Table A6_8(1)-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

External Abnormalities observed at Caesarian section on day 20 of pregnancy.

	Environ-mental Controls	Corn Oil Controls 10 ml/kg	200 mg/kg
Number examined	214	206	207
Shortening of all limbs; four digits on each paw. Tongue protruding slightly, no developed ridging of palate. Slight oedema of neck.	0	0	1

Internal Abnormalities observed at Open Dissection.

	Environ-mental Controls	Corn Oil Controls 10 ml/kg	200 mg/kg
Number examined	71	69	69
Convoluted left ureter	12	10	12
Convoluted right ureter	1	1	0
Both ureters convoluted	0	1	2

Abnormalities Observed Using Wilson's Technique.

	Environ-mental Controls	Corn Oil Controls 10 ml/kg	200 mg/kg
Number examined	71	69	69
Number with kidney pelvis and calyces dilated			
one side	0	6	2
both sides	1	2	0
Number with dilated oesophagus	0	0	1

Table A6_8(1)-3. Table for Teratogenic effects (separate data for all dosage groups) C'ntd

Skeletal Abnormalities Observed using Staples and Schnelle Method.

	Environmental Controls		Corn Oil Controls		200 mg/kg	
	No.	%	No.	%	No.	%
Number examined	71		68		69	
Hyoid poorly ossified	14	19.72	14	20.59	10	14.49
Hyoid not ossified	5	7.04	9	13.24	3	4.35
Skull						
Frontals poor/irreg. ossified	3	4.23	6	8.82	5	7.25
Parietals poor/irreg. ossified	29	40.85	35	48.53	34	49.28
Interparietals poor/irreg. ossified	28	39.44	37	54.41	33	47.83
Occipitals poor/irreg. ossified	36	50.70	46	67.65	34	49.28
Fontanelle - widened	1	1.41	4	5.88	6	8.70
Vertebral Column						
Cervicals - one or more poor. oss.	1	1.41	3	4.41	2	*2.90
Sacrals - one or more poor. oss.	6	8.45	3	4.41	8	11.59
Caudals - 5 ossified	8	11.27	3	4.41	8	11.59
- 4 ossified	46	64.79	46	67.65	50	72.46
- 3 ossified	17	23.94	19	27.94	10	14.49
- 2 ossified	0	0	0	0	1	1.45
Sternebrae						
One or more not ossified	19	26.76	15	22.06	13	*18.84
One or more poorly ossified	68	95.77	66	97.06	67	97.10
Ribs						
13 present both sides	67	94.37	68	100	69	100
14th vestigial both sides	2	2.82	0	0	0	0
14th vestigial on one side	2	2.82	0	0	0	0
Ridged	0	0	0	0	1	1.45
Pelvic Girdle						
Pubis poorly ossified	1	1.41	0	0	1	1.45
Pubis and ischium poorly ossified	1	1.41	0	0	0	0
Pubis not ossified	0	0	0	0	1	1.45

* Abnormal Foetus - with narrowed skull, and fused and pointed lower jaws, clavicle shorter on one side - shortened, malformed limbs and malformed pelvic girdle.

Section A6.8.1
Annex Point IIA6.8.1

6.8.1(2) Teratogenicity Study – oral (rabbit)

Key Study

		Official use only
	1 REFERENCE	
1.1 REFERENCE	[redacted]; 1979; 21Z: Effects of Oral Administration Upon Pregnancy in the Rabbit; [redacted]; unpublished Report No. 79/WRL005/459; 02.10.1979.	
1.2 Data protection	Yes	
1.2.1 Data owner	Sumitomo Chemical (UK) PLC	
1.2.2 Companies with letter of access	Bayer Environmental Science	
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; no guidelines available.	
2.2 GLP	No; GLP was not compulsory at the time the study was performed.	
2.3 Deviations	No	
	3 MATERIALS AND METHODS	
3.1 Test material	As given in section 2 (name used in study report: 21Z)	X
3.1.1 Lot/Batch number	Lot No. C8165-106/Batch ZJ	
3.1.2 Specification	As given in section 2	
3.1.2.1 Description	Dark brown viscous liquid	
3.1.2.2 Purity	94.8%	
3.1.2.3 Stability	Not applicable (daily doses by gavage)	
3.2 Test Animals		
3.2.1 Species	Rabbit	
3.2.2 Strain	New Zealand White	
3.2.3 Source	[redacted]	
3.2.4 Sex	♀	
3.2.5 Age/weight at study initiation	Approximately 5-6 months old/2.7-4.6 kg	

Section A6.8.1
Annex Point IIA6.8.1

6.8.1(2) Teratogenicity Study – oral (rabbit)

Key Study

3.2.6 Number of animals per group

Group	Treatment	Dose level (mg/kg/day)	Number per group*
1	Control	0	19
2	Permethrin	100	18
3	Permethrin	200	24
4	Permethrin	400	24

* Group sizes increased to replace decedent and non-pregnant animals.

3.2.7 Control animals Yes

3.2.8 Mating period Females were mated naturally with fertile males of the same strain. Following insemination, each female was injected intravenously with 25 i.u. of luteinising hormone (Pregnyl, Organon) to ensure ovulation. The day of mating was designated Day 0 of pregnancy.

3.3 Administration/ Exposure Oral

3.3.1 Duration of exposure

rabbit: day 6-18 post mating

3.3.2 Postexposure period 11 days

Oral

3.3.3 Type Gavage

3.3.4 Concentration Gavage 0, 100, 200, 400 mg/kg bw

3.3.5 Vehicle Corn (Maize) oil

3.3.6 Concentration in vehicle Not reported

3.3.7 Total volume applied 2 mL/kg

3.3.8 Controls Vehicle

3.4 Examinations

3.4.1 Body weight Yes

3.4.2 Food consumption No

3.4.3 Clinical signs Yes

3.4.4 Examination of uterine content

Number of corpora lutea

Number of implantations

Section A6.8.1 Annex Point IIA6.8.1	**6.8.1(2) Teratogenicity Study – oral (rabbit)**
	Key Study
	Number of resorption sites (classified as early or late)
3.4.5 Examination of foetuses	
3.4.5.1 General	Litter Size, Nr. of live/dead Foetuses, Foetal Weight, Sex Ratio
3.4.5.2 Skeleton	Yes
3.4.5.3 Soft tissue	Yes
3.5 Further remarks	
	4 RESULTS AND DISCUSSION
4.1 Maternal toxic Effects	Oral administration of permethrin to pregnant rabbits, from Day 6 to Day 18 of gestation inclusive, at dose levels up to 400 mg/kg/day, was without significant maternal effect. General health and condition of treated animals remained comparable with that of controls. An initial depression in body weight was observed in all groups, the effect in Group 4 (400 mg/kg/day) being slightly more pronounced. Subsequently, the rates of weight gain were comparable for all groups. At necropsy, no anomalies were observed that could be related to treatment with permethrin.
4.2 Teratogenic / embryotoxic effects	A slight treatment- but not dosage-related increase in pre-implantation loss was recorded in all treated groups. However, all values were within the background control range of 16.5% ± 8.7%. All other litter parameters of treated groups were comparable with those of the controls. External, internal and skeletal examination of foetuses revealed a number of anomalies in both treated and control groups, the majority of which were of types and incidences previously recorded in control rabbits of this strain. There was no indication of any treatment-related response.
4.3 Other effects	A total of ten animals died or were killed *in extremis*, two in Group 1 (Control), one in Group 2 (100 mg/kg/day), three in group 3 (200 mg/kg/day) and four in group 4 (400 mg/kg/day); there was no indication that the death of any of these was associated with treatment. Clinical symptoms and post-mortem observation are given in Table A6_8(2)-1. Five out of 18 Group 2 females (100 mg/kg/day), nine out of 24 Group 3 females (200 mg/kg/day) and eight out of 24 Group 4 females (400 mg/kg/day) were not pregnant at necropsy, compared with two out of 18 in the control group. There thus appeared to be a reduction in pregnancy rate in all treated groups. For this result to have been related to treatment (which commenced on Day 6) it would have had to be due to failure of the late stages of implantation or to early post-implantation death of embryos which would resorb leaving no detectable remains on Day 29 of gestation.

Section A6.8.1
Annex Point IIA6.8.1

6.8.1(2) Teratogenicity Study – oral (rabbit)

Key Study

However, in females which carried viable young to term, no reduction in the number of implantations or consistent increase in pre- or post-implantation losses was recorded in any group. Therefore, although the possibility of involvement of permethrin in pregnancy failure could not be entirely excluded, on the basis of information obtained in this study it was considered unlikely that the effect was treatment-related.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Virgin female rabbits of the New Zealand White strain were mated naturally with fertile males of the same strain. Following insemination, each female was injected intravenously with 25 i.u. of luteinising hormone (Pregnyl, Organon) to ensure ovulation. The day of mating was designated Day 0 of pregnancy.

Mated female rabbits were randomly assigned to each of four study groups: Group 1, corn oil vehicle control; Group 2, 100 mg/kg Permethrin; Group 3, 200 mg/kg permethrin; Group 4, 400 mg/kg permethrin. Dosing by gavage occurred on Days 6-18 (inclusive) of pregnancy.

Females were weighed daily and observed daily for changes in behaviour and well-being. On Day 29 of pregnancy, females were killed by cervical dislocation and were dissected. The numbers of corpora lutea, implantations, live and dead foetuses, early deaths, late deaths and foetal abnormalities were recorded. Mothers were examined for any abnormal condition which may have contributed to impairment of foetal growth or development.

Each foetus was weighed, sexed and examined for external evidence of abnormality. All foetuses were further examined by open dissection, for internal and skeletal examination of the thorax and abdomen.

5.2 Results and discussion

Oral administration of permethrin to pregnant rabbits, from Day 6 to Day 18 of gestation inclusive, at dose levels up to 400 mg/kg/day, was without significant maternal effect. General health and condition of treated animals remained comparable with that of controls. An initial depression in body weight was observed in all groups, the effect in Group 4 (400 mg/kg/day) being slightly more pronounced. Subsequently, the rates of weight gain were comparable for all groups. At necropsy, no anomalies were observed that could be related to treatment with permethrin.

A slight treatment- but not dosage-related increase in pre-implantation loss was recorded in all treated groups. However, all values were within the background control range of 16.5% ± 8.7%. All other litter parameters of treated groups were comparable with those of the controls.

