Competent Authority Report

Programme for Inclusion of Active Substances in Annex I to Council Directive 98/8/EC

Cyphenothrin (PT 18)

CAS-No. 39515-40-7

Sumitomo Chemical (U.K.) PLC

DOCUMENT III-A

Study summaries

Sections A6.3-A6.4

Toxicology section

Rapporteur: Hellas

November 2017

Annex Point IIA6.9	Neurotoxicity Study	
	Justification for non-submission of data	**Official use only**
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	Pyrethroids are considered as neurotoxicants because their target site in insects is the central nervous system. A number of acute and subchronic neurotoxicity studies have been conducted according to EPA and OECD Guidelines. However, no significantly new information have been provided by results of studies of neurotoxicity on pyrethroids, since the main adverse effects detected were clinical signs that were predicatable from general toxicity studies. Therefore further acute or subchronic neurotoxicity studies are not considered necessary and should be avoided to reduce animal testing. An overview of pyrethroid toxicity is given in : Reference : A.6.9/01 Author : Fujita, T Title : General Statement of Neurotoxicity for Pyrethroids Laboratory : Sumitomo Chemical Company Study Number : [redacted] Unpublished : Date : February 20, 2006	
Undertaking of intended data submission [ ]		

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November, 2017
Evaluation of applicant's justification	During the commenting period, the eCA re-evaluated the applicant's waiving on neurotoxicity and did not consider it acceptable. The applicant provided neurotoxicity data on cyphenothrin.
Conclusion	In light of neurotoxicity studies provided by the applicant, the waiving was no longer valid.
Remarks	-

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SHORT-TERM ACUTE ORAL (GAVAGE) TOXICITY RANGE-FINDING STUDY

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	1 REFERENCE	
1.1	**Reference**	[redacted] An Oral (Gavage) Dose Range-Finding Acute Neurotoxicity Study of Cyphenothrin in Rats. [redacted] Sumitomo Study Report No. [redacted]. July 10, 2012.
1.2	**Data protection**	Yes
1.2.1	Data owner	Sumitomo Chemical Company, Ltd 27-1, Shinkawa 2-chome Chuo-ku, Tokyo 104-8260, Japan.
1.2.2	Companies with letter of access	None
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No Range-Finding Study
2.2	**GLP**	Yes
2.3	**Deviations**	No
	3 MATERIALS AND METHODS	
3.1	**Test material**	Cyphenothrin
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Dark yellow, viscous liquid
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Test article considered stable for the duration of the testing period; certificate analysis analysed on October 21, 2011 had an expiration date of August 5, 2014.
3.2	**Reference Substance (positive control)**	Not applicable
3.3	**Test Animals**	
3.3.1	Species	Rat
3.3.2	Strain	Crl:CD(SD) rats
3.3.3	Source	[redacted]
3.3.4	Sex	14 male and 14 nulliparous and non-pregnant females

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3.3.5	Rearing conditions	All animals were housed individually in clean, stainless steel, wire-mesh cages suspended above cage-board. The cage-board was changed at least 3 times per week. Individual cage cards were affixed to each cage and displayed the animal number, group number, study number, dose level, and sex of the animal. Housing was in accordance with the Guide for the Care and Use of Laboratory Animals (Natl. Research Council, 1996)
3.3.6	Age/weight at study initiation	Animals were approximately 6 weeks old (minimum of 42 days) at the initiation of dose administration; individual body weights ranged from 197 g to 230 g for males and from 143 g to 162 g for females.
3.3.7	Number of animals per group	3 animals/sex/treatment group for groups 1, 2, and 3 including vehicle control animals; with 5 animals /sex for group 4 animals.
3.3.8	Control animals	Yes
3.4	**Administration**	oral by gavage
3.4.1	Exposure	Single oral dose
3.4.2	Dose Levels	one vehicle group plus three treatment groups; Dose 0, 50, 100, and 150 mg/kg bw
3.4.3	Vehicle	Corn oil, NF (lot no. 2AD0465, exp. Date: 15 February 2013; manufactured by Spectrum Chemical Manufacturing Corp. New Brunswick, NJ).
3.4.4	Concentration in vehicle	Mean target concentrations (actual concentration) in vehicle were as follows: Group 1 – 0 mg/ml; Group 2 – 10 (9.97) mg/ml; Group 3 – 20 (18.8) mg/ml; and Group 4 – 30 (29.3) mg/ml
3.4.5	Total volume applied	Total Volume administered – 5 ml/kg
3.4.6	Postexposure period	Not applicable
3.4.7	Anticholinergic substances used	Not applicable
3.4.8	Controls	Vehicle Control – corn oil without test article
3.5	**Examinations**	
3.5.1	Body Weight	Weights were taken on day 0 prior to dosing for dose calculations only

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3.5.2	Signs of Toxicity	All animals were observed twice daily, once in the morning and once in the afternoon for mortality. Clinical examinations were performed on all animals prior to dose administration on study day 0. The absence or presence of findings was recorded for individual animal. The observations included, but were not limited to, evaluations for changes in the appearance of skin and fur, eyes and mucous membranes, respiratory, circulatory, autonomic and central nervous system function, somatomotor activity, and behavior patterns. The following parameters were recorded in detailed clinical observations: Ease of removal from cage Lacrimation/chromodacryorrhea Piloerection Palpebral closure Red/crusty deposits Eye prominence Mobility Convulsions/tremors Grooming Bizarre/stereotypic behavior Ease of handling animal in hand Salivation Fur appearance Respiratory rate/character Mucous membranes/eye/skin color Muscle tone Gait Arousal Urination/defecation Backing
3.5.3	Observation schedule	Detailed clinical observations were recorded for all animals at approximately 1, 2, 3, 4, 5, 6, 7, and 8 hours following dose administration on study day 0.
3.5.4	Clinical Chemistry	No
3.5.5	Pathology	Yes; A complete necropsy was conducted on all animals that were euthanized *in extremis*; moribund animals were euthanized by carbon dioxide inhalation. The necropsy included examination of the external surface, all orifices, and the cranial, thoracic, abdominal, and pelvic cavities, including viscera. Organs: No
3.5.6	Histopathology	No Organs: No
3.6	**Further remarks**	None

4 RESULTS AND DISCUSSION

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4.1	**Body Weight**	Body weights were similar across all groups prior to dose administration on study day 0; no statistically significant differences were noted.
4.2	**Clinical signs of toxicity**	Two males were euthanized *in extremis* following the 5-hour post-dosing period in the 150 mg/kg bw group due to worsening condition that consisted of moderately coarse tremors, slightly soiled fur, crusty deposit around the mouth, pale skin color, splayed hindlimbs and/or dragging body, tense and hard muscle tone, slight to moderate impaired mobility, clonic convulsions, and low arousal in the detailed clinical observation. Test substance-related findings during the detailed clinical observations, consisting of tremors, slightly soiled fur, impaired mobility, altered gait, crusty deposits around the mouth, tense and hard muscle tone, clonic convulsions, low arousal, pale skin color, slightly drooping eyelids, and/or salivation were noted in the 150 mg/kg group males and females beginning 2 hours following dose administration and continuing through 8 hours following dose administration; the 2 males that were euthanized in extremis were the most severely affected. Test substance-related findings of tremors, low arousal, altered gait, and/or slightly soiled fur were also noted in the 100 mg/kg group males and females beginning as early as 2 hours (males) and 4 hours (females) following dose administration and continuing through 5 or 7 hours following dose administration for the majority of the findings. A single occurrence of tremors was noted in 1 male in the 50 mg/kg group at 4 hours following dose administration. By 6 to 7 hours the test-article related findings had ameliorated in male and female animals with the time of peak effect being determined to be 4 hours following dose administration based on the incidence and severity of the findings noted all dose levels in males and at ≥100 mg/kg bw in females.
4.3	**Clinical Chemistry**	Not applicable
4.4	**Pathology**	Two males euthanized *in extremis* had full necropsies – no macroscopic findings were observed.
4.5	**Histopathology**	Not applicable
4.6	**Other**	None
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Range-finding study; non-guideline study not conducted under GLP Cyphenothrin, in the vehicle (corn oil), was administered orally by gavage as a single dose to 3 groups (Groups 2-4) of Crl:CD(SD) rats. Dose levels were 50, 100, and 150 mg/kg. A concurrent control group (Group 1) received the vehicle on a comparable regimen. Animals were approximately 6 weeks old (minimum of 42 days) at the initiation of dose administration. Groups 1-3 each consisted of 3 rats/sex; Group 4 consisted of 5 rats/sex. The dose volume was 5 mL/kg for all groups. All animals were observed twice daily for mortality and moribundity. Clinical examinations were performed and individual body weights were recorded prior to dose administration. Detailed clinical observations were recorded for all animals at approximately 1, 2, 3, 4, 5, 6, 7, and 8 hours following dose administration on study day 0. All animals euthanized in extremis were subjected to a gross necropsy. All surviving animals were euthanized and discarded without macroscopic examination on study day 1.

