest dose tested)	**NOAEL = 2.5 mg/kg bw** (↑breathing at	**NOAEL = 2.5 mg/kg bw**

Endpoint		Target molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule
		Pyrethrins	**Bifenthrin**	**Deltamethrin**	**Alpha-cypermethrin**	**Esfenvalerate**	**Etofenprox**	**Lambda-cyhalothrin**	**Tefluthrin**
		40 mg/kg bw per day in males (↑tremors in females; ↓ rearing, ↓ ambulation and ↓ fine movement in males) Doses: 40, 125, 400 mg total pyrethrins/kg bw in males; 20, 63, 200 mg total pyrethrins/kg bw in females	changes in FOB and motor activity) Doses: 10, 35, 75 mg/kg bw	impaired mobility at 15 mg/kg bw/day) Doses: 5, 15, 50 mg/kg bw	degeneration in sciatic nerve) Doses: 4, 20, 40 mg/kg bw	(clinical signs of neurotoxicity) Doses: 1.75, 1.90, 20, 80 mg/kg bw		≥10 mg/kg bw and clinical signs of neurotoxicity noted at 35 mg/kg bw) Doses: 2.5, 10, 35 mg/kg bw	(↑breathing rate; smaller landing foot splay) Doses: 2.5, 5, 10 mg/kg bw
	Repeat dose neurotoxicity data	**No data*** LOAEL = 170 mg/kg bw/day (8-week dog) LOAEL >1000 mg/kg bw/day (13-week mouse) LOAEL = 590 mg/kg bw/day (13-week rat)	**NOAEL = 2.9 mg/kg bw/day in males and 3.7 mg/kg bw/day in females** (tremors, twitching, FOB changes) LOAEL = 6.0 mg/kg bw/day in males and 7.2 mg/kg	**NOAEL = 4 mg/kg bw per day** (Hypersensitivity to noise and gait alterations) LOAEL = 14 mg/kg bw/day in males and 16 mg/kg bw/day in females	**NOAEL = 36.1 mg/kg bw/day** LOAEL >36.1 mg/kg bw/day Doses: 3.7, 17.9, 36.1 mg/kg bw/day in males and 4.2, 21, 42 mg/kg bw/day in females	**NOAEL = 3.2 mg/kg bw/day** (↓forelimb grip strength, ↓motor activity) LOAEL = 6.4/7.3 mg/kg bw/day Doses: 3.2, 6.4/7.3, 20.1 mg/kg bw/day	**NOAEL = 604 mg/kg bw/day** (highest dose tested) LOAEL >604 mg/kg bw/day	-	**NOAEL = 11.6 mg/kg bw/day** (↑landing foot splay, clinical signs) LOAEL = 26.6 mg/kg bw/day in males and 31.2 mg/kg bw/day in females Doses: 3.8, 11.6, 26.6

Endpoint		Target molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule
		Pyrethrins	**Bifenthrin**	**Deltamethrin**	**Alpha-cypermethrin**	**Esfenvalerate**	**Etofenprox**	**Lambda-cyhalothrin**	**Tefluthrin**
		LOAEL = 686 mg/kg bw/day (18-month mouse)	bw/day in females Doses: 2.9, 6.0, 11.8 mg/kg bw/day in males and 3.7, 7.2, 14.6 mg/kg bw/day in females	Doses: 4, 14 and 54 mg/kg bw/day for males, respectively, and 4, 16 and 58 mg/kg bw/day for females					mg/kg bw/day in males and 4.4, 13.4, 31.2 mg/kg bw/day in females
	Developmental neurotoxicity data	No data	-	**Maternal NOAEL = 6.8 mg/kg bw/day** (↓ body weight gain) **Developmental neurotoxicity NOAEL = 16.1 mg/kg bw/day** Doses: 1.64, 6.78 and 16.1 mg/kg bw/day	**Maternal NOAEL = 2 mg/kg bw/day** (decreased body weight gain) **Developmental neurotoxicity NOAEL <0.25 mg/kg bw/day** (mortality; clinical signs) Doses: 0.5, 2, 5 mg/kg bw/day	-	**Maternal NOAEL = 28.4 mg/kg bw/day** (FOB changes; ↓body weight gain) **Developmental NOAEL = 28.4 mg/kg bw/day** (lower survival, ocular lesions) Doses: 28.4, 79.2, 238 mg/kg bw/day	**Maternal NOAEL = 4.9 mg/kg bw per day** (↓body weight gain noted at 11.4 mg/kg bw per day) **Developmental neurotoxicity NOAEL = 4.9 mg/kg bw per day** (brain morphological findings at 11.4 mg/kg bw per day) Doses: 2.1, 4.9, 11.4 mg/kg bw/day during	-