Section A6.8.1 Annex Point IIA6.8.1	**6.8.1(2) Teratogenicity Study – oral (rabbit)**
	Key Study
	External, internal and skeletal examination of foetuses revealed a number of anomalies in both treated and control groups, the majority of which were of types and incidences previously recorded in control rabbits of this strain. There was no indication of any treatment-related response. A total of ten animals died or were killed *in extremis*, two in Group 1 (Control), one in Group 2 (100 mg/kg/day), three in group 3 (200 mg/kg/day) and four in group 4 (400 mg/kg/day); there was no indication that the death of any of these was associated with treatment. Five out of 18 Group 2 females (100 mg/kg/day), nine out of 24 Group 3 females (200 mg/kg/day) and eight out of 24 Group 4 females (400 mg/kg/day) were not pregnant at necropsy, compared with two out of 18 in the control group. There thus appeared to be a reduction in pregnancy rate in all treated groups. For this result to have been related to treatment (which commenced on Day 6) it would have had to be due to failure of the late stages of implantation or to early post-implantation death of embryos which would resorb leaving no detectable remains on Day 29 of gestation. However, in females which carried viable young to term, no reduction in the number of implantations or consistent increase in pre- or post-implantation losses was recorded in any group. Therefore, although the possibility of involvement of permethrin in pregnancy failure could not be entirely excluded, on the basis of information obtained in this study it was considered unlikely that the effect was treatment-related.
5.3 Conclusion	There were no indications that permethrin gave rise to any teratogenic response.
5.3.1 LO(A)EL maternal toxic effects	> 400 mg/kg
5.3.2 NO(A)EL maternal toxic effects	400 mg/kg
5.3.3 LO(A)EL embryotoxic / teratogenic effects	> 400 mg/kg
5.3.4 NO(A)EL embryotoxic / teratogenic effects	400 mg/kg
5.3.5 Reliability	2
5.3.6 Deficiencies	Yes; not GLP.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*8/12/05*
Materials and Methods	***3.1*** *21Z is not one of the codes referred to in Section 2.* *Applicants version is acceptable*

Section A6.8.1 Annex Point IIA6.8.1	**6.8.1(2) Teratogenicity Study – oral (rabbit)**
	Key Study
Results and discussion	*Adopt applicant's version.*
Conclusion	*Adopt applicant's version.*
Reliability	*2*
Acceptability	*Acceptable.*
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_8(2)-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects

Modify if necessary and give historical data if available

Table of mortality

Group	:	1	2	3	4
Compound	:	Control	------	21Z	------
Dosage (mg/kg/day)	:	0	100	200	400

Group	Female number	Day FDC or KIE (post coitum)	Clinical signs	Post mortem observations
1	240	FDC Day 23	Blood around anus.	Fluid in thorax. Blood in trachea.
	747	FDC Day 13	Blood around mouth and nares.	Cardiac lung lobe perforated.
2	261	KIE Day 15	Slight respiratory noise. Dyspnoea. Eyes pale.	Fluid in trachea. Lung lobes haemorrhagic and compacted. Liver pale. Gastro-intestinal tract distended with gas.
3	069	KIE Day 8	Apparent respiratory distress following dosing.	Blood around mouth and nares. Left lung lobe and diaphragm perforated; blood around liver and mesenteric tissue.
	230	FDC Day 18	Emaciated. Fur loss on tail. Anus inflamed.	Abdomen contained approx. 10 ml serous fluid. Gastro-intestinal tract gas- and fluid-filled. Total depletion of body fat.
	587	FDC Day 3	-	Exudate from nares. Blood-tinged urine stain around perineum. Caecal contents compacted. Colon contained gelatinous material.
4	226	FDC Day 7	-	Fluid in trachea. Lung lobes haemorrhagic. Numerous pale punctate subpleural nodules on all lung lobes. Caecum distended with gas.

Group	Female number	Day FDC or KIE (post coitum)	Clinical signs	Post mortem observations
4	244	KIE Day 8	Abdomen distended. Animal anoxic and lethargic. Dried nasal discharge. Urine staining around perineum.	Exudate from nares. Stomach distended with gas. Gastro-intestinal tract contained gelatinous material, remainder of contents compacted.
	245	KIE Day 10	-	Blood stains around mouth and nares. Tracheal intubation.
	265	FDC Day 9	Eyes pale. Slight respiratory noise. Apparent respiratory distress.	Slight blood staining around mouth. Left lung lobe congested.

FDC Found dead in cage.
KIE Killed in extremis.

Table A6_8(2)-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Group mean litter data (± S.D.)

Group	:	1	2	3	4
Compound	:	Control	------	212	------
Dosage (mg/kg/day)	:	0	100	200	400

Group		Number of pregnant animals	% Abortion and total litter loss	Corpora lutea count	Implantations	Viable young			Resorptions			Implantation loss (%)		Litter weight (g)	Foetal weight (g)
						♂	♀	Total	Early	Late	Total	Pre-	Post-		
1	Mean S.D.	15	0.0	9.9 3.0	9.1 3.2	4.6 1.7	3.5 1.7	8.1 2.9	0.5 0.7	0.5 0.7	1.0 1.0	8.1	10.9	314.6 113.1	36.7 6.4
2	Mean S.D.	12	0.0	9.7 1.4	7.8 2.5	3.9 2.2	3.2 1.5	7.1 2.1	0.1 0.3	0.6 0.8	0.7 0.8	19.8	8.6	287.4 71.7	40.6 6.2
3	Mean S.D.	12	0.0	9.3 1.8	7.7 1.8	3.9 1.7	3.2 2.1	7.1 1.6	0.2 0.4	0.4 0.6	0.6 0.8	17.1	7.6	295.9 67.6	41.8 7.0
4	Mean S.D.	12	0.0	9.5 2.1	8.2 2.4	4.0 1.5	3.6 1.2	7.6 2.1	0.1 0.3	0.5 0.7	0.6 0.8	14.0	7.1	311.5 90.9	41.1 5.9
Control value	Mean S.D.	195	Recorded range: 0.0- 6.8	11.1 1.3	9.3 1.4	4.2 0.9	4.2 0.9	8.4 1.2	0.3 0.5	0.5 0.3	0.9 0.9	16.5 8.7	9.1 5.7	333.8 45.2	39.9 2.4

The mean is derived from all animals that survived to term and bore evidence of implantation.
S.D. Standard deviation.

Table A6_8(2)-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Summary of foetal observations at examination post mortem

Group	:	1	2	3	4
Compound	:	Control	------	212	------
Dosage (mg/kg/day)	:	0	100	200	400

Group:	1	2	3	4	Control value
Number of foetuses examined :	122	85	85	91	2622
% incidence:					
Grossly abnormal foetus.	0.0	0.0	1.2	0.0	0.00
Heart enlarged; ventricular septal defect; slight forelimb flexure; short tail.	0.0	0.0	0.0	1.1	0.00
Enlarged thyroid glands, salivary glands and submandibular fat pad.	2.5	0.0	0.0	0.0	0.11
Thickened cardiac septum.	0.8	0.0	0.0	0.0	0.00
Ductus arteriosus 50% closed.	0.0	1.2	1.2	0.0	0.42
Gas in stomach.	0.8	2.4	0.0	3.3	2.71
Free blood in stomach.	0.0	0.0	0.0	3.3	0.00
Gall bladder variants	18.0	12.9	16.5	17.6	8.39
Unilateral agenesis of kidney.	0.0	0.0	1.2	1.1	0.04
One adrenal rudimentary.	0.0	0.0	0.0	1.1	0.00
Haemorrhage on urinary bladder.	0.0	0.0	1.2	0.0	0.00
Haemorrhagic areas on hind quarters.	0.0	0.0	0.0	3.3	0.42
Small foetus (< 32.0 g).	16.4	11.8	10.6	2.2	15.10

Results of skeletal analysis

Group	:	1	2	3	4
Compound	:	Control	------	21Z	------
Dosage (mg/kg/day)	:	0	100	200	400

Group:	1	2	3	4
Number of foetuses examined*:	122	85	85	91
Head - % with:				
Size of fontanelle - small	22.1	27.1	34.1	40.7
- medium	68.9	61.2	61.2	51.6
- large	9.0	11.8	3.5	7.7
Acephalostomia	-	-	1.2	-
Incomplete and/or irregular ossification of cranial bones	1.6	4.7	2.4	3.3
Frontal bones fused; frontal/nasal sutures misaligned	0.8	-	-	-
Additional cranial sutures	4.9	3.5	1.2	3.3
Abnormalities of anterior fontanelle	2.5	-	-	-
Misshapen hyoid cornu	-	1.2	-	-
Reduced superior occipital bone	-	-	-	1.1
Vertebral column and rib-cage - % with:				
Number of ribs - 12	46.7	51.8	35.3	28.6
- 12/13	11.5	10.6	10.6	5.5
- 13	41.8	37.6	54.1	64.8
Incomplete ossification of one or more thoracic vertebral centra	4.9	3.5	2.4	2.2
Rib-cage and vertebral column abnormalities	-	1.2	3.5	3.3
Incomplete ossification of lumbar vertebral arches	25.4	23.5	37.6	28.6
Incomplete ossification of one or more sternebrae	78.7	70.6	69.4	60.4
Irregular ossification of sternebrae/sternebrae bipartite and offset	2.5	-	4.7	7.7
Limbs - % with:				
Heads of long bones unossified	37.7	23.5	25.9	38.5
Incomplete ossification of phalanges	29.5	15.3	27.1	11.0
Bilateral forelimb flexure	-	1.2	-	1.1
Absence of pollices	-	-	1.2	-
Others - % with				
Small foetus	-	2.4	-	-
Caudal vertebrae abnormal and reduced in number	-	-	-	1.1

* Some foetuses have more than one abnormality.

Section A6.8.2
Annex Point IIA6.8.2

6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)

Key Study

Official use only

	1 REFERENCE
1.1 Reference	[redacted]; 1979; A Multigeneration Reproduction Study of 21Z73 (Permethrin) in the Rat; [redacted]; unpublished Report No. BPAT 79/3; 26.01.1979.
1.2 Data protection	Yes
1.2.1 Data owner	Sumitomo Chemical (UK) PLC
1.2.2 Companies with letter of access	Bayer Environmental Science
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; no guidelines available.
2.2 GLP	Yes
2.3 Deviations	No
	3 MATERIALS AND METHODS
3.1 Test material	As given in section 2 (name used in study report: 21Z73)
3.1.1 Lot/Batch number	Lot No. C8165-106/Batch ZJ
3.1.2 Specification	As given in section 2
3.1.2.1 Description	As given in section 2
3.1.2.2 Purity	93.3% (26.3%/73.7% *cis/trans*)
3.1.2.3 Stability	There was no appreciable change in the concentration of the isomers or of the isomer ratio over the period of the study. Diet pre-mix batches were consistent with a mean value for intended concentration of 100.85%.
3.2 Test Animals	
3.2.1 Species	Rat
3.2.2 Strain	Wistar (COBS)
3.2.3 Source	[redacted]
3.2.4 Sex	♂ and ♀
3.2.5 Age/weight at study initiation	6 weeks of age
3.2.6 Number of animals per group	20 males and 20 females

Section A6.8.2 Annex Point IIA6.8.2	6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)	
	Key Study	
3.2.7 Mating	i) In each generation, mating pairs were maintained for two pregnancies (-A and -B), unless death of the male partner occurred. In the latter event an alternative mate was provided from within the same dose group. ii) Females in pro-oestrus were caged with the mate overnight. Mating was confirmed the next morning by the presence of sperm in the vagina, designated Day 0 of pregnancy. iii) The products of the first mating in each generation were suffixed -A. The products of the second mating in each generation were suffixed -B. See table below	
3.2.8 Duration of mating	Females in pro-oestrus were caged with the mate overnight. Mating was confirmed the next morning by the presence of sperm in the vagina, designated Day 0 of pregnancy.	
3.2.9 Deviations from standard protocol	Second mating of parent, F_1 and F_2 generations, standardisation of litter size.	
3.2.10 Control animals	Yes	
3.3 Administration/ Exposure	Oral	
3.3.1 Animal assignment to dosage groups	P generation, random; F_1 and F_2 generations, random from litters between the ages of 21 and 35 days post-partum at selection date. *See table below*	
3.3.2 Duration of exposure before mating	P generation 84 days; F_1 and F_2 generations, 63 days.	
3.3.3 Duration of exposure in general P, F1, F2 males, females	P generation, 27 weeks; F_1 and F_2 generations, 26 weeks.	
	Oral	
3.3.4 Type	In food	
3.3.5 Concentration	food ..... 0, 5, 30, 180 mg/kg bw food consumption per day ..... ad libitum	
3.3.6 Vehicle	Not reported	X
3.3.7 Concentration in vehicle	Not reported	
3.3.8 Total volume applied	Not reported	
3.3.9 Controls	Plain diet	
3.4 Examinations		
3.4.1 Clinical signs	Yes	