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SHORT-TERM ACUTE ORAL (GAVAGE) TOXICITY RANGE-FINDING STUDY

5.2	**Results and discussion**	Cyphenothrin, when administered orally (gavage) to rats once at dose levels of 50, 100, and 150 mg/kg, tremors were observed in both sexes at 100 mg/kg bw and higher; a single male in the 50 mg/kg group had tremors 4 hours following dose administration. In addition to markedly coarse tremors, severe neuromuscular findings (including impaired mobility, dragging body, and clonic convulsions) were noted in 2 males in the 150 mg/kg, resulting in the euthanasia of these animals following the 5-hour post-dose detailed clinical observations. The time of peak effect was considered to be 4 hours following dose administration based on the increase in incidence and severity of detailed clinical findings occurring at all dose levels in the males and at ≥100 mg/kg in the females. It is considered that approximately 100 mg/kg is suitable as the high-dosage level for the definitive study.
5.3	**Conclusion**	
5.3.1	LOAEL	50 mg/kg bw based on a single male observed with tremors 4 hours post-dose
5.3.2	NOAEL	Not determined
5.3.3	Reliability	1
5.3.4	Deficiencies	No

	EVALUATION BY COMPETENT AUTHORITIES
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November, 2017
Materials and Methods	The applicant's version is acceptable.
Results and discussion	The applicant's version is acceptable.
Conclusion	The applicant's version is acceptable.
Reliability	2
Acceptability	Acceptable only as range finding study. This study is not performed according to guideline and has many deviations from the OECD TG 424 on neurotoxicity testing. However, the purpose of the study was to provide preliminary data for dose selection in the definitive acute oral neurotoxicity study (see Doc IIIA6.9/02) and it is therefore included in the evaluation of cyphenothrin neurotoxic potential as a range finding study.
Remarks	No further remarks.

TABLE A6.9-1. TABLE FOR DELAYED NEUROTOXICITY (MODIFY IF NECESSARY)

Specify lesions and effects in type and severity, if any

Clinical Observations at Time of Peak Effect (4-hours post dose)

Males	low dose 50 mg/kg		mid dose 100 mg/kg		high dose 150 mg/kg	
Number of animals at the start	3		3		5	
Deaths	0	0 %	0	0 %	2	40 %
Showing lesions	0	0 %	0	0 %	0	0 %
Clinical Observations						
Day 0						
Tremors (slight, moderate, marked)	1	33%	2	66%	5	100%
Convulsions	0	0%	0	0%	2	40%
Mobility (slight to moderate)	0	0%	0	0%	2	40%
Gait (body drags or splayed hindlimbs)	0	0%	0	0%	2	40%
Muscle tone (tense, hard)	0	0%	0	0%	1	20%
Arousal	0	0%	0	0%	1	20%
Skin color (pale)	0	0%	0	0%	1	20%
Salivation (slight)	0	0%	0	0%	0	0%
Crusty deposits - mouth	0	0%	0	0%	1	20%
Females	low dose 50 mg/kg		mid dose 1000 mg/kg		high dose 150 mg/kg	
Number of animals at the start	3		3		5	
Deaths	0	0 %	0	0 %	0	0 %
Showing lesions	0	0 %	0	0 %	0	0 %
Clinical Observations						
Day 0						
Tremors (slight to moderate)	0	0 %	2	66 %	5	100%
Convulsions	0	0%	0	0%	0	0%
Mobility (slightly impaired)	0	0%	1	33%	1	20%
Gait (hindlimb splay or walk on tiptoes)	0	0%	1	33%	1	20%
Muscle tone	0	0%	0	0%	0	0%
Arousal	0	0%	0	0%	0	0%
Skin color	0	0%	0	0%	0	0%
Fur appearance (slightly soiled)	0	0%	0	0%	1	20%
Slightly drooping eyelids[a]	0	0%	0	0%	0	0%

[a]: drooping eyelids were observed in female animals at 150 mg/kg bw in 1 (20%) animal at 5, 6, & 7 hours post dose

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1 REFERENCE

1.1	**Reference**	[redacted]; An Oral (Gavage) Acute Neurotoxicity Study of Cyphenothrin in Rats. [redacted]. Sumitomo Report No. [redacted]; December 06, 2012.
1.2	**Data protection**	Yes
1.2.1	Data owner	Sumitomo Chemical Company, Ltd. 27-1, Shinkawa 2-Chrome Chuo-ku, Tokyo 104-8260 Japan
1.2.2	Companies with letter of access	None
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes USEPA OPPTS Guideline 870.6200 OECD Guideline 424 JMAFF Notification No. 12 Nohsan No. 8147
2.2	**GLP**	*Yes*
2.3	**Deviations**	Yes, deviations did not negatively impact the quality or integrity of the data or the outcome of the study. ***i.* Protocol Section 6.1** states that weanling animals (less than 35 days of age) would be housed 2-3 per cage by sex in an environmentally controlled room in suspended wire-mesh cages for a minimum of 3 days. Thereafter, all animals would be housed individually. Animals were housed 2-3 per cage upon arrival on 24 January 2012. On 30 January 2012, the animals were randomized into treatment groups and placed into clean cages. However, there was not documentation that the animals were housed individually. **Reason for Deviation:** Technician error. This deviation had no impact on the study as it is standard procedure that all animals are single-housed into clean caging at randomization. ***ii.* Protocol Section 8.6** states that locomotor activity sessions would be 60 minutes in duration, consisting of twelve 5-minute intervals. Following completion of the study day 7 motor activity assessment on 13 February 2012, it was discovered that the session was only 59 minutes in length. Data for the 60th minute could be retrieved for all animals except male no. 40052 in the 50 mg/kg group. Therefore, the 12th interval for this animal contains only 4 minutes of motor activity data instead of 5 minutes. **Reason for Deviation:** Technician error. This deviation had no impact on the study because there were no test substance-related effects on motor activity at any dose level on study day 7.

3 MATERIALS AND METHODS

3.1	**Test material**	Cyphenothrin

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3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in section 2	
3.1.2.1	Description	Dark yellow, viscous liquid	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Test article considered stable for the duration of the testing period; certificate analysis analysed on October 21, 2011 had an expiration date of August 5, 2014.	
3.2	**Reference Substance (positive control)**	No positive control reference substance was administered in the study. Laboratory historical data with various reference substance was provided.	
3.3	**Test Animals**		
3.3.1	Species	rat	
3.3.2	Strain	Crl:CD(SD)	
3.3.3	Source	Charles River Laboratories, Inc., Raleigh, NC	
3.3.4	Sex	Male and Female	
3.3.5	Rearing conditions	Animals were housed in individual clean, stainless steel, wire-mesh cages suspended above cage-board. The cage-board was changed at least 3 times each week. Individual cage cards were affixed to each cage and displayed the animal number, group number, study number, dose level, and sex of the animal. Housing was in accordance with the Guide for the Care and Use of Laboratory Animals (Natl. Research Council, 1996)	X
3.3.6	Age/weight at study initiation	Young adult animals 6 weeks old (minimum of 42 days) with weights ranging from 195-254 g Males & 142-200 g Females	
3.3.7	Number of animals per group	12 males and 12 females per treatment groups including Vehicle control.	
3.3.8	Control animals	Yes; vehicle control	
3.4	**Administration**	oral by gavage	
3.4.1	Exposure	Single dose of test article to 3 dose groups and a single dose of vehicle to the vehicle control group animals.	
3.4.2	Dose Levels	one vehicle group plus three treatment groups; Dose: 0, 25, 50, or 100 mg/kg bw	
3.4.3	Vehicle	Corn oil was used for vehicle;	
3.4.4	Concentration in vehicle	Grp 1 - 0 mg/ml; Grp 2 – 5 mg/ml; Grp 3 - 10 mg/ml; and Grp 4 – 20 mg/ml	
3.4.5	Total volume applied	5 mL/kg	
3.4.6	Postexposure period	14 days	
3.4.7	Anticholinergic substances used	Not Applicable	
3.4.8	Controls	Vehicle	
3.5	**Examinations**		
3.5.1	Body Weight	Weights were taken one week prior to dose and just prior to the single oral dose and then weekly thereafter.	