Endpoint		Target molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule	Source molecule
		Pyrethrins	**Bifenthrin**	**Deltamethrin**	**Alpha-cypermethrin**	**Esfenvalerate**	**Etofenprox**	**Lambda-cyhalothrin**	**Tefluthrin**
								gestation; post-partum equivalents were 0, 4.6, 10.7, 26.3 mg/kg bw/day	
ADI (mg/kg bw/day)		0.04	0.015	0.01	0.00125	0.0175	0.03	0.0025	0.005
ARfD (mg/kg bw)		0.2	0.03	0.025	0.00125	0.0175	1.0	0.005	0.005
AOEL (mg/kg bw/day)		0.07	0.0075	0.0075	0.005	0.011	0.06	0.00063	0.0015
AAOEL (mg/kg bw)		0.11	-	0.019	0.005	-	-	-	-
Current harmonised classification in Regulation (EC) No 1272/2008		Acute Tox. 4 (H332) Harmful if inhaled Acute Tox. 4 (H302) Harmful if swallowed Acute Tox. 4 (H312) Harmful in contact with skin	Acute Tox. 2 (H300) Fatal if swallowed Acute Tox. 3 (H331) Toxic if inhaled Skin Sens. 1B (H317) May cause an allergic skin reaction Carc. 2 (H351) Suspected of causing cancer STOT RE 1 (H372 – nervous system)	Acute Tox. 3 (H301) Toxic if swallowed Acute Tox. 3 (H331) Toxic if inhaled	Acute Tox. 3 (H301) Toxic if swallowed STOT SE 3 (H335 – respiratory irritation) STOT RE 2 (H373 – nervous system)	Acute Tox. 3 (H301) Toxic if swallowed Acute Tox. 3 (H331) Toxic if inhaled Skin Sens. 1 (H317) May cause an allergic skin reaction STOT SE 1 (H370 - nervous system) STOT RE 2 (H373)	Lact. (H362) May cause harm to breastfed babies	Acute Tox. 3 (H301) Toxic if swallowed Acute Tox. 2 (H330) Fatal if inhaled Acute Tox. 4 (H312) Harmful in contact with skin	Acute Tox. 2 (H330) Fatal if inhaled Acute Tox. 2 (310) Fatal if in contact with skin Acute Tox. 2 (300) Fatal if swallowed

* No sub-chronic neurotoxicity data are available for pyrethrins, but the LOAELs for clinical signs of neurotoxicity in repeated dose studies are presented for comparison reasons.

3.6 ToxCast data

A search was conducted on EPA's CompTox database (https://comptox.epa.gov/dashboard) to identify any available ToxCast data for pyrethrins and the potential source pyrethroids. The data are presented in Table 3.2.

For pyrethrins there was no ToxCast Pathway Model (AUC) for the estrogen or androgen receptor. However, CERAPP Potency Level (From Literature) and CERAPP Potency Level (Consensus) identified pyrethrins to be inactive for agonist, antagonist or binding activity towards the estrogen receptor. A ToxCast Pathway Model (AUC) for the estrogen or androgen receptor was available for all the potential source pyrethroids: bifenthrin, deltamethrin, alpha-cypermethrin, esfenvalerate, etofenprox, lambda-cyhalothrin and tefluthrin. Deltamethrin, alpha-cypermethrin, esfenvalerate, etofenprox, lambda-cyhalothrin and tefluthrin were not identified as agonists, antagonists or having binding potential for the estrogen and androgen receptors. Bifenthrin, however, has inconclusive results for agonist activity for the estrogen receptor and antagonistic activity for the androgen receptor.