Section A6.8.2 Annex Point IIA6.8.2	**6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)**
	Key Study
3.4.2 Body weight	Yes
3.4.3 Food/water consumption	Food consumption: Yes. Water consumption: No.
3.4.4 Oestrus cycle	Yes
3.4.5 Sperm parameters	Not reported (fertility assessed via test-mating)
3.4.6 Offspring	number and sex of pups stillbirths live births presence of gross anomalies weight gain physical or behavioural abnormalities
3.4.7 Organ weights P and F1	Not applicable (addressed in other multiple-dose studies)
3.4.8 Histopathology P and F1	Not applicable (addressed in other multiple-dose studies)
3.4.9 Histopathology F1 not selected for mating, F2	Not applicable (addressed in other multiple-dose studies)
3.5 Further remarks	ORIGINAL PRE-MIX At the commencement of the study the pre-mix supplied was 5% w/w (permethrin/diet). Difficulties were encountered in obtaining a homogeneous final mix from this pre-mix and from Week 11 of the study a 1% pre-mix was supplied in order to achieve a more satisfactory final mixture. **Foetal toxicity and teratogenicity** The second pregnancy of the F_2 generation was processed as for a foetal toxicity and teratogenicity study. **Reproductive failure** i) A record was made of all successful and unsuccessful matings. ii) Mating pairs were permitted two attempts to produce a pregnancy. iii) At -A matings, animals which failed to produce a pregnancy remained in the study to continue as normal in their dose-groups. iv) At -B matings, animals which failed to produce a pregnancy were removed from the study and immediately test-mated to untreated partners in order to establish whether infertility was attributable to the male or the female of the mating pair.

Section A6.8.2 **6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)**

Annex Point IIA6.8.2

Key Study

v) All animals in the test-mating routine were maintained for one month on control diet.

vi) At the end of the month, animals which had failed to produce a pregnancy at the first test-mating were once again test-mated to an untreated partner in order to assess recovery of fertility.

vii) Animals which went through the complete test-mating routine without producing a pregnancy were finally killed and examined to elucidate the cause of infertility.

viii) At any stage of the test-mating routine, animals which proved fertile were killed and no further examination was carried out.

ix)

4 RESULTS AND DISCUSSION

4.1 Effects

4.1.1 Parent males

There were no significant differences in body weight between groups.

After a sharp rise during the first 6 weeks of the study, all groups showed a marked drop in food intake values at Week 7. From Week 7 all groups continued to show a fluctuating, but steadily increasing intake.

One male in the control group showed fits on two occasions (Week 22 and Week 24). One 5 mg/kg male was twitching and appeared very lethargic on one occasion (Week 22). Three 30 mg/kg males had one fit (Weeks 22, 23 and 26), and one 30 mg/kg male had a fit on two occasions (Week 13 and Week 14). One 180 mg/kg male had a fit on one occasion (Week 24). There were no further observations of aberrant behaviour or condition to indicate any disturbing effect of permethrin.

There were no deaths among males.

4.1.2 Parent females

There were no significant differences in body weight between groups.

A sharp rise in food intake values in all groups from Week 16 to Week 19 corresponds to the period of lactation -A. A similar sharp rise, beginning at Week 23, corresponds to the period of lactation -B. The high values observed for all groups during these periods reflect the presence of the growing offspring, which consumed an increasing quantity of the maternal diet.

One control female had a fit when her litter was removed (Week 20). One 5 mg/kg female showed twitching and became rigid when handled on one occasion (Week 17). One 180 mg/kg female showed twitching on one occasion (Week 17). There were no further observations of aberrant behaviour or condition to indicate any disturbing effect of permethrin.

Section A6.8.2
Annex Point IIA6.8.2

6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)

Key Study

There were no deaths among females during the pre-mating period.

Pregnancy

There was no indication of any effect of treatment on the outcome of matings.

There were no significant differences in body weight between groups.

There were no signs of adverse effects.

One control female died on Day 2 after mating -B. Examination did not reveal the cause of death.

Parturition and post-partum

There were no significant differences between groups regarding the period of gestation.

There were no significant differences in body weight between groups.

There were no signs of adverse effects during lactation.

There were no deaths during the periods of lactation.

4.1.3 F1 males

There were no significant differences in body weight between groups.

After a sharp rise during the first 6 weeks of the study, all groups maintained a satisfactory but fluctuating food intake.

There were no signs of adverse effects.

One control male died in Week 2.

4.1.4 F1 females

There were no significant differences in body weight between groups.

A sharp rise in food intake observed at Weeks 15 and 23 reflects the presence of the growing offspring during the periods of lactation -A and lactation -B. During these periods the offspring consumed increasing quantities of the maternal diet.

There were no signs of adverse effects throughout the pre-mating period.

One 30 mg/kg female showed a very swollen left eye shortly after commencement of the F_1 generation. This female was sacrificed and the eye was examined by light microscopy. There were no further deaths among females during the pre-mating period.

Pregnancy

There was no indication of any effect of treatment on the outcome of matings.

There were no significant differences in body weight between groups.

There were no signs of adverse effects.

There were no deaths.

Section A6.8.2
Annex Point IIA6.8.2

6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)

Key Study

Parturition and post-partum

There were no significant differences between groups regarding the period of gestation.

There were no significant differences in body weight between groups.

Two females in the control group, two in the 5 mg/kg group and three in the 180 mg/kg group developed mastitis during period of lactation -A. In most, the condition lasted only two or three days. In two of these females in the 180 mg/kg group however, the condition lasted for two or three weeks but with no apparent discomfort. There were no observations of aberrant behaviour or signs to indicate any adverse effects of treatment on the females during the periods of lactation.

There were no deaths during the periods of lactation.

4.1.5 F2 males

At the commencement of the F_2 generation there were statistically significant differences between groups regarding mean body weight. However, the growth curves were similar in all groups and there were no statistical differences regarding % weight gain.

After a sharp rise during the first 5 weeks of the study, all groups maintained a satisfactory but fluctuating food intake.

There were no signs of adverse effects.

There were no deaths.

4.1.6 F2 females

There were no significant differences in body weight between groups.

A sharp rise in food intake observed in all groups at Week 15 reflects the presence of the growing offspring during the period of lactation -A. During this period the offspring consumed increasing quantities of the maternal diet.

One female in the 30 mg/kg group and one female in the 180 mg/kg group showed eye irritation during the pre-mating period. There were no further signs of adverse effects throughout the pre-mating period.

One female in the 5 mg/kg group died in Week 2. Post-mortem examination did not reveal the cause of death. There were no further deaths among females during the pre-mating period.

Pregnancy

There was no indication of any effect of treatment on the outcome of matings.

There were no significant differences in body weight between groups.

There were no signs of adverse effects.

There were no deaths.

Section A6.8.2
Annex Point IIA6.8.2

6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)

Key Study

Parturition and post-partum

There were no significant differences between groups regarding the period of gestation.

There were no significant differences in body weight between groups.

One female in the control group gave birth to 15 dead offspring and subsequently appeared very sick and showed haemorrhage and discharge at the vagina. This female was killed and examined but showed nothing abnormal to indicate the cause of the condition. One female in the 180 mg/kg group showed swelling of the left abdominal mammary gland which subsequently restricted movement of the left hind leg. This female was killed and examination revealed a large abscess in the mammary tissue.

4.2 Other

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Groups of 20 male and 20 female Wistar rats were treated with permethrin in the diet for three generations (P, F_1, F_2) at doses equivalent to 0, 5, 30 and 180 mg/kg/day. Pre-mating dosing periods were 84 days for the P generation, and 63 days for the F_1 and F_2 generations. Each generation was allowed to produce offspring from two matings (F_1A and F_1B from P; F_2A and F_2B from F_1; F_3A and F_3B from F_2). Litters were examined, sexed and weighed, and all litters of more than 8 offspring were randomly culled to 8. Prospective parents to produce the subsequent generation were randomly selected from -B litters between the ages of 21 and 35 days post-partum. Animals selected to produce the next generation were maintained in the dose groups of their origin. Routine observations included body weight, food consumption, general behaviour and well-being, and mortality. The second pregnancy of the F_2 generation was processed as for a foetal toxicity and teratogenicity study.

5.2 Results and discussion

P generation

There was no apparent effect of treatment on body weight of males or females throughout the first generation. On isolated occasions males or females in all groups showed behavioural aberrations of apparently nervous nature but these did not bear any relation to treatment.

Treatment with permethrin apparently had no effect on reproduction. There were no differences between groups regarding the number of births or the survival and growth of the offspring in both -A and -B pregnancies. One female in Group 2 (5 mg/kg) delivered on Day 18 of pregnancy -B but all offspring appeared normal and this litter eventually contributed to the next phase of the study.

Section A6.8.2
Annex Point IIA6.8.2

6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)

Key Study

Anomalies of the eye were observed in all groups at examination of offspring from both pregnancies. These anomalies occurred in a small number of litters and did not occur in the same dams at each pregnancy.

One female in Group 2 (5 mg/kg) exhibited progressive left eye opacity from Week 19. After completing the test-mating procedure, in Week 35, this dam was sacrificed and the eye was removed for histological examination. This dam did not contribute to the next phase of the study (second generation) and so it was not possible to relate this finding genetically to those occurring in the F_1 generation. However, F_1A offspring of this dam did not show eye abnormalities.

Other spontaneous anomalies were observed in pups from all groups in both pregnancies. However, there was no statistical correlation between the incidence of anomalies and treatment with permethrin, either between groups or between -A and -B litters.

F_1 generation

There was no apparent effect of treatment on body weight of males or females throughout the second generation. In contrast to the P generation, there were no signs of aberrant behaviour in either males or females.

There was no apparent effect of treatment on reproduction. There were no differences between groups regarding the number of births or survival and growth of the offspring in both -A and -B pregnancies.

In common with the findings in the P generation, anomalies of the eye were observed in all groups on examination of offspring from both pregnancies. Similarly, these anomalies occurred in a small number of litters and did not occur in the same dams at each pregnancy. Further, there was no apparent familial connection with the dams of those litters which had shown these anomalies in the P generation. One female in Group 3 (30 mg/kg) developed a swollen eye in Week 2 of the F_1 generation. This female was from litter 433 of the P generation -B pregnancy. No other progeny in this litter had exhibited this anomaly when P generation -A or -B offspring were examined.

Other spontaneous anomalies were observed in all groups and at each pregnancy but there were no statistical differences between groups regarding the incidences, nor were there any other remarkable findings common to both sets of weanlings.

Section A6.8.2
Annex Point IIA6.8.2

6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)

Key Study

F_2 generation

The finding of eye abnormalities among F_3A offspring was consistent with similar findings in previous generations (F_1 and F_2).