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3.5.2	Signs of Toxicity	All animals were observed twice daily, once in the morning and once in the afternoon, for mortality and moribundity. Clinical examinations were performed once daily on all animals beginning on the day of dose administration. The absence or presence of findings was recorded for individual animals The observations included, but were not limited to, evaluation for changes in the appearance of the skin and fur, eyes, mucous membranes, respiratory and circulatory systems, autonomic and central nervous systems, somatomotor activity and behavior patterns. Functional observation battery and motor activity evaluation: FOB findings were recorded for all animals during pretest (study day -6), at the time of peak effect (4 hours post-dosing) on study day 0, and on study days 7 and 14. The time of peak effect was considered to be 4 hours post-dosing based on the increase in incidence and severity of detailed clinical observations at 4 hours following a single oral (gavage) dose of cyphenothrin in the preliminary. Parameters monitored were: HOME CAGE OBSERVATIONS; Posture, Convulsions/tremors, Feces consistency, Biting, Palpebral (eyelid) closure HANDLING OBSERVATIONS; Ease of removal from cage, Lacrimation/chromodacryorrhea, Piloerection, Palpebral closure, Eye prominence, Red/crusty deposits, Ease of handling animal in hand, Salivation, Fur appearance, Respiratory rate/character, Mucous membranes/eye/skin color Muscle tone OPEN FIELD OBSERVATIONS: Mobility, Rearing, Convulsions/tremors, Grooming, Bizarre/stereotypic behavior, Time to first step (seconds), Gait, Arousal, Urination/defecation, Gait score, Backing, Note: Open field observations were evaluated over a 2-minute observation period. SENSORY OBSERVATIONS: Approach response, Startle response, Pupil response, Forelimb extension, Air righting reflex, Touch response, Tail pinch response, Eyeblink response, Hindlimb extension, Olfactory orientation NEUROMUSCULAR OBSERVATIONS: Hindlimb extensor strength, Hindlimb foot splay, Grip strength - hind and forelimb, Rotarod performance PHYSIOLOGICAL OBSERVATIONS: Catalepsy, Body temperature, Body weight Locomotor Activity: Locomotor activity was assessed for all animals (study day -6), at the time of peach effect (4 hours post-dosing) on study day 0, and on study days 7 and 14. Data were collected in 5-minute epochs, and the test session duration was 60 minutes. These data were compiled as six 10-minute subintervals for tabulation. Data for ambulatory and total motor activity were tabulated. Total motor activity was defined as a combination of fine motor skills (*i.e.*, grooming, interruption of 1 photobeam) and ambulatory motor activity (interruption of 2 or more consecutive photobeams)
3.5.3	Observation schedule	As described in Section 3.5.2
3.5.4	Clinical Chemistry	No

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3.5.5	Pathology	Yes A complete necropsy was conducted on all unscheduled deaths. The necropsy included examination of the external surface, all orifices, and the cranial, thoracic, abdominal, and pelvic cavities, including viscera. On Study day 15, all surviving animals were anesthetized an intraperitoneal injection of sodium pentobarbital and then perfused *in situ* with a 4.0% paraformaldehyde/0.1M phosphate buffer solution. The central and peripheral nervous system tissues were dissected and preserved. Fixed brain weight and brain dimensions (length [excluding olfactory bulbs] and width) recorded. Any observable gross changes and abnormal coloration or lesions of the brain and spinal cord were recorded.		
3.5.6	Histopathology	Yes	The following nerve tissues were prepared for a microscopic neuropathological examination from 6 randomly selected animals/sex in the control and 100 mg/kg groups: (Note: The tissues listed below were prepared for a qualitative histopathological examination by embedding in paraffin (central nervous system tissues) or plastic (peripheral nervous system tissues), sectioning, and staining with hematoxylin and eosin.)	X
		Organs:	Brain - olfactory bulbs, cerebral cortex (2 levels), hippocampus/dentate gyrus, basal ganglia, thalamus, hypothalamus, midbrain, cerebellum, pons, and medulla oblongata Spinal cord - at cervical swellings C3-C7 and at lumbar swellings T13-L4 Trigeminal ganglia/nerves Lumbar dorsal root ganglia at T13-L4 Lumbar dorsal root fibers at T13-L4 Lumbar ventral root fibers at T13-L4 Cervical dorsal root ganglia at C3-C7 Cervical dorsal root fibers at C3-C7 Cervical ventral root fibers at C3-C7 Cervical spinal nerve Lumbar spinal nerve Sciatic nerves (mid-thigh region) (2) Sciatic nerves (at sciatic notch) (2) Sural nerves (2) Tibial nerves (2) Peroneal nerves (2) Optic nerves Eyes Skeletal muscle (gastrocnemius)	
3.6	**Further remarks**	None		
		4 RESULTS AND DISCUSSION		
4.1	**Body Weight**	Body weights were unaffected by test substance administration. There were no statistically significant differences when the control and test substance-treated groups were compared.		
4.2	**Clinical signs of toxicity**	One female in the 100 mg/kg group was found dead during FOB evaluations at the time of peak effect (approximately 4 hours following dose administration)		

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on study day 0.

The only test substance-related finding in the daily observations was a single occurrence of severe tremors in one female in the 100 mg/kg group at approximately 6.75 hours after dose administration (approximately 2.75 hours after the time of peak effect). This female also had moderately to extremely coarse tremors during the FOB evaluations.

4 hours post dose – Home Cage Observations

100 mg/kg: One and 2 males in the 100 mg/kg group had slight and markedly coarse tremors, respectively. Two females (including one female that was found dead) had flattened posture and extremely coarse tremors (locomotion impossible). In addition, the female that was found dead had repetitive movements of the mouth and jaws, asphyxial clonic-tonic convulsions, and biting of the cage

50 mg/kg: Slight tremors, biting the cage, and repetitive movement of the mouth and jaws were noted for 1 female at the peak effect (4 hours post dose) on study day 0. There were no test -substance related changes in home cage observations in the 50 mg/kg group males

25 mg/kg: No statistically significant differences for the test substance treated males and females when compared to the control group at time of peak effect on study day 0.

Days 7-14 – Home Cage Observations

100 mg/kg: There were no test substance related changes in home cage observations in males or females on study days 7 and 14.

50 mg/kg: There were no test substance related changes in home cage observations in males and females on study days 7 and14.

25 mg/kg: No statistically significant differences for the test substance treated males and females when compared to the control group on study days 7 and 14.

4 hours post dose – Handling Observations

100 mg/kg: one female died on study day 0 and was observed with decreased respiration. Another female had slight lacrimation on day 0.

Days 7-14 – Handling Observations

100 mg/kg: No test substance related effects observed in the males or females.

Day 0 & Days 7-14 – Handling Observations

25 & 50 mg/kg: No statistically significant differences for the test-substance treated males and females when compared to the control group at the time of peak effect.

4 hours post dose - Open Field Observations

100 mg/kg: mobility was slight to moderately impaired for 1 and 2 males, respectively. Two and 1 males were also observed dragging their body and splayed or dragging hindlimbs, respectively. Five males were observed with slight tremors, 1 male with moderately coarse tremors, and 2 males with markedly coarse tremors. Slight but definite impairment in gait and considerable impairment in gait without falling were observed in 2 and 1 males (same males with mobility deficits).

There was a lower mean number of rearing counts in male and female animals compared to control group animals.

The mean time to the first step in females was much longer than what was observed in control animals – 10.6 seconds treated females compared to 0.3 seconds for controls. Although the one female dying on study contributed to the large difference, it was not statistically significant. When the value for the dead female was excluded, the mean time to first step (0.6 seconds) in the 100

mg/kg was within the historical control data range of this laboratory.
Slight mobility impairment was observed in 3 females, moderate mobility impairment observed in 2 females and total mobility impairment in 1 female when compared to control animals. Two females experiencing mobility impairment were observed dragging their bodies and/or hindlimbs that were splayed.
Slight, moderately coarse, and markedly coarse tremors were observed in 5, 3, and 2 female animals, respectively. Also, impairment of gait that was gauged as slight but definite to considerable impairment was observed 5, 1, and 1 female animals, respectively.

50 mg/kg: males and females were observed with a lower mean number of rearing when compared to control animals.
Three females observed with slight tremors at time of peak effect
25 mg/kg: Increased number of grooming's in females when compared to control animals; but no dose response – considered not test substance-related.

Days 7-14 – Open Field Observations

100 mg/kg: No test substance-related effects were observed in males or females on days 7-14.
50 mg/kg: No test substance-related effects were observed in males or females on days 7-14.
25 mg/kg: No test substance-related effects were observed in males or females on days 7-14.

4 hours post dose – Sensory Observations

100 mg/kg: One male had no reaction to approach, touch, or tail pinch and no orientation to an olfactory stimulant. This male and a second male had a slight uncoordinated air righting reflex. Although, when compared to controls these effects were not deemed statistically significant. Two males also had a bizarre reaction to the startle response (jumping, biting, or attacking).
Three females had a slightly uncoordinated air righting reflex. One, 2, and 3 females were noted to a bizarre reaction to the startle response, lack reaction to tail pinch, and no orientation to an olfactory stimulus respectively.
50 mg/kg: 1 female had a slightly uncoordinated air righting reflex, although it was considered not to be statistically significant when compared to controls.
25 mg/kg: Sensory parameters were unaffected by the test substance at 25 mg/kg in males or females.

Days 7-14 - Sensory Observations

No test substance-related effects were noted in either sex at any dose tested for sensory parameters.