Table 1.2: ToxCast data for pyrethrins and pyrethroids

Name	Model	Receptor	Agonist	Antagonist	Binding
Pyrethrins	CERAPP Potency Level (From Literature)	**Estrogen**	Inactive	Inactive	Inactive
	CERAPP Potency Level (Consensus)	**Estrogen**	0.00	0.00	0
Bifenthrin	ToxCast Pathway Model (AUC)	**Androgen**	0.00	1.99e-2	-
	ToxCast Pathway Model (AUC)	**Estrogen**	6.93e-5	0.00	-
	COMPARA (Consensus)	**Androgen**	0.00	1.00	1
	CERAPP Potency Level (From Literature)	**Estrogen**	Inactive	Inactive	Inactive
	CERAPP Potency Level (Consensus)	**Estrogen**	0.00	0.00	0
Deltamethrin	ToxCast Pathway Model (AUC)	**Androgen**	0.00	0.00	-
	ToxCast Pathway Model (AUC)	**Estrogen**	0.00	0.00	-
	COMPARA (Consensus)	**Androgen**	0.00	0.00	0
	CERAPP Potency Level (From Literature)	**Estrogen**	Inactive	Inactive	Inactive
	CERAPP Potency Level (Consensus)	**Estrogen**	0.00	0.00	0
Alpha-cypermethrin	COMPARA (Consensus)	**Androgen**	0.00	0.00	0

Name	Model	Receptor	Agonist	Antagonist	Binding
	CERAPP Potency Level (From Literature)	**Estrogen**	Inactive	Inactive	Inactive
	CERAPP Potency Level (Consensus)	**Estrogen**	0.00	0.00	0
Esfenvalerate	ToxCast Pathway Model (AUC)	**Androgen**	0.00	0.00	-
	ToxCast Pathway Model (AUC)	**Estrogen**	0.00	0.00	-
	COMPARA (Consensus)	**Androgen**	0.00	0.00	0
	CERAPP Potency Level (From Literature)	**Estrogen**	Inactive	Inactive	Inactive
	CERAPP Potency Level (Consensus)	**Estrogen**	0.00	0.00	0
Etofenprox	ToxCast Pathway Model (AUC)	**Androgen**	0.00	0.00	-
	ToxCast Pathway Model (AUC)	**Estrogen**	0.00	0.00	-
	COMPARA (Consensus)	**Androgen**	0.00	0.00	0
	CERAPP Potency Level (From Literature)	**Estrogen**	Inactive	Inactive	Very weak
	CERAPP Potency Level (Consensus)	**Estrogen**	0.00	0.00	0
Lambda-cyhalothrin	ToxCast Pathway Model (AUC)	**Androgen**	0.00	0.00	-
	ToxCast Pathway Model (AUC)	**Estrogen**	0.00	0.00	-
	COMPARA (Consensus)	**Androgen**	0.00	0.00	0

Name	Model	Receptor	Agonist	Antagonist	Binding
	CERAPP Potency Level (From Literature)	**Estrogen**	Inactive	Inactive	Inactive
	CERAPP Potency Level (Consensus)	**Estrogen**	0.00	0.00	0
Tefluthrin	ToxCast Pathway Model (AUC)	**Androgen**	0.00	0.00	-
	ToxCast Pathway Model (AUC)	**Estrogen**	0.00	0.00	-
	COMPARA (Consensus)	**Androgen**	0.00	0.00	0
	CERAPP Potency Level (From Literature)	**Estrogen**	Inactive	Inactive	Inactive
	CERAPP Potency Level (Consensus)	**Estrogen**	0.00	0.00	0

4. Selection of (a) read across substance(s)

As already discussed under Section 1, the potential source pyrethroid substances discussed in this justification were selected on the basis of the common insecticidal MoA. Subsequently, their toxicity profiles were presented in Table 3.1 and discussed in Section 3.

When the toxicity profiles are compared to that of pyrethrins, bifenthrin and etofenprox have obviously different toxicity properties to that of pyrethrins. Bifenthrin is more acutely toxic than pyrethrins, it has been identified as having carcinogenic properties and its ToxCast model does not compare to that of pyrethrins. In addition, neurotoxic effects of persistent nature were seen in repeat dose studies sufficient to justify classification for STOT RE 1 (H372 – nervous system). On the other hand, etofenprox has less severe toxicity profile to that of pyrethrins, it is not acutely toxic and no obvious treatment-related neurotoxic effects were observed in the available data. Even though etofenprox and pyrethrins have both been demonstrated to affect the liver, the less severe toxicity profile of etofenprox make it a non-suitable candidate to read across from. Therefore, bifenthrin and etofenprox are not considered appropriate source substances for sub-chronic neurotoxicity data.