Two F_2 dams, one in Group 3 (30 mg/kg) and one in Group 4 (180 mg/kg) showed eye irritation during the course of the F_2 generation. Neither had issued from parents with a history of eye problems and there was no observation of eye abnormality in the offspring of these females at –A weanling examination.

At examination of the F_3B foetuses, the observed lower mean foetal weight in Group 3 (30 mg/kg) was not consistent with birth-weight records for neonates in previous pregnancies. In view of this, and since mean foetal weights in Group 4 (180 mg/kg) appeared normal, the finding was considered unrelated to treatment.

Similarly, three litters in Group 4 (180 mg/kg) contained one foetus with brain or cranial abnormality. However, there were no similar findings among neonates in previous pregnancies and these occurrences were considered unrelated to treatment.

General discussion

The only remarkable findings observed, among offspring from all pregnancies and in all generations were a small number of eye abnormalities.

Blood around the eye was observed in pups from all groups and is considered unrelated to treatment.

Unilateral opacity of lens or cornea was observed in some offspring from all groups. Unilateral swelling of the eye was observed in a small number of offspring from the three treatment groups. Histological examination of the affected eye from three animals revealed abnormality of the retina and optic nerve. The findings were indicative of glaucoma. However, since routine histology of the eye was not performed on all offspring it is not possible to report the incidence of the occurrence.

The incidence of the macroscopic findings of glaucoma was very low and was not statistically correlated with treatment.

Examination of the F_3B foetuses did not reveal any foetotoxic or teratogenic effect which could be related to treatment.

5.3 Conclusion

5.3.1 LO(A)EL	> 180 mg/kg (highest dose tested)
5.3.1.1 Parent males	> 180 mg/kg (highest dose tested)
5.3.1.2 Parent females	> 180 mg/kg (highest dose tested)
5.3.1.3 F1 males	> 180 mg/kg (highest dose tested)
5.3.1.4 F1 females	> 180 mg/kg (highest dose tested)

Section A6.8.2 Annex Point IIA6.8.2	**6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)**
	Key Study
5.3.1.5 F2 males	> 180 mg/kg (highest dose tested)
5.3.1.6 F2 females	> 180 mg/kg (highest dose tested)
5.3.2 NO(A)EL	
5.3.2.1 Parent males	180 mg/kg
5.3.2.2 Parent females	180 mg/kg
5.3.2.3 F1 males	180 mg/kg
5.3.2.4 F1 females	180 mg/kg
5.3.2.5 F2 males	180 mg/kg
5.3.2.6 F2 females	180 mg/kg
5.3.3 Reliability	2
5.3.4 Deficiencies	Yes. Duration of exposure before mating was only 63 days for the F_1 and F_2 generations, rather than the guideline 70 days in order to elicit any adverse effects on spermatogenesis by the test substance. However, no indication of any effect on fertility was noted in the P generation which was exposed for 84 days before mating.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*8/12/05*
Materials and Methods	***3.3.6*** *Presumably the TS is mixed directly with the diet - BP RM No.3 expanded breeding diet.*
Results and discussion	*Adopt applicant's version.*
Conclusion	*Adopt applicant's version.*
Reliability	*2*
Acceptability	Acceptable.
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*

Section A6.8.2 Annex Point IIA6.8.2	6.8.2 Multigeneration Reproduction Toxicity Study – oral (rat)
	Key Study
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_8_2-1. Table for reproductive toxicity study

If effects are found in one generation, the figures for the other generation(s) should be given as well. Give only information on endpoints with effects, delete other endpoints.

Generation	Subject	Pregnancy	Finding	Group			
				1	2	3	4
				Permethrin Dose (mg/kg/day)			
				0	5	30	180
P	Adult ♀	A	Corneal opacity	-	402*	-	-
	Offspring		Swollen eye	-	407	-	436
			Corneal opacity	-	-	-	446
			Blood around eye	386	-	423	443
		B	Swollen eye or retinal haem.	-	-	418	446
			Blood around eye	-	396 399	415	-
F_1	Adult ♀	A	Swollen eye	-	-	088*	-
	Offspring		Swollen eye	-	-	075	100
			Lens opacity	038	050 062	-	-
			Blood around eye	035 038	064	078	-
		B	Swollen eye	-	-	-	097 105
			Blood around eye	038 042 046 047	057	076	089
F_2	Offspring	A	Swollen eye or retinal haem.	833	862 855	-	907*
			Lens opacity	-	862	-	-
			Blood around eye	834 841	852 853 864 866 867	876 880 883	896

* Histology reported.

The numbers reported in the table are the individual numbers of affected animals

Appendix 1 to Doc III-A6

Bayer Environmental Science is a an affiliated company of Bayer CropScience, therefore the studies submitted by Bayer Environmental Science are owned by Bayer CropScience AG.

Reference List Doc. III-A6. sorted by reference no.

Section No/ Reference No	AUTHOR (S)	Year	Title. Source, Report No. GLP /(Un) Published	Data Protection Claimed (Yes/No)	Owner
6,1,1(1)	[redacted]	1975	Acute Oral Toxicity in Rats with Compound FMC 33297. [redacted] Report No. 2739-75 (Unpublished)	Yes	Sumitomo Chemical
6,1,1(2)	[redacted]	1974	Comparative Acute Oral Toxicity in Mice with FMC 33297, FMC 37400, FMC 35171 and FMC 30960. [redacted] Report No. HEFG 79-C76 (Unpublished)	Yes	Sumitomo Chemical
6,1,2	[redacted]	1975	Acute Dermal Toxicity in Rabbits. Compound FMC 33297. [redacted] Report No. 2908-75 (Unpublished)	Yes	Sumitomo Chemical
6,1,3	[redacted]	1976	Acute Inhalation. Compound No. FMC 33297. [redacted]. Report No. 2911-75 (Unpublished)	Yes	Sumitomo Chemical
6,1,4(1)	[redacted]	1975	Rabbit Eye Irritation. Compound No. FMC 33297. [redacted]. Report No. 2910-75 (Unpublished)	Yes	Sumitomo Chemical
6,1,4(2)	[redacted]	1975	Rabbit Primary Dermal Irritation. Compound No. FMC 33297. [redacted]. Report No. 2909-75 (Unpublished)	Yes	Sumitomo Chemical
6,1,5	[redacted]	1991	Skin Sensitisation in the Guinea Pig of a Permethrin 25/75 cis/trans Isomer RatioThe [redacted]. Report No. 91626D/WLC 159/SS	Yes	Sumitomo Chemical
6,2 (1)	Gaughan LC, Unai T & Casida JE	1977	Permethrin Metabolism in Rats; Department of Entomological Sciences, University of California, Berkeley, California 94720, USA; J. Agric. Food Chem., Vol. 25, No. 1, pp 9-17; 1977.	No	

6,2	Bartelt, N. & Hubbell, J.	1987	Percutaneous Absorption of Topically Applied 14C-Permethrin in Volunteers. Final Medical ReportBurroughs Wellcome Co. Report No. THRD/86/0047	Yes	Sumitomo Chemical
6,3,3	[redacted]	1980	Permethrin Technical. Inhalation Study in Rats – 16 x 6 Hour Exposures Over a 3 Week Period. [redacted]. Report No. WLC34/80323.	Yes	Sumitomo Chemical
6,4,1 (1)	[redacted]	1975	21z73, Rat Oral 90 Day Study. [redacted]. Report No. HEFG 76-1 (Unpublished)	Yes	Sumitomo Chemical
6,4,1 (2)	[redacted]	1978	Permethrin Oral Administration to Dogs for 6 Months. [redacted]. Report No. HEFG 78-14	Yes	Sumitomo Chemical
6,5 (1)	[redacted]	1980	21z: Potential Toxicity and Oncogenicity in Dietary Administration to Rats for a Period of 104 weeks. [redacted]. Report No. 80/WRL003/283 (Unpublished)	Yes	Sumitomo Chemical
6,5 (2)	Ishmael, J. & Litchfield, M.H.	1988	Chronic Toxicity and Carcinogenic Evaluation of Permethrin in Rats and Mice. Fundamental and Applied Toxicology. Vol. 11. pp308-322	No	N/A
6,6,1	Haworth SR	1979	Salmonella/Mammalian-Microsome Plate Incorporation and Pre-Incubation Mutagenesis Assays of Burroughs Wellcome Compound Permethrin Tech BW 0021Z73 #8E8026 and 8I8012; EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland 20852, USA; unpublished Report (Study) No. 015-560-150A-1 and 015-560-150A-2; 16.10.1979.	Yes	Sumitomo Chemical
6,6,2	Barrueco, C. et al	1994	Induction of structural chromosomal aberrations in human lymphocyte cultures and CHO cells by permethrin. Teratogenesis, Carcinogenesis, and Mutagenesis 14:31-38.	No	N/A
6,6,3	Clive, D.	1977	Mutagenicity of BW 21z73 in L5178Y/TK+/- Mouse Lymphoma Cells With and Without Exogenous Metabolic ActivationThe Wellcome Foundation Ltd. Report No. TTEP/77/0001	Yes	Sumitomo Chemical
6,6,4	[redacted]	1997	Micronucleus Test of Permethrin Technical in Mice. [redacted] Report No. 1270/JRF/TOX/97. (Unpublished)	Yes	Bayer CropScience AG

6,6,5	[redacted]	1997	Chromosomal Aberration Study of Permethrin Technical in Mice	Yes	Bayer CropScience AG
6,6,6	[redacted]	1975	21z73 Dominant Lethal Study in Male Mice. [redacted]. Report No. HEFG 75-10 (Unpublished)	Yes	Sumitomo Chemical
6,7 (2)	Ishmael, J. & Litchfield, M.H.	1988	Chronic Toxicity and Carcinogenic Evaluation of Permethrin in Rats and Mice. Fundamental and Applied Toxicology. Vol. 11. pp308-322	No	N/A
6,7 (1)	[redacted]	1980	21z: Potential Toxicity and Oncogenicity in Dietary Administration to Rats for a Period of 104 weeks. [redacted]. Report No. 80/WRL003/283 (Unpublished)	Yes	Sumitomo Chemical
6,8,1 (1)	[redacted]	1974	Foetal Toxicity of 21z73 (NRDC 143) in the Rat. [redacted] Report No. BPAT 74/10 (Unpublished)	Yes	Sumitomo Chemical
6,8,1 (2)	[redacted]	1979	21z: Effects of Oral Administration upon Pregnancy in the Rabbit. [redacted] Report No. HEFG 80-4.	Yes	Sumitomo Chemical
6,8,2	[redacted]	1979	A Multigeneration Reproduction Study of 21z73 (Permethrin) in the Rat. [redacted] No. BPAT 79/3.	Yes	Sumitomo Chemical
6,9	[redacted]	1997	Motor activity measurements in male and female mice postnatally exposed to Permethrin by inhalation; [redacted] unpublished Report No. 26418; 03.07.1997.	Yes	Sumitomo Chemical
6,13	[redacted]	1978	Permethrin Oral Administration to Dogs for 6 Months. [redacted] Report No. HEFG 78-14	Yes	Sumitomo Chemical

Competent Authority Report

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

Permethrin (PT 8)

CAS-No. 52645-53-1

DOCUMENT IIIA (A6)

Evaluation Report

Bayer Environmental Science

Sumitomo Chemical (UK) Plc.