4 hours post dose – Neuromuscular Observations

100 mg/kg: 2 males and 5 females were observed with reduced hindlimb resistance.
50 mg/kg: 1 female observed with reduced hindlimb weakness
25 mg/kg: No test substance-related effects were noted

Days 7-14 – Neuromuscular Observations

100 mg/kg: No test substance-related effects were noted
50 mg/kg: No test substance-related effects were noted

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		25 mg/kg: No test substance-related effects were noted Physiological observations Physiological parameters were not affected by test substance administration at any dose level. Locomotor Activity Within-session repeated measures analyses of variance were conducted across the subintervals of each test session for total and ambulatory counts and for the overall interval means (representing the entire 60-minute session activity) during each test session. 100 mg/kg: Males - Lower mean total and ambulatory activity counts during the first 10-minute interval at the pretest evaluation (prior to dose administration) and during the first 10-minute on Day 0. Because the values on Day 0 were similar to the pretest values and there were no effects on mean cumulative total and ambulatory counts, these findings were not considered test substance-related. A higher mean total motor activity counts during interval 21-30 at peak effect on day 0 was observed. This difference was attributed to an atypically low mean value in the control group. 100 mg/kg: Females – Higher mean total activity and/or ambulatory counts during intervals 21-30, 31-40, and/or 51-60 minutes of the session on study day 0. NOTE: 2 females in the group were severely affected and when removing the results for these 2 females the group was similar to control animals. With the exception of the 100 mg/kg female animals, no remarkable shifts in pattern of habituation was observed in the 100 mg/kg males and female animals when evaluated on days 0, 7, and 14. 25 & 50 mg/kg: Locomotor activity patterns were unaffected by test substance administration on days 0, 7, or 14.	
	Clinical Chemistry	Clinical Chemistry was not carried out	
4.3	**Pathology**	There were no macroscopic changes observed for animals in this study. Brain weights and measurements were unaffected by administration of cyphenothrin at 25, 50, and 100 mg/kg. The only statistically significant ($p<0.05$) difference from the control group was a lower mean brain length in the 100 mg/kg group females. There were no effects on mean brain weight or width in these females. In addition, the value (20.66 mm) in the 100 mg/kg group females was similar to the mean brain length value in the WIL historical control data version 1.1 for acute studies (20.4 mm). The value (21.00 mm) in the control group females was higher than the WIL historical control data. Therefore, the slightly shorter mean brain length in the 100 mg/kg group females was not considered test substance-related.	X
4.4	**Histopathology**	There were no test substance-related histologic changes. All histologic changes were considered to be incidental findings or related to some aspect of experimental manipulation other than administration of the test substance.	
4.5	**Other**	None	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The study was conducted according to OECD guideline 424, EPA OPPTS guideline 870.6200 and JMAFF Notification No. 12 Nohsan No. 8147	
5.2	**Results and discussion**	Test substance-related neurotoxicity was evidenced by FOB findings in the 100 mg/kg group males and females at the time of peak effect (4 hours post-dosing); some findings were noted to a lesser extent in the 50 mg/kg group females and were attributed to the test substance. Females were more severely affected than males, the effects including the death of 1 female that occurred during the FOB evaluations at the time of peak effect on study day 0. Findings considered test substance-related were minimal or not present during the pretest evaluation of	

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		the 50 mg/kg group females and 100 mg/kg group males and females, were outside of the ranges of the WIL Research historical control data, and/or the differences were statistically significant compared to the control group. A lower mean number of rearing counts was noted in the 50 mg/kg group males; because there were no signs of neurotoxicity in males at this dose level, this finding was attributed to transient systemic toxicity. No effects on motor activity were noted at any dose level at the time of peak effect on study day 0 or on study days 7 and 14. Apparent increases in motor activity in the 100 mg/kg group females at the time of peak effect were attributed to 2 females in this group with moderate to extremely coarse tremors, potentially resulting in the breaking of more photobeams. There were no test substance-related macroscopic or microscopic findings of the neural tissues or effects on mean brain weights or brain measurements observed at any dose level. No macroscopic changes were observed for the female in the 100 mg/kg group that was found dead on study day 0. The test substance, cyphenothrin, was administered as a single oral dose to Crl:CD(SD) rats at levels of 25, 50, and 100 mg/kg. Neurotoxic effects were observed at 100 mg/kg as evidenced by mortality of 1 female during the FOB evaluation at the time of peak effect on study day 0, alterations in gait and mobility, tremors and/or convulsions, abnormal air righting reflex, the lack of response to various stimuli, lower mean rearing counts, and deficits in limb extension ability and/or strength. Findings in the 50 mg/kg group females consisted primarily of tremors. A lower mean rearing count, which was attributed to transient systemic toxicity, was noted in the 50 mg/kg group males. No test substance-related effects on motor activity were noted at any dose level. There were no signs of neurotoxicity at 25 mg/kg.
5.3	**Conclusion**	
5.3.1	LOAEL	Female LOAEL for neurotoxicity and systemic toxicity – 50 mg/kg; based on the observations of tremors on day 0 - 4 hours post administration in home cage observations. Male LOAEL for neurotoxicity – 100 mg/kg; based on tremors and slight to moderate reduction of mobility on day 0 four hours post dose and a decrease number of rearing. Male LOAEL for systemic toxicity – 50 mg/kg; based on a decrease number of rearing with no signs of neurotoxicity.
5.3.2	NOAEL	Female NOAEL for neurotoxicity and systemic toxicity – 25 mg/kg Male NOAEL for neurotoxicity– 50 mg/kg Male NOAEL for systemic toxicity– 25 mg/kg
5.3.3	Reliability	1
5.3.4	Deficiencies	*No*

SECTION A6.9/02 **ACUTE NEUROTOXICITY**
Annex Point IIA6.9

EVALUATION BY COMPETENT AUTHORITIES

EVALUATION BY RAPPORTEUR MEMBER STATE

Date November, 2017

Materials and Methods Point 3.3.5: The statement that *"Animals were housed in individual clean, stainless steel, wire-mesh cages"* is contradictory to study limitation presented under point 2.3, where it is stated that ***"i. Protocol Section 6.1 …** there was not documentation that the animals were housed individually"*. This point remains unclear.

Point 3.5.6: Neurohistopathology was only performed in control and high dose animals, instead of 5 animals/sex/group as indicated in the OECD TG 424.

Results and discussion Point 4.3: The mean brain length value in the WIL historical control data version 1.1 for acute studies was not submitted and could not be considered.

Data on brain weight and measurements are included in Table 4.3-1:

Table 4.3-1 Summary of brain weights and measurements

Dose (mg/kg bw)	0	25	50	100
Males				
Final body weigth (g)	330.0 ± 23.6	328.0 ± 31.9	329.0 ± 23.3	328.0 ± 22.1
Brain (g)	2.17 ± 0.067	2.15 ± 0.115	2.19 ±0.079	2.24 ± 0.103
Brain length (mm)	21.01 ± 0.325	20.95 ± 0.553	21.19 ± 0.303	21.36 ± 0.394
Brain width (mm)	15.38 ± 0.242	15.31 ± 0.300	15.53 ± 0.258	15.45 ± 0.349
Females				
Final body weigth (g)	209.0 ± 20.2	207.0 ± 22.1	211.0 ± 12.2	206.0 ±12.3
Brain (g)	2.06 ± 0.047	2.02 ± 0.115	2.08 ± 0.047	2.01 ± 0.058
Brain length (mm)	21.00 ± 0.220	20.74 ± 0.244	20.97 ± 0.271	20.66* ± 0.389
Brain width (mm)	15.12 ± 0.174	15.05 ± 0.320	15.23 ± 0.318	15.05 ± 0.228

* Significantly different from the control group at 0.05 using Dunnett's test

Conclusion NOAEL neurotoxicity = 25 mg/kg bw, based on increased incidence of tremors on day 0 - 4 hours post administration in home cage observations (females) and decreased number of rearing animals from day 0 and persisting until study termination (day 14) (males) at 50 mg/kg.

Systemic toxicity testing was limited to body weight measurements in line with the OECD TG 424 protocol and it is therefore not appropriate to set a NOAEL systemic. It is noted bodyweights were unaffected by treatment.

Reliability 1

Acceptability Acceptable.

It is noted that although neurohistopathology was only performed in control and high dose animals and not in the low and mid dose treatment groups, this is not considered to be a deviation from the OECD TG 424. As no neurohistopathological findings were observed in the high dose group, the decision to skip histopathology for the low and mid dose groups is considered acceptable.