Lambda-cyhalothrin is another pyrethroid molecule which is not a suitable source substance as it lacks a sub-chronic neurotoxicity data.

The data package for alpha-cypermethrin identifies the nervous system as a target organ of toxicity, which is supported by neuropathological changes seen in the acute neurotoxicity study. The neurotoxic effects across the data were judged sufficient enough to trigger classification for STOT RE 2 (H373 – nervous system). For esfenvalerate neurotoxicity was seen at non-lethal doses in acute studies leading to classification STOT SE 1 (H370 – nervous system), while no STOT RE classification was triggered for nervous system as the same target organ toxicity of similar severity was affected in acute and repeat dose studies. The data package for pyrethrins demonstrate that transient clinical signs of neurotoxicity not indicative of significant organ damage are seen on the day of administration in acute studies. In short-term repeat dose toxicity studies neurotoxicity was only observed at dose levels that exceeded the MTD in all species and resolved within the first two weeks of dosing. No signs of neurotoxicity were observed in the longer-term studies in rodents and dogs and no lesions were observed in nerve tissue that could be directly attributed to pyrethrins administration. There is no evidence that the neurotoxic effects observed following a single administration of pyrethrins progress to more severe effects on repeat administration at the same dose level, in fact repeat dose studies show that neurotoxicity decreases with repeated dosing. The liver was the identified target organ for pyrethrins in short-term oral studies. When comparing the acute neurotoxicity data for pyrethrins with that for lambda-cyhalothrin and esfenvalerate (see Table 3.1), lambda-cyhalothrin and esfenvalerate appear to be more potent. In addition, no lesions were observed in nerve tissue that could be directly attributed to pyrethrins administration. Therefore, reading across sub-chronic neurotoxicity data from either of these substances, would potentially lead to overprediction of the neurotoxic profile of pyrethrins and thus, lambda-cyhalothrin and esfenvalerate are not considered to be suitable source substances.

The toxicity profile of deltamethrin and tefluthrin differs to that of pyrethrins in their more potent acute toxicity and lack of skin sensitisation potential. Tefluthrin also causes acute toxicity by the dermal route. However, their neurotoxic potential appears to be comparable to that of pyrethrins. Clinical signs of neurotoxicity were reported in the repeated dose toxicity data for deltamethrin. In some studies, the effects are either transient in nature or observed at lethal doses. Clinical signs of neurotoxicity were consistently observed across the data package for tefluthrin, which were mainly of transient nature and indicative of acute toxicity. Deltamethrin and tefluthrin appear to be more potent in causing clinical signs of

neurotoxicity as demonstrated by the lower LOAELs in the acute neurotoxicity data (see Table 3.1). In addition, the doses at which clinical signs of neurotoxicity were seen for deltamethrin and tefluthrin in sub-chronic neurotoxicity studies are below those at which similar signs were seen for pyrethrins in repeated dose toxicity data (see Table 3.1). However, it all three cases neurotoxicity observed after repeated dose exposure is not considered to be a concern as it is either transient in nature or observed at doses associated with mortality or indicative of acute toxicity. Therefore, reading across from these substances is a conservative approach that overpredicts the neurotoxic potential of pyrethrins. Nevertheless, these two substances appear to have the most comparable toxicity potential to that of pyrethrins. In addition, deltamethrin and tefluthrin are representatives of pyrethroid type I and II substances, for which the α-cyano phenoxybenzyl moiety could affect the overall toxicity potential.

Conclusion

Reading across sub-chronic neurotoxicity data from deltamethrin and tefluthrin is considered to be appropriate because of to the common MoA and the comparable toxicity profiles, but yet conservative approach due to their more potent neurotoxic properties as demonstrated by the lower dose levels at which clinical signs indicative of neurotoxicity are seen when compared to those for pyrethrins. In addition, deltamethrin and tefluthrin represent pyrethroid substances with and without the α-cyano phenoxybenzyl moiety, thus, addressing the potential of this moiety to contribute to overall neurotoxic potential.