Rapporteur: Ireland

August 2009

Permethrin PT8

Document IIIA (A6)

CONTENTS

Section A6.9 6.9(1) Neurotoxicity in the mouse

Annex Point IIA6.9

Key Study

		Official use only
	1 REFERENCE	
1.1 Reference	[redacted]; 1997; Motor activity measurements in male and female mice postnatally exposed to Permethrin by inhalation; [redacted]; unpublished Report No. 26418; 03.07.1997.	
1.2 Data protection	Yes	
1.2.1 Data owner	Sumitomo Chemical (UK) PLC	
1.2.2 Companies with letter of access	Bayer Environmental Science	
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; no guidelines available.	
2.2 GLP	Yes	
2.3 Deviations	Yes; the computer software for the motor activity measurements was tested with positive control compounds but not validated according to GLP requirements.	
	3 MATERIALS AND METHODS	
3.1 Test material	As given in section 2	
3.1.1 Lot/Batch number	Batch No. 1409035	
3.1.2 Specification	As given in section 2	
3.1.3 Description	Clear to pale brown viscous liquid/semi liquid	
3.1.4 Purity	96.8%	
3.1.5 Stability	The stability of the test substance in the vehicle was confirmed analytically in regular intervals.	
3.2 Reference Substance (positive control)	Not applicable	
3.3 Test Animals		
3.3.1 Species	Mouse	
3.3.2 Strain	NMRI	
3.3.3 Source	[redacted]	
3.3.4 Sex	Male and female	
3.3.5 Rearing conditions	Not applicable (applicable to hen studies)	
3.3.6 Age/weight at study initiation	Pups 9 days of age	

Section A6.9 **6.9(1) Neurotoxicity in the mouse**

Annex Point IIA6.9

	Key Study	
3.3.7 Number of animals per group	80	
3.3.8 Control animals	Yes	
3.4 Administration/ Exposure	Inhalation	
3.4.1 Postexposure period	10 days	X
	Inhalation	
3.4.2 Concentrations	Nominal concentration 2.5, 25, 250..... [mg/m³]	
	Analytical concentration 2.7, 25.2, 204.6 [mg/m³]	
3.4.3 Particle size	MMAD (mass median aerodynamic diameter) 1.8, 1.9, 1.7 [µm] ± GSD (geometric standard deviation) 1.8, 2.0, 1.9 [µm]	
3.4.4 Type or preparation of particles	Not applicable	
3.4.5 Type of exposure	Whole body	
3.4.6 Vehicle	Polyethylene glycol 400	
3.4.7 Concentration in vehicle	The maximal stable concentrations of test compound in the vehicle (@ ca. 50°C) were determined to be 0.75, 5.4 and 36.5% w/v for the low, medium and high dose groups, respectively.	
3.4.8 Duration of exposure	6.3 hours per day for 7 consecutive days	
3.4.9 Controls	Yes	
3.5 Examinations		
3.5.1 Body Weight	The body weights of the experimental animals were recorded on-line at their age 10, 12, 14 and 17 days. The young mice of the second motor activity measurement were weighed on-line and their data recorded by computer beginning with study week 2 (age of mice 3 weeks).	
3.5.2 Signs of Toxicity	Any clinical signs (findings) and abnormalities were recorded. Detailed examination of individual animals was performed. The body surfaces, orifices, posture, general behaviour, respiration and excretory products were carefully examined, with any significant findings being registered. Measurements of spontaneous motor activity (horizontal activity (HA), number of movements (NM), number of stereotypies (NS), total distance (TD), vertical activity (VA), vertical time (VT), movement time (MT), and stereotypy time (ST)) of mice (number of animals per group 19-20).	

Section A6.9 **6.9(1) Neurotoxicity in the mouse**

Annex Point IIA6.9

Key Study

3.5.3 Observation schedule	The experimental animals were inspected twice daily before and after the inhalation period for the first 7 study days. After termination of inhalation exposure all animals were inspected at least twice daily (once daily at weekends and bank holidays). Detailed examination of individual animals was performed once a week. Measurements of spontaneous motor activity of mice were evaluated at the age of 17 days and 4 months.
3.5.4 Clinical Chemistry	Yes Number of animals: 20 Time points: age 17 days (young), age 4 months (adult) Parameters: Acetyl cholinesterase activity Choline acetyltransferase activity Binding studies of the muscarinic acetylcholine receptor
3.5.5 Pathology	No Organs:
3.5.6 Histopathology	No Organs:
3.6 Further remarks	
	4 RESULTS AND DISCUSSION
4.1 Body Weight	No treatment related effects on body weight of young mice were seen during the inhalation period. The statistical evaluation of body weights (weeks 2 to 14) after the end of the inhalation period indicates that male and female mice of the treatment groups lay, sometimes statistically significantly, above the mean body weights of the control groups. The weight difference between the treatment groups and the controls started in week 2 (20 animals per group), while during treatment no obvious difference existed between groups (40 animals per group). The difference in body weight starting in week 2 of the study can be attributed to the reduction in number of animals per group from 40 to 20 due to the random selection of 5 litters per group for biochemical investigations on day 8 of the study (mice age 17 days) [biochemical investigations were performed after measuring motor activity]. It is concluded that no treatment related difference in body weights existed throughout the study.

Section A6.9 **6.9(1) Neurotoxicity in the mouse**

Annex Point IIA6.9

Key Study

4.2 Clinical signs of toxicity

Mortality

Animal number 213 died after falling off the table during the study. Animals number 265 and 292 were cannibalised.

Clinical signs

During the course of the study no treatment related clinical signs were seen in the mice.

4.3 Clinical Chemistry

Changes in the muscarinic acetylcholine receptor (mAchR) behaviour in the brain just after dosing the animals with permethrin (17 days) could be determined with the specific binding capacity by atropine and with replacement curves using Carbachol. In the low dose group (2.5 mg/m^3), a significant increase of the mAchR occurred in both sexes, whereas in the intermediate group (25 mg/m^3) this effect changed to the opposite also in both sexes. Only in the high dose group (250 mg/m^3) were sex differences observed. In the female group, a slight decrease of the mAchR was obvious, but in the male mice, an additional increase of the receptor density occurred again.

After 4 months, the specific binding efficiency with QNB to the mAchR was unchanged in all dose groups in the male. In the females the intermediate and high dose groups showed a significant reduction of the receptors.

The displacement curves with QNB/Carbachol reflected the same effects seen in the determination of the specific binding. In young mice, an enhancement of the receptor density was produced by low concentrations of permethrin (2.5 mg/m^3) in both sexes, whereas in the intermediate dose group (25 mg/m^3) this effect changed to the opposite. The high dose group (250 mg/m^3) resulted in contrasting results for the sexes. In male mice, the receptor behaviour was like the low dose group, whereas in the female mice, a slight reduction of the receptor became obvious. However, in the adult animals, no changes occurred in the male mice and in the female mice only the high dose group was affected. Here, a significant decrease of the mAchR was observed.

The determinations of the two cholinergic enzymes acetyl cholinesterase and choline acetyltransferase remained at the control level.

In summary, a treatment with high dosages of a type I (no cyano group) pyrethroid (permethrin) over 7 days during the brain growth spurt, resulted in acute changes of the mAchR.

4.4 Pathology

Not applicable.

4.5 Histopathology

Not applicable.

Section A6.9 **6.9(1) Neurotoxicity in the mouse**

Annex Point IIA6.9

Key Study

4.6 Other

Measurement of Spontaneous Motor ActivityMeasurement at the age of 17 daysNo statistically significant effect of treatment or treatment over time was seen in mice age 17 days. In some, the vertical activity (VA), and vertical time (VT) tested in young mice a non-significant difference of groups compared to control can be seen (males middle dose only; females all dose groups). The parameters VA and VT recorded at this age show relatively high variations since mice are too small to interrupt the vertical sensors by rearing. Since there are no statistically significant effects seen and since the other parameters including horizontal activity are not changed compared to controls it is concluded that no effect of treatment with permethrin is seen in the mice at age 17 days.

Measurement at the age of 4 monthsIn male mice the analysis of the parameter horizontal activity (HA) indicated a significant effect of treatment over time ($p < 0.01$). Post hoc analysis (t-test, LSD) revealed that the control group was significantly different to the dose group 25 mg/m3 (linear trend). This dose group was marginally below the control but close to the mean of historical control data pooled from 119 male mice. Since the difference seen is small and only seen in the dose group 25 mg/m3 it can be concluded that there is no effect of treatment with permethrin in horizontal activity in male mice. The horizontal activity data of female mice indicates a higher activity in the highest dose group and possibly at the two latest time points investigated (50 and 60 minutes) for the two lowest dose groups 2.5 and 25 mg/m3. The statistical analysis of the treatment effect shows that the effect is close to significance.

The vertical activity of male mice exposed to 2.5, 25, or 250 mg/m^3 permethrin was higher comparing group means to the control with the highest dose above the other groups. Statistical analysis showed that the treatment effect was statistically significant ($p<0.05$). Post hoc analysis showed that the highest dose group 250 mg/m^3 was different to control. In females a similar tendency can be seen but no statistical significance is reached. Although the effects in male and female mice are not or only at a low level statistically significant it is possible that the increase of the vertical activity in the highest dose is induced by treatment with permethrin at the age of 10 to 16 days. Whether the medium and low dose are affected by treatment cannot be excluded with the present data set.

In addition to the described effects the parameter VT of males showed a significant effect of treatment ($P<0.05$). Post hoc analysis showed that the medium and highest dose is different to control.

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The parameters NM (treatment over time), and ST (treatment over time) were also statistically significant in the male mice. Post hoc analysis showed that for NM the dose groups 2.5 and 25 mg/m3 were different from each other. No difference to control existed. For ST the control group was different to the group treated with 25 mg/m3.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 MATERIALS AND METHODS

A study was conducted to investigate the effect of inhalation of permethrin during the phase of rapid brain development in mice on motoric activity and muscarinic acetylcholine receptors. Groups of dams with their pups were exposed to target concentrations of 0 (vehicle control), 2.5, 25, and 250 mg/m^3 of permethrin for 6.3 hours per day over seven consecutive days. Analytical monitoring of the aerosol test atmosphere from the breathing zone indicated that the exposure conditions were stable over the exposure period.

The spontaneous motor activity of 20 young and additional 20 adult mice per dose and sex was measured at age 17 days and 4 months (the latter to investigate possible lasting changes). Binding studies of the muscarinic acetylcholine receptor were used to investigate the possible effects of permethrin on postnatal brain development. Additionally, measurements of the cholinergic enzyme activities were performed, to exclude effects due to alteration of the acetylcholine content in the brain.

5.2 RESULTS AND DISCUSSION

Characterisation of the test atmosphere revealed actual concentrations of 0, 2.7, 25.2, and 204.6 mg/m^3.

The inhalation of the test compound for 6.3 hours on 7 consecutive days did not induce any treatment related clinical symptoms typical for pyrethroids. The body weight of the mice was not influenced by treatment throughout the course of the study. No animal died in relation to treatment with permethrin.

The results of the measurements of spontaneous motor activity at the age of 17 days did not indicate treatment related effects in the eight parameters investigated: horizontal activity (HA), number of movements (NM), number of sterotypies (NS), total distance (TD), vertical time (VT), vertical activity (VA), movement time (MT), and stereotypy time (ST).