Remarks *No further remarks.*

TABLE A6.9-1. TABLE FOR ACUTE NEUROTOXICITY

Specify lesions and effects in type and severity, if any

Males	vehicle control		low dose 25 mg/kg		mid dose 50 mg/kg		high dose 100 mg/kg	
Number of animals at the start	12		12		12		12	
Deaths	0	0 %	0	0 %	0	0 %	0	0 %
Showing lesions	0	0 %	0	0 %	0	0 %	0	0 %
Functional observation battery								
Day0/Day7/Day14								
Tremors	0/0/0	0%	0/0/0	0%	0/0/0	0%	8/0/0	67%
Mobility	0/0/0	0%	0/0/0	0%	0/0/0	0%	3/0/0	25%
Gait	0/0/0	0%	0/0/0	0%	0/0/0	0%	3/0/0	25%
Rearing	5.3/9.9/7.7	-	3.3/6.8/5.0	-	2.3*/6.8/4.8	-	1.3*/3.9*/4.0	-
Touch response	0/0/0	0%	0/0/0	0%	0/0/0	0%	1/0/0	8%
Startle response	0/0/0	0%	0/0/0	0%	0/0/0	0%	2/0/1	16/8%
Tail pinch response	0/0/0	0%	0/0/0	0%	0/0/0	0%	0/0/0	0%
Olfactory response	0/0/0	0%	0/0/0	0%	0/0/0	0%	0/0/0	0%
Air Righting Reflex	0/0/1	8%	0/0/0	0%	0/0/0	0%	3/0/0	25%
Females	vehicle control		low dose 25 mg/kg		mid dose 50 mg/kg		high dose 100 mg/kg	
Number of animals at the start	12		12		12		12/11	
Deaths	0	0 %	0	0 %	0	0 %	**1**	**8 %**
Showing lesions	0	0 %	0	0 %	0	0 %	0	0 %
Functional observation battery								
Day0/day7/day14								
Tremors	0/0/0	0 %	0/0/0	0 %	3/0/0	25 %	10/0/0	83%
Mobility	0/0/0	0%	0/0/0	0%	0/0/0	0%	6/0/0	50%
Gait	0/0/0	0%	0/0/0	0%	0/0/0	0%	4/0/0	33%
Rearing	4.9/11.7/9.5	-	4.3/10.0/7.9	-	2.9/9.0/8.8	-	1.6*/8.9/7.6	-
Touch Response	0/0/0	0%	0/0/0	0%	0/0/0	0%	3/0/0	25%
Startle	0/0/0	0%	0/0/0	0%	0/0/0	0%	5/0/0	42%
Tail Pinch Response	0/0/0	0%	2/0/0	17%	0/0/0	0%	0/0/1	9%
Olfactory Response	0/0/0	0%	0/0/0	0%	0/0/0	0%	0/0/0	0%
Air Righting Reflex	0/1/0	8%	0/00	0%	1/0/0	8%	4/0/0	33%

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Annex Point IIA, VI. 6.9

SHORT-TERM REPEATED TOXICITY (28-DAY) RANGE-FINDING STUDY (NEUROTOXICITY)

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	1 REFERENCE	
1.1	**Reference**	[redacted] A 28-day Dietary Dose Range-Finding Subchronic Study of Cyphenothrin in Rats. [redacted] Sumitomo Study Report No. [redacted]. November 30, 2012.
1.2	**Data protection**	Yes
1.2.1	Data owner	Sumitomo Chemical Company, Ltd 27-1, Shinkawa 2-chome Chuo-ku, Tokyo 104-8260, Japan.
1.2.2	Companies with letter of access	None
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No Range-Finding Study
2.2	**GLP**	No
2.3	**Deviations**	No
	3 MATERIALS AND METHODS	
3.1	**Test material**	Cyphenothrin
3.1.1	Lot/Batch number	[redacted]
3.1.2	Specification	As given in section 2
3.1.2.1	Description	Dark yellow, viscous liquid
3.1.2.2	Purity	[redacted]
3.1.2.3	Stability	Test article considered stable for the duration of the testing period; certificate analysis analysed on October 21, 2011 had an expiration date of August 5, 2014.
3.2	**Reference Substance (positive control)**	Not applicable
3.3	**Test Animals**	Non-entry field
3.3.1	Species	Rat
3.3.2	Strain	Crl:CD(SD) rats
3.3.3	Source	[redacted]
3.3.4	Sex	15 male and 15 nulliparous and non-pregnant females
3.3.5	Rearing conditions	Upon arrival, all animals were housed 2-3 per cage by sex for 6 days. Thereafter, all animals were housed individually in clean, stainless steel, wire-mesh cages suspended above cage-board. The cage-board was changed at least 3 times each week.
3.3.6	Age/weight at study initiation	Animals were approximately 6 weeks old (minimum of 42 days) at the initiation of test diet administration; individual body weights ranged

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SHORT-TERM REPEATED TOXICITY (28-DAY) RANGE-FINDING STUDY (NEUROTOXICITY)

		from 187 g to 261 g for males and from 139 g to 181 g for females.
3.3.7	Number of animals per group	Each group (Groups 1-3) consisted of 5 males and 5 females.
3.3.8	Control animals	Yes
3.4	**Administration**	In the diet
3.4.1	Exposure	The control and test diets were offered continuously for 28 consecutive days.
3.4.2	Dose Levels	Group 1 – Controls: Basal diet no test article; Group 1 – 1000 PPM test article; Group 3 – 2000 PPM test article
3.4.3	Vehicle	Dietary study; however, test article was dissolved in acetone and basal diet included acetone at a similar vol-to-diet ratio as the test diet.
3.4.4	Concentration in vehicle	Dietary Study: mg/kg/day below: Diet Conc. Males Females 1000 PPMa) 93 mg/kg/day 101 mg/kg/day 2000 PPMb) 164 mg/kg/day 199 mg/kg/day a) study day 0 to 21 (see section 4.2) b) study day 0 to 7 (due to termination on study day 9)
3.4.5	Total volume applied	Dietary study
3.4.6	Postexposure period	No post-exposure period
3.4.7	Anticholinergic substances used	Not applicable
3.4.8	Controls	Control animals were fed basal diet without test article
3.5	**Examinations**	
3.5.1	Body Weight	Individual body weights were recorded weekly, beginning approximately 1 week prior to test diet administration.
3.5.2	Food Consumption	Individual food consumption was recorded weekly, beginning approximately 1 week prior to test diet administration (study days -8 to 0). Food intake was calculated as g/animal/day and g/kg/day for the corresponding body weight change intervals.
3.5.3	Signs of Toxicity	All animals were observed twice daily, once in the morning and once in the afternoon, for mortality and moribundity. Daily Clinical observations we re performed once daily for all animals beginning on the day of dose administration. Beginning one week prior to dose administration, detailed physical examinations were recorded weekly. Functional observation battery: <u>Home Cage Observations:</u> Posture, convulsions/tremors, feces consistency, biting, and eyelid closure. <u>Handling Observations:</u> Ease of removal from cage, lacrimation/chromodacryorrhea, piloerection, eyelid closing, red/crusty deposits, eye prominence, ease of handling animal in hand, salivation, fur appearance, respiratory rate/character, mucous membrane/eyes/skin color, and muscle tone. <u>Open Field Observations:</u> Mobility, rearing, convulsions/tremors, grooming, bizarre/stereotypic behavior, time to first step, gait, arousal, urination/defecation, gait score, and backing.

		Sensory Observations: Approach response, startle response, pupil response, forelimb extension, air righting reflex, touch response, tail pinch response, eyeblink response, hindlimb extension, and olfactory orientation. Neuromoscular Observations: Hindlimb extensor strength, hindlimb foot splay, grip strength – hindlimb and forelimb, and rotarod performance. Physiological Observations: Catalepsy, body temperature, and body weight.
3.5.4	Observation schedule	Clinical observations were recorded once daily for all animals during the course of the study, with the exception of the days of the detailed physical examinations. Detailed physical examinations were recorded weekly, beginning approximately 1 week prior to test diet administration and continuing until the scheduled necropsy and functional observational battery (FOB) findings were recorded for all animals during pretest (study week -1) and for all surviving animals during the last week of test diet administration (week 3).
3.5.5	Clinical Chemistry	No
3.5.6	Pathology	Yes; A complete necropsy was conducted on all animals that were euthanized *in extremis*; moribund animals were euthanized by carbon dioxide inhalation. The necropsy included examination of the external surface, all orifices, and the cranial, thoracic, abdominal, and pelvic cavities, including viscera. The brain from each animal was retained in 10% neutral-buffered formalin for possible future histopathological examinations. Organs: No
3.5.7	Histopathology	No Organs: No
3.6	**Further remarks**	None
		4 RESULTS AND DISCUSSION
4.1	**Body Weight**	In Group 3, 2000 ppm a decrease in bodyweight gain was noted in both males and females during the first week of the study (day 0-7), this resulted in lower mean body weights in both males and females, 13.4% and 5.6%, respectively. However, due to moribunidity the entire group was euthanized on study day 9. In Group 2, 1000 ppm: Mean body weights and body weight gains in the 1000 ppm group males were unaffected by test substance exposure. Differences from the control group were transient, slight and/or not statistically significant.
4.2	**Food Consumption**	On study day 28, the data of food consumption was not collected for animals in the control and 1000 ppm groups due to technical error; therefore, no food consumption data exists during study days 21-28 in these groups. Lower mean food consumption, evaluated as g/animal/day and g/kg/day, was noted in the 2000 ppm group males and females compared to the control group during study days 0-7; differences were generally significant ($p<0.05$ or $p<0.01$). The lower mean food consumption noted in this group corresponded to the lower mean body weight gains noted during the same interval. Further evaluation of food consumption data was precluded in this group due to the moribundity

		and subsequent euthanasia of all animals by study day 9. In the 1000 ppm group males and females, mean food consumption was similar to the control group values during study days 0-21. Differences from the control group were slight and not statistically significant.
4.3	**Clinical signs of toxicity**	Moribundity was noted for males and females in the 2000 ppm group during the treatment period. One female (no. 34645) and 2 males (nos. 34633 and 34637) in the 2000 ppm group were euthanized in extremis on study day 6 or 8 due to clinical findings of persistent tremors (slight to severe in nature) and/or clonic convulsions noted at the daily examinations and/or weekly detailed physical examinations. Tremors in these animals were noted at as early as study day 2 and continued through the day of euthanasia, whereas clonic convulsions were limited to the day of euthanasia. Male no. 34637 was also noted to be rocking, lurching, or swaying while ambulating on study day 7 and male no. 34633 had red material around the nose between study days 4-8. For the remaining males and females in the 2000 ppm group, findings of persistent tremors (all 2000 ppm group animals), clonic convulsions (male nos. 34629, 34630, and 34631 and female no. 34657), and rocking lurching or swaying while ambulating (male no. 34630) were noted at similar incidences to the aforementioned animals during the daily examinations and/or the weekly detailed physical examinations. Based on the presence of these findings, all remaining animals in this group were euthanized in extremis on study day 9, thus, FOB evaluations were precluded at this exposure level. All animals in the control and 1000 ppm groups survived to the scheduled necropsy on study day 28. No noteworthy clinical findings were noted for males and females in these groups at the daily examinations or the weekly detailed physical examinations. Clinical findings were limited to hair loss on the forelimbs and clear material around the mouth; these findings occurred infrequently, similarly in the control group, and in a manner that was not exposure-related. None of the parameters evaluated were affected in FOB evaluations.
4.4	**Clinical Chemistry**	Not applicable
4.5	**Pathology**	All males and females in the 2000 ppm group were euthanized in extremis on study day 6, 8, or 9. No internal findings noted at necropsy for males and females euthanized *in extremis* in the 2000 ppm group. Red matting around the nasal area was noted for male no. 34633 in the 2000 ppm group, which corresponded to findings of red material around the nose at the daily examinations. No macroscopic findings were observed for males and females in the control and 1000 ppm groups.
4.6	**Histopathology**	Not applicable
4.7	**Other**	None
		5 APPLICANT'S SUMMARY AND CONCLUSION

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Annex Point IIA, VI. 6.9

SHORT-TERM REPEATED TOXICITY (28-DAY) RANGE-FINDING STUDY (NEUROTOXICITY)

5.1	**Materials and methods**	Range-finding study; non-guideline study not conducted under GLP Cyphenothrin was offered on a continuous basis in the diet for approximately 28 days to 2 groups (Groups 2 and 3) of Crl:CD(SD) rats at concentrations of 1000 and 2000 ppm. A concurrent control group (Group 1) was offered the basal diet on a comparable regimen. All animals were observed twice daily for mortality and moribundity. Clinical observations were recorded daily, with the exception of the days of the detailed physical examinations. Detailed physical examinations, body weights, and food consumption were recorded weekly. Functional observational battery (FOB) data were recorded for all animals during the pretest period and the last week of test diet administration (week 3). All surviving animals were necropsied on study day 28. The brain from each animal was retained for possible future histopathological examination.
5.2	**Results and discussion**	The test substance, cyphenothrin, was administered in the diet to male and female Crl:CD(SD) rats at exposure levels of 1000 and 2000 ppm. At 2000 ppm, clinical findings (primarily consisting of slight to severe persistent tremors and clonic convulsions) were noted in both sexes during the first week of test substance exposure, resulting in the moribundity and eventual euthanasia of all animals in this group by study day 9; thus, FOB evaluations were precluded at this exposure level. Lower mean body weights, body weight gains, and food consumption were also noted for males and females in the 2000 ppm group during the first week of test substance exposure. Mean body weights, body weight gains, and food consumption in the 1000 ppm group males and females were unaffected by test diet administration. There were no indications of neurotoxicity observed in daily and weekly detailed clinical observations and during the FOB evaluations at 1000 ppm. Based on the results of this study, exposure levels of 300, 600, and 1200 ppm were selected for use in a definitive 90-day neurotoxicity study in Crl:CD(SD) rats.
5.3	**Conclusion**	
5.3.1	LOAEL	2000 ppm; based on clinical findings (primarily consisting of slight to severe persistent tremors and clonic convulsions) were noted in both sexes during the first week of test substance exposure, resulting in the moribundity and eventual euthanasia of all animals in this group by study day 9
5.3.2	NOAEL	1000 ppm
5.3.3	Reliability	1
5.3.4	Deficiencies	No

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Annex Point IIA, VI. 6.9

SHORT-TERM REPEATED TOXICITY (28-DAY) RANGE-FINDING STUDY (NEUROTOXICITY)

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November, 2017
Materials and Methods	The applicant's version is acceptable.
Results and discussion	The applicant's version is acceptable.
Conclusion	The applicant's version is acceptable. Point 3.5.1: The dose of 2000 mg/kg bw exceeds the Maximum Tolerated Dose based on neurotoxic effects.
Reliability	2
Acceptability	Acceptable only as range finding study. This study is not performed according to guideline and has many deviations from the OECD TG 424 on neurotoxicity testing. However, the purpose of the study was to provide preliminary data for dose selection in the definitive subchronic oral neurotoxicity study (see Doc IIIA6.9/04) and it is therefore included in the evaluation of cyphenothrin neurotoxic potential as a range finding study.
Remarks	No further remarks.

SECTION A6.9/04 **90-DAY SUBCHRONIC NEUROTOXICITY**
Annex Point IIA6.9

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] A 90-day Oral Dietary Neurotoxicity Study of Cyphenothrin in Rats. [redacted] Sumitomo Report No. [redacted]; December 03, 2012.	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Sumitomo Chemical Company, Ltd. 27-1, Shinkawa 2-Chrome Chuo-ku, Tokyo 104-8260 Japan	
1.2.2	Companies with letter of access	None	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes OPPTS Guideline 870.6200 OECD Guideline 424 JMAFF Notification No. 12 Nousan No. 8147	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Cyphenothrin	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	As given in section 2	
3.1.2.1	Description	Dark yellow, viscous liquid	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Test article considered stable for the duration of the testing period; certificate analysis analysed on October 21, 2011 had an expiration date of August 5, 2014.	
3.2	**Reference Substance (positive control)**	No positive control reference substance was administered in the study. Laboratory historical data with various reference substances was provided.	
3.3	**Test Animals**	Non-entry field	
3.3.1	Species	Rat	
3.3.2	Strain	Crl:CD(SD)	
3.3.3	Source	[redacted]	
3.3.4	Sex	Male and female animals	
3.3.5	Rearing conditions	Animals were housed individually in clean, stainless steel, wire-mesh cages suspended above cage-board. The cage-board was changed at least 3 times each week. Individual cage cards were affixed to each cage and displayed the animal number, group number, study number, dosage level, and sex of the animal. Animals were maintained in accordance with the *Guide for the Care and Use of Laboratory Animals*	
3.3.6	Age/weight at study initiation	Young adults 6 weeks and males ranged from 176 g to 260 g and females ranged from 127 to 176 g.	

SECTION A6.9/04 90-DAY SUBCHRONIC NEUROTOXICITY
Annex Point IIA6.9

3.3.7	Number of animals per group	12 males and 12 females per group Control – 12 males and 12 females fed basal diet with 0 PPM test article
3.3.8	Control animals	Yes, control animals were fed basal diet with no test article
3.4	**Administration**	Dietary exposure
3.4.1	Exposure	12 animals/sex/group (1-4) fed basal diet (no test article) or test diet for about 13 weeks.
3.4.2	Dose Levels	Group No. Treatment Diet Conc. No. Males No. Females 1 Basal Diet 0 PPM 12 12 2 Cyphenothrin 300 PPM 12 12 3 Cyphenothrin 600 PPM 12 12 4 Cyphenothrin 1200 PPM 12 12
3.4.3	Vehicle	Dietary study; however, test article was dissolved in acetone and basal diet included acetone at a similar vol-to-diet ratio as the test diet.
3.4.4	Concentration in vehicle	Dietary Study: mg/kg day below: Diet Conc. Males Females 300 PPM 18 mg/kg/day 22 mg/kg/day 600 PPM 37 mg/kg/day 45 mg/kg/day 1200 PPM 73 mg/kg/day 90 mg/kg/day
3.4.5	Total volume applied	Not applicable
3.4.6	Postexposure period	No post-exposure period
3.4.7	Anticholinergic substances used	Not Applicable
3.4.8	Controls	Control – 12 males and 12 females fed basal diet with 0 PPM test article
3.5	**Examinations**	
3.5.1	Body Weight	Detailed physical examinations, body weights, and food consumption were recorded weekly
3.5.2	Signs of Toxicity	All animals were observed for mortality/moribundity twice daily, once in the morning and once in the afternoon from the day of animal receipt until study termination. Clinical observations were performed once daily for all animals beginning on the day of dose administration. Observations included, but are not limited to, changes in the skin, fur, eyes and mucous membranes; respiratory, circulatory, autonomic and central nervous system function; somatomotor activity and behavior. Findings (or absence of findings) noted at the clinical observation were recorded for all animals. Beginning one week prior to dose administration, detailed physical examinations were recorded weekly. The animals were removed from their home cages and placed in a standard arena for observation of changes in gait, posture or clonic or tonic movements. The observations included, but are not limited to, evaluations for changes in appearance of skin and fur, eyes, mucous membranes, respiratory and circulatory systems, autonomic and central nervous systems, somatomotor activity and behavior. Functional observation battery and motor activity evaluation: FOB findings were recorded for all animals during pretest (study week -1) and during study weeks 1, 3, 7, and 12. Parameters monitored were posture, convulsions/tremors, feces consistency, biting, palpebral closure, lacrimation/chromodacryorrhea, piloerection, salivation, fur appearance, respiratory rate/character,