In male mice the horizontal activity (HA) revealed that the control group was significantly different to the dose group 25 mg/m^3 at the age of 4 months. This dose group was marginally below the control but close to the mean of historical control data pooled from 119 male mice. Since the difference seen was very small and only seen in this group it can be concluded that there is no effect of treatment with permethrin on horizontal activity in male mice. The horizontal activity

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(HA) data of adult female mice indicated no statistically significant increase of activity although the highest dose group had higher activity counts compared to control. A similar observation was made in the other treatment groups at the two latest time points; the differences, however, are not at a statistically significant level.

The vertical activity (VA) of male mice was higher comparing group means of the treatment groups to control. Statistical analysis showed that the highest dose group 250 mg/m^3 was different to control. In females a similar tendency could be seen but no statistical significance was reached. Although the effects in male and female mice were not, or only at a low level, statistically significant, it is likely that the increase of the vertical activity in the highest dose is induced by treatment with permethrin at the age of 10 to 16 days. Whether the medium and low dose groups are affected by treatment cannot be decided with the present data set.

In addition to the described effects the parameter vertical time (VT) of males showed that the medium and highest dose were different to control. For the parameter number of movements (NM) analysis showed that the dose groups 2.5 and 25 mg/m^3 were different from each other; no difference to control existed. For stereotypy time (ST) the control group was different to the group treated with 25 mg/m^3.

Changes in the muscarinic acetylcholine receptor (mAchR) in the brain just after exposure (mice age 17 days) could be determined. At the age of 4 months, the specific binding with [^{3}H] quinuclidinyl bencyclate (QNB) to the mAchR was unchanged in all dose groups in male mice. In the females the intermediate and high dose groups showed a significant reduction of receptors. Therefore the NOEL at age 4 months for receptor changes is 250 mg/m^3 in male mice and 2.5 mg/m^3 in females..

5.3 CONCLUSION

5.3.1 LOAEL 25 mg/m^3 (based on receptor changes at age 4 months in females)

5.3.2 NOAEL 2.5 mg/m^3

5.3.3 Reliability 2

5.3.4 Deficiencies Yes.

From the data described above it cannot be excluded that permethrin did influence the spontaneous motor activity of mice at the age of 4 months in the highest dose of 250 mg/m^3. The changes in the two lower dose groups, which were mostly not statistically significant, may have occurred due to spontaneous variations between groups. To clarify this question an additional experiment with lower doses is suggested.

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	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*14/12/05*
Materials and Methods	***3.4.1*** *Postexposure period was either 1 day (for half of the animals) or approx 14 week later for the other half of the animals (when they were 4 months of age).*
Results and discussion	*Adopt applicant's version.*
Conclusion	*Adopt applicant's version.*
Reliability	*2*
Acceptability	*Acceptable.*
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6.9-1(3). Table for neurotoxicity in the mouse

Specify lesions and effects in type and severity, if any

Cortex (17 days)

	male mean/%	Stddev./%	female mean/%	Stddev./%
control	100	6,8	100	6,66
2.5mg/m3	**124,9	3,9	**129,28	6,08
25 mg/m3	**70,77	5,75	**81,42	9,32
250 mg/m3	**128,23	6,22	*88,62	7,63

Cortex (4 month)

	male mean/%	Stddev./%	female mean/%	Stddev./%
control	100	9,79	100	6,59
2.5 mg/m3	107,23	9,11	92,05	8,95
25 mg/m3	90,94	10,31	**74,92	9,58
250 mg/m3	98,54	9,12	**56,11	11,16

** = p< 0.001 Man Whittney U-test

Tab. 1: Determination of the total amount of the muscarinic receptor in young and adult mice after treatment withPermethrin. The amount of the muscarinic receptors was determined by QNB. The specific binding was quantified by the substraction of the remain dpm after replacing the radioactive QNB by atropin. N = 10 male mice

Section A6.9 Annex Point IIIA1	**A6.9(2) Developmental neurotoxicity study**	
	Justification for non-submission of data	Official use only
Other existing data [ ] **Limited exposure** [ ]	**Technically not feasible** [ ] **Scientifically unjustified** [ ] **Other justification** [ ]	
Detailed justification:	The effects of permethrin on motor activity and muscarinic acetylcholine receptors has been submitted (Ivens et al., 1997). However, this study is of very limited interest based on the following: • this study was conducted in order to investigate potential effects following some published results from Per Eriksson et al. However, the interpretation and relevance of muscarinic receptor measurements to human is still unclear. • the tested species was the mouse. In a Special Meeting of the Working Group "Pesticides - Evaluation" held by the European Commission in Brussels on 19th June 2002 to discuss questions related to developmental neurotoxicity, the testing of rats and mice was considered. However, the minutes of this meeting state that "This proposal is largely rejected. The rat should be the preferred species for many reasons, which are also cited in the OECD-Guideline 426". The rat is the species of choice for the conduct of toxicity studies and most specifically for neurotoxicity, neurobehavioral and neuropathological assessment. In addition, the availability of historical control data in the rat for various toxicological endpoints including developmental neurotoxicity is of great importance when selecting an animal species for testing. • the mode of administration was via inhalation. Owing to the nature of permethrin wood preservation uses, this is not a relevant route of exposure for children. Exposure of children to permethrin would occur via contact with treated timber according to the following scenarii: Child playing on preserved timber equipment. This would result to a potential chronic exposure via dermal contact. This should only concern children aging from around 18 months to 2 years old and above. However, the levels of exposure are expected to be very low; (5.33×10^{-4} mg/kg bw based on very conservative exposure scenario with worse case assumptions involved.)	

Section A6.9 Annex Point IIIA1	**A6.9(2) Developmental neurotoxicity study**	
	Justification for non-submission of data	Official use only
Other existing data [ ] **Limited exposure** [ ]	**Technically not feasible** [ ] **Scientifically unjustified** [ ] **Other justification** [ ] Infant chewing preserved timber off-cuts would result in an acute exposure via the oral route. It is unlikely that this scenario will occur before a child is able to crawl i.e. around 6 months of age; Infant playing on a weathered treated timber surface and making mouthing contacts with the treated timber. Such an exposure is unlikely to occur before 6 months old and would potentially be chronic through both dermal and oral routes. The levels of exposure are also expected to be very low. ($8.8x10^{-3}$ mg/kg bw based on very conservative exposure scenario with worse case assumptions involved.) The inhalation of volatile residues from treated timber is unlikely since permethrin is not volatile. Available data from DNT studies conducted with other pyrethroids including type I (transfluthrin) and type II (deltamethrin, beta-cyfluthrin) pyrethroids indicate that there is no concern for developmental neurotoxic effects. The offspring No Observed Adverse Effect Levels (NOAEL) derived from these studies are the following: - Deltamethrin: 6.78 to mg/kg bw/day based on decreased body weight and body weight gain, and delayed balanopreputial separation at the next higher dose. [redacted] (2006)[1]. Summary available in annex I of the justification - Beta-cyfluthrin: 11 mg/kg bw/day based on decreased body weight and startle response reduction at the next higher dose. [redacted] (2003)[2]. Summary available in annex I of the justification - Transfluthrin: 161 mg/kg bw/day in the case of transfluthrin based on decreased bw and bw gain at the next higher dose. [redacted] (2007)[3]Summary available in annex I of the justification	

Section A6.9 Annex Point IIIA1	A6.9(2) Developmental neurotoxicity study	
	Justification for non-submission of data	Official use only
Other existing data [ ] **Limited exposure** [ ]	**Technically not feasible** [ ] **Scientifically unjustified** [ ] **Other justification** [ ] These effects reported in the offspring for these active ingredients were observed only at doses where clear maternal toxicity was evident and it was concluded that there was no potential for developmental neurotoxicity. These studies account for potential direct exposure of infants/toddlers/children through the oral route i.e. milk from maternal origin or from formula, via gradual consumption of food and via potential incidental exposure to biocidal products. Therefore, since a/potential exposure of infants and children to permethrin treated timber would result in very low levels of exposure and b/other data available for type I and type II pyrethroids have shown no concern for developmental neurotoxic effects, a DNT study for permethrin is not required. Reference : 1) [redacted](2006) ; A Developmental Neurotoxicity Screening Study with Technical Grade Deltamethrin in Wistar Rats, [redacted]– USA,Report Number 201469 6.9.3/0103 April 2006.Unpublished Submitted in the deltamethrin dossier to Sweden, the RMS on 28th April 2006 2) [redacted]. (2003) ; A developmental Neurotoxicity sceening study with technical beta-cyfluthrin in wistar rat, Bayer CropScience, Toxicology, [redacted]. Report-No. 200620, BES Ref : M-103213-01-1, 29 July 2003, unpublished Submitted in the cyfluthrin dossier to Germany, the RMS on 6th April 2006 3) [redacted](2007), A developmental neurotoxicity study with technical grade transfluthrin in Wistar rats, [redacted]; Report No. 201619 [BES Ref: M-285100-01-1], Report date: February 16, 2007, Unpublished Submitted in the transfluthrin dossier to The Netherland, the RMS on 6th April 2006	

Section A6.9 **Annex Point IIIA1**	**A6.9(2) Developmental neurotoxicity study**	
	Justification for non-submission of data	Official use only
Other existing data [ ]	**Technically not feasible** [ ] **Scientifically unjustified** [ ]	
Limited exposure [ ]	**Other justification** [ ]	
Undertaking of intended data submission [ ]	*Give date on which the data will be handed in later (Only acceptable if test or study is already being conducted and the responsible CA has agreed on the delayed data submission.)*	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	Evaluation by Rapporteur Member State	
Date	21 May 2009	
Evaluation of applicant's justification	The applicant has referenced DNT studies on 3 pyrethroids other than permethrin as part of the justification for non-submission. This approach appears justified as pyrethroids have similar toxicities. In the referenced studies effects in offspring appear to occur at maternally toxic doses and NOAELs are higher than those seen in some of the sub-chronic and chronic studies (12 month dog). In addition a mouse DNT study (Farag et al. 2006) is available in the literature. This study reports a maternal and developmental NOAEL of 4.9 mg/kg bw/d and concludes "although permethrin can produce behavioural alterations in F1 mice at toxic doses (9.8 and 19.6 mg/kg bw/d). These behavioural effects are most likely due to maternal toxicity and stunt of growth of the pups rather than the neurotoxicity of permethrin". Deltamethrin, beta-cyfluthrin and transfluthrin are stucturally similar to permethrin but contain the alpha-cyano substituent in the 3-phenoxybenzyl alcohol moiety. This groups enhances insecticidal activity and is also expected to enhance acute neurotoxicity. Thus, these substances may be seen as a worst case regarding neurotoxicity when compared to permethrin. The $AEL_{MEDIUM/LONG-TERM}$ has been derived form the 12 month dog study (NOAEL 5 mg/kg bw/d) and is set at 0.05 mg/kg bw/day. This value is equal or lower than the values derived from DNT studies.	
Conclusion	The applicants justification for non-submission is acceptable.	
Remarks		
	Comments from other Member State *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Annex I

[redacted] (2006) A Developmental Neurotoxicity Screening Study with Technical Grade Deltamethrin in Wistar Rats

The principal objective of this developmental neurotoxicity study, of which the rat is the preferred test species, was to investigate the potential for technical grade deltamethrin to produce functional and morphological effects on the nervous system of offspring from oral (dietary) exposure during pregnancy and lactation.
Technical grade deltamethrin (98.8-99.6%) was administered via the diet from gestation day (GD) 6 through lactation day (LD) 21 to mated female Wistar rats at nominal concentrations of 0, 20, 80 and 200 ppm, with adjustments during lactation to maintain a more consistent dosage throughout exposure. All test diets (including control) were provided for *ad libitum* consumption throughout the study, except during neurobehavioral testing. Concentration in the diet, as well as the homogeneity and stability of deltamethrin in the dietary ration, was confirmed.
On postnatal day (PND) 4, litters with a minimum of seven pups, including at least three per sex, were culled to yield, as closely as possible, four males and four females. Subsets of surviving offspring, representing at least 20 litters per level, were subjected to evaluation using the following observations and measurements: detailed clinical observations and a functional observational battery, preputial separation or vaginal patency, body weight, automated measures of activity (figure-eight maze), auditory startle habituation, learning and memory (passive avoidance after weaning and a water maze task beginning on PND 60±2 days) and an ophthalmic examination. Neural tissues were collected from 10/sex/dietary level (representing approximately 20 litters) on PND 21 (brain only) and at study termination (approximately 75 days of age) for microscopic examination and morphometry.
The mean daily intake of the test substance (mg deltamethrin/kg bw/day) based on the average dietary consumption for the last two weeks of gestation and three weeks of lactation at nominal dietary concentrations of 20, 80 or 200 ppm, respectively, was 0, 1.64, 6.78 and 16.1 mg/kg bw/day.
Treatment-related effects attributed to exposure to deltamethrin were as follows:

Maternal

20 ppm - There were no treatment-related findings during gestation or lactation.
80 ppm - There were no treatment-related findings during gestation or lactation.
200 ppm - Body weight (6-7%) and body weight gain (17%) were significantly decreased from GD 13 through GD 20 and body weight was significantly reduced (6-8%) from LD 0 through LD 7. Food consumption was significantly decreased on GD 6-13 (17%) and on LD 0-7 (9%).
Thus, the maternal LOAEL is 16.1 mg/kg bw/day, based on decreased body weight, weight gain and food consumption during gestation and decreased body weight and food consumption during lactation. The maternal NOAEL is 6.78 mg/kg bw/day.

Offspring

20 ppm - There were no treatment-related findings.
80 ppm - There were no treatment-related findings.
200 ppm - Significantly reduced pre-weaning body weight (maximum 10%) and weight gain (maximum 18%) that began on PND 4 and persisted through four weeks after weaning in males (maximum 8%) and through one week after weaning in females (7%). Increased incidence of vocalizations with handling in males on PND 4. In addition, there was a statistically-significant delay in balanopreputial separation, compared to concurrent controls (45.1 days vs. 43.5 days for controls).
Thus, the offspring LOAEL is 16.1 mg/kg bw/day, based on delayed balanopreputial separation, reduced body weight and weight gain before weaning for both sexes, with recovery after weaning. The offspring NOAEL is 6.78 mg/kg bw/day.

[redacted] **(2003), A developmental Neurotoxicity sceening study with technical beta-cyfluthrin in wistar rat**

Technical-grade beta-cyfluthrin was administered via the diet from gestation day (GD) 0 through lactation day (LD) 21 to mated female Wistar rats, at nominal concentrations of 0, 30, 125 and 200 ppm.

Brain tissues were assayed for beta-cyfluthrin in the dams on LD 21 and in the offspring on postnatal day (PND) 4 and PND 21. The offspring were evaluated using detailed clinical observations, body weight, body temperature, food consumption, developmental landmarks for sexual maturation, automated measures of activity (the figure-eight maze), acoustic startle habituation, learning and memory (passive avoidance and a water maze task), and an ophthalmic examination. Tissues were collected for morphometry and microscopic examination on PND 21 (brain) and at study termination (brain, an assortment of additional neural tissues and skeletal muscle).

Based on analytical results, the average concentrations of beta-cyfluthrin in the diet were 0.0, 29.0, 133 and 215 ppm and the average daily intake of active ingredient was as follows :

Gestation: 0, 2.4, 11.0 and 17.8 mg/kg/day, respectively; and

Lactation: 0, 5.9, 25.4 and 40.9 mg/kg/day, respectively.

There were no effects on reproduction parameters at any dietary level. Beta-Cyfluthrin was detected in brain tissue from the dams (LD 21) and the offspring (PND 4 and 21) at all dietary levels, providing clear evidence of exposure during postnatal development.

Effects on dams were limited to decreased body weight during gestation and lactation and decreased food consumption during lactation at 200 ppm

Effects on offsprings were limited to decreased body weight during lactation and after weaning at 200 ppm, with complete recovery of females and incomplete recovery of males by study termination, and decreased startle amplitude in males at the end of exposure on PND 22

The present study established an overall NOAEL of 125 ppm in maternal animals, based on decreased body weight and food consumption. For the offspring, 125 ppm was a NOEL, based on decreased body weight in both sexes during lactation and after weaning

[redacted] **(2007), A developmental neurotoxicity study with technical grade transfluthrin in Wistar rats**

The principal objective of this developmental neurotoxicity study was to investigate the potential for technical grade transfluthrin to produce functional and morphological effects on the nervous system of offspring from oral (dietary) exposure during pregnancy and lactation. Technical grade transfluthrin was administered via the diet from gestation day (GD) 6 through lactation day (LD) 21 to mated female Wistar rats at nominal concentrations of 0, 500, 2000 and 7000 ppm, with adjustments during lactation to maintain a more consistent dosage throughout exposure. All test diets (including control) were provided for *ad libitum* consumption throughout the study, except during neurobehavioral testing. Concentration in the diet, as well as the homogeneity and stability of deltamethrin in the dietary ration, was confirmed.

On postnatal day (PND) 4, litters with a minimum of seven pups, including at least three per sex, were culled to yield, as closely as possible, four males and four females. Subsets of surviving offspring, representing at least 19-20 litters per dietary level, were subjected to

evaluation using the following observations and measurements: detailed clinical observations and a functional observational battery, preputial separation or vaginal patency, body weight, automated measures of activity (figure-eight maze), auditory startle habituation, learning and memory (passive avoidance after weaning and a water maze task beginning on

PND 60±2 days) and an ophthalmic examination. Neural tissues were collected from 10/sex/dietary level (representing 20 litters) on PND 21 (brain only) and at study termination (approximately 75 days of age) for microscopic examination and morphometry. The mean daily intake of the test substance (mg transfluthrin/kg bw/day) based on the average dietary consumption for the last two weeks of gestation and three weeks of lactation at nominal dietary concentrations of 20, 80 or 200 ppm, respectively, was 0, 42.1, 161 and 534 mg/kg bw/day.

Treatment-related effects attributed to exposure to transfluthrin were as follows:

Maternal

500 ppm - There were no treatment-related findings during gestation or lactation.

2000 ppm - There were no treatment-related findings during gestation or lactation.

7000 ppm - There were no treatment-related findings during gestation or lactation. Bodyweight gain during gestation was reduced 10% compared to controls and bodyweight was statistically reduced (6% maximum) on LD0, 4 and 7. These differences from control were ascribed to palatability and were not considered an adverse effect.

Thus, the maternal NOAEL is 534 mg/kg bw/day.

Offspring

500 ppm - There were no treatment-related findings.

2000 ppm - There were no treatment-related findings.

7000 ppm - Bodyweight was statistically decreased (9%) in females on PND 11. Bodyweight gain was statistically decreased on PND 4-11 in females and combined males and females (11% and 10%, respectively). Also, bodyweight gain was statistically decreased 8-9% on PND 4-21 in males and females.

Thus, the offspring NOAEL is 161 mg/kg bw/day, based on decreased bodyweight in PND 11 females, reduced bodyweight gain on PND 4-11 in females and in combined males and females and on PND 4-21 in both sexes and combined sex that were observed at 534 mg/kg bw/d (= offspring LOEL). These effects at the highest dose level were associated with decreased bodyweight in the dams, compared to controls.

Transfluthrin is not a developmental neurotoxicant when administered at the highest tolerated dose (7000 ppm = 534 mg/kg bw/day) to pregnant rats from GD6 to LD 21.

Section A6.10	6.10 Mechanistic study	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [X]	
Detailed justification:	The toxicity of permethrin in particular and pyrethroids in general has been extensively studied in several species. Furthermore, the mechanisms of toxicity and the metabolic fate of permethrin have been summarised by several international organisations (for example Environmental Health Criteria 94: Permethrin. IPCS. World Health Organisation). Further mechanistic studies are only required if, according to the guidance, effects reported in toxicity studies need clarification. Several further references have been provided and summarised in IUCLID Section 5.9 (Dayan AD & Creasy DM; 1976, Smith TW & Springote CE; 1978, Follenfant RL & Oliver P; 1978, Follenfant MJ; 1978) Because of the extensive database available on pyrethroid toxicity, and the in-depth knowledge base available, further mechanism studies are not considered necessary.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements.*	
Conclusion	*Applicant's justification is acceptable.*	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.11	6.11 Studies on other routes of administration	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [ ]	
Detailed justification:	Data on the toxicity of permethrin via oral, dermal and inhalation routes have been provided. The mechanistic studies available indicate that, regardless of the route of dosing the behaviour of permethrin in mammals is the same, i.e. Rapid adsorption, metabolism and excretion. This is supported by the toxicities observed in [redacted]; 1975a; 21Z73 (25/75) acute toxicity studies by various routes of administration in the rat, mouse and chick, which is summarised in IUCLID Section 5.1.1.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements.*	
Conclusion	*Applicant's justification is acceptable.*	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.12.1	6.12.1 Medical data in anonymous form	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [ ]	
Detailed justification:	The following reference is in IUCLID: [redacted]; 1991; Permethrin 25/75 Technical; [redacted]; unpublished Report (Ref.) No. MAG/214/hsc; 05.12.1991. The wording of the message is as follows; "[redacted], Manufacturing Manager; 5th December 1991; Subject Permethrin 25/75 Technical: Permethrin 25/75 Technical has been used at the [redacted] for many years. To the best of my knowledge operators involved in the handling and use of this material have not suffered any adverse effects." No other data are available for review.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements*	
Conclusion	*Applicant's justification is acceptable.*	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.12.2	6.12.2 Direct observations, eg. Clinical cases, poisoning incidents if available	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [ ]	
Detailed justification:	In a reported suicide attempt, a 59-year-old male drank approximately 600 mL of 20 percent permethrin emulsion. Vomiting and diarrhea occurred after ingestion. On admission to the hospital, loss of consciousness and metabolic acidosis were observed. When he regained consciousness, the patient complained of a burning sensation in the oral cavity. He received fluid therapy after gastric lavage and recovered without severe complications. Apart from initially impaired consciousness, no clinical neurotoxicity occurred. Reference: Gotoh, Y., M Kawakami, N Matsumoto, and Y Okada; 1998; Permethrin Emulsion Ingestion: Clinical Manifestations and Clearance of Isomers; Clinical Toxicology, vol. 36, no. 1&2, p. 57-58	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements*	
Conclusion	*Applicant's justification is acceptable.*	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.12.3	6.12.3 Medical data in anonymous form	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible** [ ] **Scientifically unjustified** [ ]	
Limited exposure [ ]	**Other justification** [ ]	
Detailed justification:	The following reference is in IUCLID: [redacted]; 1991; Permethrin 25/75 Technical; [redacted]; unpublished Report (Ref.) No. MAG/214/hsc; 05.12.1991. The wording of the message is as follows; "[redacted]; Memorandum from [redacted], Manufacturing Manager; 5th December 1991; Subject Permethrin 25/75 Technical: Permethrin 25/75 Technical has been used at the Berkhamsted Site for many years. To the best of my knowledge operators involved in the handling and use of this material have not suffered any adverse effects." No other data are available for review.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements*	
Conclusion	*Applicant's justification is acceptable*	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.12.4	6.12.4 Epidemiological studies on the general population, if available	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [ ]	
Detailed justification:	In a population investigation into exposure to pyrethroid exposure from all potential sources, (not directly related to permethrin exposure from wood preservatives) a total of 1,177 persons took part, including 331 children under 6 years of age and 247 children between 6 and 12 years of age. None of them reported exposure to pyrethroids at home or at work. Levels of permethrin found in household dust from their homes were lower than expected (median < limit of detection; 95th percentile, 4.8 mg/kg; maximum value, 19 mg/kg). Urine specimens were analyzed for *cis*-3-(2,2-dibromo-vinyl)-2,2-dimethylcyclopropanecarboxylic acid (Br_2CA), *cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid (*cis*-Cl_2CA and *trans*-Cl_2CA), and 4-fluoro-3-phenoxybenzoic acid (F-PBA) using a gas chromatographic method with mass-selective detection. The limit of detection for pyrethroid metabolites was between 0.1 and 0.2 µg/L. *trans*-Cl_2CA was detected in 65% of the urine specimens tested, *cis*-Cl_2CA was detected in 30%, and Br_2CA and F-PBA were found in 19% and 16%, respectively, of the urine specimens. The urinary metabolite levels in children did not differ from those in adults, and there was no correlation between the levels of metabolites and indoor exposure to permethrin in household dust. Moreover, no seasonal correlations could be found. The 95th percentile levels in urine specimens were as follows: Br_2CA, 0.30 µg/L; *cis*-Cl_2CA, 0.51 µg/L; *trans*- Cl_2CA, 1.43 µg/L; F-PBA, 0.27 µg/L. Background exposure to pyrethroids was found in the general population; it was suggested to be caused by the uptake of pyrethroids with the diet. This hypothesis needs to be tested in duplicate diet studies combined with biomonitoring. The rounded 95th percentile values obtained in the study for pyrethroid metabolites in urine samples from the population in Germany were as follows: Br*2*CA, 0.3 µg/L; *cis*-Cl_2CA, 0.5 µg/L; *trans*-Cl_2CA, 1.5 µg/L; and F-PBA, 0.3 µg/L. **Reference: Heudorf, U, Angerer, J; 2001; Metabolites of pyrethroid insecticides in urine specimens: Current exposure in an urban population in Germany; Environ Health Perspect 109:213–217.** In WHO trials in Nigeria, following indoor use at doses of 0.5 g/m3, volunteers to exposure made no complaint about adverse effects nor were any observed.	
Undertaking of intended data submission [ ]		