		muscle tone; plus sensory observations such as startle response, pupil response, forelimb extension, air righting flex, touch response and olfactory orientation. Neuromuscular observations included hindlimb extensor strength, hindlimb foot splay, grip strength, and rotarod performance. Locomotor Activity: Locomotor activity was monitored at approximately the same time during pretest (study week -1) and each day on 12 animals/sex/group at pretest and during the 2nd, 4th, 8th and 13th weeks of the exposure period (study weeks 1, 3, 7 and 12, respectively). The same animals were monitored at each interval. The test session was 60 minutes in duration, consist of twelve 5-minute intervals and be reported in six 10-minute intervals. Locomotor activity measures evaluated are ambulatory and total (fine + ambulatory) activity counts obtained for the 60-minute test session.
3.5.3	Observation schedule	Refer to Section 3.5.2
3.5.4	Clinical Chemistry	Not conducted
3.5.5	Pathology	Yes; unscheduled deaths received a full necropsy that included examination of the external surface, all orifices, and the cranial, thoracic, abdominal, and pelvic cavities, including viscera. Gross lesions were retained in 10% neutral-buffered formalin for possible future histopathology. Neuropathology was performed on all surviving animals at the termination of the study (week 13). Animals were deeply anesthetized with sodium pentobarbital and the perfused in situ with 4.0% paraformaldehyde in a 0.1 M phosphate buffer solution. The central and peripheral nervous system tissues were dissected and preserved. Any observable gross changes, abnormal coloration, or lesions of the brain and spinal cord were recorded. Organs: Brain, spinal cord, and central and peripheral nervous system tissues.
3.5.6	Histopathology	Yes Organs: Brain - olfactory bulbs, cerebral cortex (2 levels), hippocampus/dentate gyrus, basal ganglia, thalamus, hypothalamus, midbrain, cerebellum, pons, and medulla oblongata Spinal cord - at cervical swellings C3-C7 and at lumbar swellings T13-L4 Trigeminal ganglia/nerves Lumbar dorsal root ganglia at T13-L4 Lumbar dorsal root fibers at T13-L4 Lumbar ventral root fibers at T13-L4 Cervical dorsal root ganglia at C3-C7 Cervical dorsal root fibers at C3-C7 Cervical ventral root fibers at C3-C7 Cervical spinal nerve Lumbar spinal nerve Sciatic nerves (mid-thigh region) (2)c Sciatic nerves (at sciatic notch) (2)c

Sural nerves (2)
Tibial nerves (2)
Peroneal nerves (2)
Optic nerves
Eyes
Skeletal muscle (gastrocnemius)
Other sites (if deemed necessary)

3.6 Further remarks None

4 RESULTS AND DISCUSSION

4.1 Body Weight

There were no test substance-related effects on mean body weight, body weight gain, or food consumption in the 300, 600, and 1200 ppm groups. Differences from the control group were slight and not statistically significant, with the following exceptions:

Significantly ($p<0.05$) lower mean body weight gain was noted for the 300 ppm group males during study days 42-49 and

Significantly ($p<0.05$) higher mean body weight gains were noted in the 600 ppm group males during study days 63-70 and in the 1200 ppm group females during study days 28-35.

These differences from the control group were transient and/or did not occur in an exposure-related manner.

4.2 Clinical signs of toxicity

A single male in the 600 ppm group was found dead on study day 35. There were no remarkable clinical findings noted for this male and as no mortality was observed in the 1200 ppm group, the death of this male was not attributed to test substance exposure. All other males and females survived to the scheduled necropsy. There were no test substance-related clinical findings noted at the daily examinations or the detailed physical examinations at any exposure level.

Functional observation battery and motor activity evaluation

Home cage parameters were unaffected by consumption of test diet.

Handling parameters were unaffected by test diet consumption, as no statistical differences between control and test substance exposed groups at study week 1, 3, 7, and 12 evaluations

Open field observation parameters were unaffected by test-diet consumption.

Sensory observation parameters were unaffected by test diet consumption.

Neuromuscular observation parameters were unaffected by test diet consumption. Significantly higher ($p<0.05$) mean hindlimb grip strength was observed for the 300 PPM group females during week 3; however, it was transient change and did not occur in dose-dependent fashion and was not considered test-article related.

Physiological parameters were unaffected by test diet consumption.

Locomotor Activity

Locomotor activity patterns (mean ambulatory and total motor activity counts) were unaffected by test diet consumption. There were no statistically significant differences between the control and test substance-exposed groups when values obtained from the 6 subintervals (0-10 minutes, 11-20 minutes, 21-30 minutes, 31-40 minutes, 41-50 minutes, and 51-60 minutes) and the overall 60-minute test session were evaluated during study weeks 1, 3, 7, and 12.

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		The only significant ($p \leq 0.012$) difference between the control and test substance-exposed groups was a decrease in total and ambulatory counts for the 1200 ppm females during 11-20 minute interval at the pretest evaluation, but this period was prior to dose administration, indicating that this change was not biologically relevant and not due to test-article exposure.	
4.3	**Clinical Chemistry**	Clinical chemistry was not conducted	
4.4	**Pathology**	A single male (no. 40438) in the 600 ppm group was found dead on study day 35. Macroscopic findings for this male consisted of red fluid in the thoracic cavity. As no mortality was observed in the 1200 ppm group, the highest exposure level evaluated, the death and the macroscopic finding of this male was not attributed to test substance exposure. All other males and females survived to the scheduled necropsy where no significant macroscopic findings were observed.	
4.5	**Histopathology**	There were no test substance-related microscopic findings observed in the 1200 ppm group males and females that were examined microscopically.	X
4.6	**Other**	None	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	OPPTS Guideline 870.6200; OECD Guideline 424; and JMAFF Notification No. 12 Nousan No. 8147	
5.2	**Results and discussion**	A single male in the 600 ppm group was found dead on study day 35; macroscopic findings consisted of red fluid in the thoracic cavity. Due to the fact that no other deaths were observed including at the highest concentration tested (1200 PPM)), this death was not attributed to test substance exposure. All other animals survived to the scheduled necropsy. There were no test substance-related clinical findings or effects on mean body weight, body weight gain, or food consumption in the 300, 600, and 1200 ppm groups. No test substance-related effects on home cage, handling, open field, sensory, neuromuscular, or physiological parameters were noted at any exposure level during the study week 1, 3, 7, and 12 evaluations. Locomotor activity was also unaffected by test diet consumption; no changes in the pattern of habituation were noted. No test substance-related macroscopic or microscopic findings were observed at any exposure level.	
5.3	**Conclusion**		
5.3.1	LOAEL	No systemic or neurotoxic effects were noted at any dietary exposure level for cyphenothrin. Dietary levels were selected based on the results of a previous dose range-finding study (Herberth, 2012, WIL-118076) in which dose levels of 1000 and 2000 ppm were evaluated and the 2000 ppm group males and females were terminated early due to severe conditions such as persistent tremors and incidences of clonic convulsions. There were no significant clinical observations noted in the 1000 ppm group males or females. As a result, a high dose of 1200 ppm, which was more than half of the exposure levels evaluated in previous studies, was chosen as the high dose for the current study. It was therefore expected that slight clinical signs would be noted in the 1200 ppm group	
5.3.2	NOAEL	The NOEL for males and females was the highest concentration tested, 1200 PPM, 73 mg/kg/day and 90 mg/kg/day, respectively.	
5.3.3	Reliability	1	

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5.3.4 Deficiencies No

EVALUATION BY COMPETENT AUTHORITIES

EVALUATION BY RAPPORTEUR MEMBER STATE

Date November, 2017

Materials and Methods Point 3.5.6: Neurohistopathology was only performed in control and high dose animals, instead of 5 animals/sex/group as indicated in the OECD TG 424.

Results and discussion Points 4.2 & 5.2: A summary of selected FOB observations on week 12 is presented in Table 6.9/04-1:

Table 6.9/04-1: Summary on selected FOB observations

Functional Observation Battery (FOB) (No. of animals showing each observation on week 12)	Dose (ppm) – Males				Dose (ppm) – Females			
	0	300	600	1200	0	300	600	1200
Home cage observations								
Clonic convulsions absent	12	12	11	12	12	12	12	12
Tonic convulsions absent	12	12	11	12	12	12	12	12
Tremors	12	12	11	12	12	12	12	12
Handling observations								
Respiratory character normal	12	12	11	12	12	12	12	12
Muscle tone normal	12	12	11	12	12	12	12	12
Open field observations								
Mobility normal	12	12	11	12	12	12	12	12
Clonic convulsions absent	12	12	11	12	12	12	12	12
Tonic convulsions absent	12	12	11	12	12	12	12	12
Tremors	12	12	11	12	12	12	12	12
Rearing (mean values of n = 12)	6.7	9.1	5.5	9.5	15.4	18.4	12.3	13.5
Sensory observations								
Startle response normal	12	12	11	12	12	12	12	12
Neuromuscular observations								
Grip strength normal forelimb (g)	1158.3	1145.8	1214.2	1250.0	879.1	896.7	1075.8	1008.8
Grip strength normal hindlimb (g)	648.4	564.9	763.0	627.8	607.8	608.0	616.1	520.9
Physiological observations								
Catalepsy (seconds)	0.9	0.7	0.6	0.6	0.4	0.4	0.4	0.5
Body weight (g)	522.8	541.9	565.4	543.3	281.3	292.2	297.2	286.2
Locomotor activity								
Motor activity counts, total								
mean	2842	3226	3253	3376	3168	3611	3404	3838
% difference from control	NA	13.5	14.5	18.8	NA	14.0	7.4	21.1

SECTION A6.9/04 90-DAY SUBCHRONIC NEUROTOXICITY

Annex Point IIA6.9

Motor activity counts, ambulatory								
mean	463	554	546	543	664	816	761	932
% difference from control	NA	19.7	17.9	17.3	NA	22.9	14.6	40.4

Conclusion NOAEL neurotoxicity = 1200 ppm (~ 73 and 90 mg/kg bw in males and females, respectively), based on the absence of statistically significant treatment-related neurotoxicity at all doses tested.

Systemic toxicity testing was limited to body weight measurements in line with the OECD TG 424 protocol and it is therefore not appropriate to set a NOAEL systemic. It is noted bodyweights were unaffected by treatment.

Reliability 2

Acceptability Acceptable.

The following study protocol deviation from the OECD TG 424 were noted:

- Neurohistopathology was only performed in control and high dose animals and not in the low and mid dose treatment groups. This does not compromise the validity of the study since there were no adverse neurohistopathology effects at 1200 ppm.
- The top dose did not induce toxicity. However, it is considered that overall cyphenothrin has been tested at sufficiently high doses since in the range finding study, at 2000 ppm severe toxicity was observed in the form the slight to severe persistent tremors and clonic convulsions, resulting in moribundity and eventual euthanasia of all animals.

Remarks No further remarks.

TABLE A6.9-1. TABLE FOR 90-DAY SUBCHRONIC NEUROTOXICITY

		Control diet		300 PPM		600 PPM		1200 PPM	
Number of animals at the start		12M/12F		12M/12F		12M/12F		12M/12F	
		Give number of animals affected / percentage of animals affected							
Deaths		0	0 %	1	4 %	0	0%	0	0%
Showing lesions		0	0 %	0	0 %	0	0 %	0	0 %
Showing effects in	**FOB/MA[1]**	0	0 %	0	0 %	0	0 %	0	0 %
Showing other effect, state other effect		0	0 %	0	0 %	0	0 %	0	0 %

[1]: FOB – Functional Observational Battery; MA – Motor Activity

Annex Point IIA6.10 Mechanistics Studies

	Justification for non-submission of data	**Official use only**
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ] Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	None of the toxicological findings requires clarification through mechanistic studies.	
Undertaking of intended data submission [ ]		
	EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	November, 2017	
Evaluation of applicant's justification	The applicant's justification is acceptable.	
Conclusion	No mechanistic studies are required.	
Remarks	-	

Annex Point IIA6.11	**Other routes of administration**	
	Justification for non-submission of data	**Official use only**
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	The use patterns of cyphenothrin containing biocides do not require investigations into other routes of administration.	
Undertaking of intended data submission [ ]		
	EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	November, 2017	
Evaluation of applicant's justification	The applicant's justification is acceptable in general. Nevertheless an intravenous or a bile-cannulation metaboilism study would clarify the issue of oral absortion of cyphenothrin.	
Conclusion	No toxicity studies from other routes are required.	
Remarks	The possible requirement of a DNT study does not concern "other routes" studies.	

Annex Point IIA6.12		Medical data in anonymous form	
		1. REFERENCE	**Official use only**
1.1	**Reference**	A6.12/01 Author : [redacted] Title : Review on medical evaluation of factory workers exposed to pyrethroids Facility : Sumitomo Chemical Company Study No : [redacted] Date : November 21, 2005	
		2. GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3. MATERIALS AND METHODS	
3.1	**Substance**	Cyphenothrin and other pyrethroids (d-alletrhin, d-phenothrin, prallethrin, tetramethrin, d-tetramethrin, imiprothirin, esfenvalerate and empenthrin	
3.2	**Persons exposed**		
3.2.1	Sex	Males	
3.2.2	Age/weight	Age: 49 – 61 years	
3.2.3	Known diseases	None recorded	
3.2.4	Number of persons	7	
3.2.5	Other information		
3.3	**Exposure**		
3.3.1	Reason of exposure	Operators in the packing plant	
3.3.2	Frequency of exposure	Daily (to pyrethroids)	
3.3.3	Overall time period of exposure	8 hours per day	
3.3.4	Duration of single exposure	8 hours per day	
3.3.5	Exposure concentration / dose	Not measured	
3.3.6	Other information	Workers wore protective glasses, chemical resisitant rubber gloves, helmets with face-shields and masks	
3.4	**Examinations**	Body weight, visual acuity, aural acuity, chest x-ray, blood pressure, urinanalysis and biochemistry	
3.5	**Treatment**	None	
3.6	**Remarks**	3 of the operators had been employed in the packaging department for between 1 – 5 years 1 for between 6 – 10 years and 3 for over 10 years	
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	None	

4.2	**Results of examinations**	No findings attributable to pyrethroid exposure
4.3	**Effectivity of medical treatment**	Not relevant
4.4	**Outcome**	Not relevant
4.5	**Other**	

5. APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Operators in the pyrethroid packaging department were monitored every 6 months for 3 years. Examinations included body weight, visual acuity, aural acuity, chest x-ray, blood pressure, urinanalysis and biochemistry
5.2	**Results and discussion**	No findings attributable to pyrethroid exposure were identified in the examinations.
5.3	**Conclusion**	

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November, 2017
Materials and methods	The applicant's version is acceptable in general.
Conclusion	The applicant's version is acceptable in general.
Reliability	Not applicable.
Acceptability	Accepted as indicative.
Remarks	It is noted that the submitted report concerns worker exposure during the manufacturing process which is not relevant for the use as a biocide in EU.

Annex Point IIA6.12.2 Direct observation

	Justification for non-submission of data	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ] Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	Data on direct observation are only required if available. No further data are available for cyphenothrin.	
Undertaking of intended data submission [ ]		
	EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	November, 2017	
Evaluation of applicant's justification	The applicant's justification is acceptable.	
Conclusion	No data on direct observation are required.	
Remarks	-	

Annex Point IIA6.12.3 Health records

	Justification for non-submission of data	**Official use only**
Other existing data [ ]	**Technically not feasible [ ] Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	Data from health records are only required if available. No further data are available for cyphenothrin.	
Undertaking of intended data submission [ ]		
	EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	November, 2017	
Evaluation of applicant's justification	The applicant's justification is acceptable.	
Conclusion	No health records data are required if not already available.	
Remarks	-	

Annex Point IIA6.12.5	**Diagnosis of poisoning**	
	Justification for non-submission of data	**Official use only**
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	Data on the diagnosis of poisoning is only required if available. No further data are available for cyphenothrin.	
Undertaking of intended data submission [ ]		
	EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	November, 2017	
Evaluation of applicant's justification	The applicant's justification is acceptable.	
Conclusion	No data on the diagnosis of poisoning are required if not already available.	
Remarks	-	

Annex Point IIA6.12.6	Sensitisation/allergenicity observations	
	Justification for non-submission of data	**Official use only**
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	Data on sensitization and allergenicity observations are only required if available. No further data are available for cyphenothrin.	
Undertaking of intended data submission [ ]		
	EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	November, 2017	
Evaluation of applicant's justification	The applicant's justification is acceptable.	
Conclusion	No data on sensitization and allergenicity observations are required if not already available.	
Remarks	-	

Annex Point IIA6.12.7	Specific treatment in case of accident

	Justification for non-submission of data	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	Data on specific treatment in case of accident are only required if available. No further data are available for cyphenothrin.	
Undertaking of intended data submission [ ]		
	EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	November, 2017	
Evaluation of applicant's justification	The applicant's justification is acceptable.	
Conclusion	No data on specific treatment in case of accident are required if not already available.	
Remarks	-	

Annex Point IIA6.12.8	**Prognosis following poisoning**	
	Justification for non-submission of data	**Official use only**
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	Data on prognosis following poisoning are only required if available. No further data are available for cyphenothrin.	
Undertaking of intended data submission [ ]		
	EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	November, 2017	
Evaluation of applicant's justification	The applicant's justification is acceptable.	
Conclusion	No data on specific treatment in case of accident are required if not already available.	
Remarks	-	

Annex Point IIA6.12.4	Epidemiological studies on the general population	
	Justification for non-submission of data	**Official use only**

Other existing data [ ]	**Technically not feasible [ ]**
Limited exposure [ ]	**Other justification [ ]**
Detailed justification:	**Data from epidemolgical studies on the general population are only required if available. No further data are available for cyphenothrin.**
Undertaking of intended data submission [ ]	

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	November, 2017
Evaluation of applicant's justification	The applicant's justification is acceptable.
Conclusion	No data from epidemolgical studies on the general population are required.
Remarks	-