Section A6.12.4	6.12.4 Epidemiological studies on the general population, if available
	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*14/12/05*
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements.*
Conclusion	*Applicant's justification is acceptable.*
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.5	6.12.5 Diagnosis of poisoning including specific signs of poisoning and clinical tests	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [ ]	
Detailed justification:	A monograph (UKPID Monograph: Permethrin) has been produced by staff of the National Poisons Information Service Centre in the United Kingdom. The work was commissioned and funded by the UK Departments of Health, and was designed as a source of detailed information for use by poisons information centres. The summary concludes; **Toxicity** Dermal and inhalational exposures are associated usually with no or only mild adverse effects. Following substantial ingestion, patients may develop coma, convulsions and severe muscle fasciculations and may take several days, occasionally weeks, to recover. Fatalities have occurred rarely after pyrethroid exposure, usually following ingestion. No known fatalities have been reported after permethrin exposure. **Features** ***Dermal exposure*** Tingling and pruritus with blotchy erythema on the face or other exposed areas, exacerbated by sweating or touching. Systemic toxicity may ensue following substantial exposure. ***Ocular exposure*** Lacrimation and transient conjunctivitis may occur. ***Inhalation*** Brief exposure: Respiratory tract irritation with cough, mild dyspnoea, sneezing and rhinorrhea. Substantial and prolonged exposure: Systemic toxicity may ensue. ***Ingestion*** May cause nausea, vomiting and abdominal pain. Systemic toxicity may ensue following substantial ingestion.	

Section A6.12.5	6.12.5 Diagnosis of poisoning including specific signs of poisoning and clinical tests
	Systemic toxicity Systemic symptoms may develop after widespread dermal exposure, prolonged inhalation or ingestion. Features include headache, dizziness, anorexia and hypersalivation. Severe poisoning is uncommon. It usually follows substantial ingestion and causes impaired consciousness, muscle fasciculations, convulsions and, rarely, non-cardiogenic pulmonary oedema. ***Chronic exposure*** Long-term exposure is no more hazardous than short-term exposure.
Undertaking of intended data submission [ ]	
	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*14/12/05*
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements*
Conclusion	*Applicant's justification is acceptable.*
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.6	6.12.6 Sensitisation/allergenicity observations, if available	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [ ]	
Detailed justification:	No directly related data are available, and sensitisation/allergenicity are not discussed in any of the IPCS reviews of permethrin. A test to determine the efficacy of permethrin-impregnated mattress liners in reducing house dust mites in the homes of volunteers with no previous recorded history of asthma, atopic eczema, or perennial rhinitis has recently been reported. The field trial using permethrin-impregnated (450 mg/m2 of pure permethrin in polyester netting weighing 35 g/m2) mattress liners (n = 9) was conducted for 27 months. The permethrin-impregnated bedding significantly reduced house dust mites in mattresses for at least 27 months. Allergen concentrations were significantly lowered at 15-months postintervention. No adverse side-effects were reported. **Cameron, M M., Hill, N; 2002; Permethrin-Impregnated Mattress Liners: a Novel and Effective Intervention Against House Dust Mites (Acari: Pyroglyphididae); Journal of Medical Entomology Volume: 39, 755-762**	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements*	
Conclusion	*Applicant's justification is acceptable.*	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.12.7	6.12.7 Specific treatment in case of an accident or poisoning: First aid measures, antidotes and medical treatment, if known	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [ ]	
Detailed justification:	The following information has been extracted from the UKPID monograph; **Dermal** 1. Remove soiled clothing and wash contaminated skin with soap and water. 2. Institute symptomatic and supportive measures as required. Topical vitamin E (tocopherol acetate) has been shown to reduce skin irritation if applied soon after exposure (Flannigan et al, 1985), but it is not available as a pharmaceutical product in the UK. 3. Symptoms usually resolve within 24 hours without specific treatment. **Ocular** 1. Irrigate with lukewarm water or 0.9 per cent saline for at least ten minutes. 2. A topical anaesthetic may be required for pain relief or to overcome blepharospasm. 3. Ensure no particles remain in the conjunctival recesses. 4. Use fluorescein stain if corneal damage is suspected. 5. If symptoms do not resolve following decontamination or if a significant abnormality is detected during examination, seek an ophthalmological opinion. **Inhalation** 1. Remove to fresh air. 2. Institute symptomatic and supportive measures as required. **Ingestion** 1. Do not undertake gastric lavage because solvents are present in some formulations and lavage may increase risk of aspiration pneumonia. 2. Institute symptomatic and supportive measures as required. 3. Atropine may be of value if hypersalivation is troublesome, 0.6-1.2 mg for an adult, 0.02 mg/kg for a child.	

Section A6.12.7	6.12.7 Specific treatment in case of an accident or poisoning: First aid measures, antidotes and medical treatment, if known
	4. Mechanical ventilation should be instituted if non-cardiogenic pulmonary oedema develops. 5. Isolated brief convulsions do not require treatment but intravenous diazepam should be given if seizures are prolonged or recur frequently. Rarely, it may be necessary to give intravenous phenytoin or to paralyze and ventilate the patient. **Reference: UKPID monograph: Permethrin; National Poisons Information Service**
Undertaking of intended data submission [ ]	
	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*14/12/05*
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements*
Conclusion	*Applicant's justification is acceptable.*
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.8	6.12.8 Prognosis following poisoning	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [ ]	
Detailed justification:	**Toxicity** Dermal and inhalational exposures are associated usually with no or only mild adverse effects. Following substantial ingestion, patients may develop coma, convulsions and severe muscle fasciculations and may take several days, occasionally weeks, to recover. Fatalities have occurred rarely after pyrethroid exposure, usually following ingestion. No known fatalities have been reported after permethrin exposure. **Reference; UKPID Monograph: Permethrin; National Poisons Information Service Centre**	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements.*	
Conclusion	*Applicant's justification is acceptable.*	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.13 **6.13 Toxic effects on livestock and pets**

Annex Point IIA6.13

Key Study

		Official use only
	1 REFERENCE	
1.1 Reference	[redacted] 1978; Permethrin Oral Administration to Dogs for 6 Months; [redacted]; unpublished Report No. HEFG 78-14; 01.12.1978.	
1.2 Data protection	*Yes*	
1.2.1 Data owner	Sumitomo Chemical (UK) PLC	
1.2.2 Companies with letter of access	Bayer Environmental Science	
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; no guidelines available.	
2.2 GLP	No; GLP was not compulsory at the time the study was performed.	
2.3 Deviations	No	
	3 MATERIALS AND METHODS	
3.1 Test material	As given in section 2	X
3.1.1 Lot/Batch number	Batch ZJ	
3.1.2 Specification	*As given in section 2*	X
3.1.2.1 Description	Liquid	
3.1.2.2 Purity	94.5%	
3.1.2.3 Stability	As given in section 2	X
3.2 Test Animals		
3.2.1 Species	Dog	
3.2.2 Strain	Beagle	
3.2.3 Source	[redacted]	
3.2.4 Sex	♂ and ♀	
3.2.5 AGE/WEIGHT AT STUDY INITIATION	20-22 weeks	
3.2.6 Number of animals per group	8	
3.2.7 Control animals	Yes	
3.3 Administration/ Exposure	*Oral*	

Section A6.13 Annex Point IIA6.13	6.13 Toxic effects on livestock and pets	
	Key Study	
3.3.1 Duration of treatment	180 days	
3.3.2 Frequency of exposure	daily	
3.3.3 Postexposure period	not applicable	
3.3.4 Oral		
3.3.4.1 Type	capsule (gelatin)	
3.3.4.2 Concentration	capsule 0, 10, 50 and 250 mg/kg bw	
3.3.4.3 Vehicle	not applicable	
3.3.4.4 Concentration in vehicle	not applicable	
3.3.4.5 Total volume applied	not applicable	
3.3.4.6 Controls	not reported (incidence of vomiting suggests empty capsule)	X
3.4 Examinations		
3.4.1 Observations		
3.4.1.1 Clinical signs	Yes; daily.	
3.4.1.2 Mortality	Yes; daily.	
3.4.2 Body weight	Yes; twice weekly.	
3.4.3 Food consumption	Yes; daily, excluding weekends and Bank holidays when all animals were fed approximately 400 g of fresh diet/day but the residue was not weighed.	
3.4.4 WATER CONSUMPTION	No	
3.4.5 Ophthalmoscopic examination	Yes; days -6, 28, 91 and 173.	
3.4.6 Haematology	Yes number of animals: all animals time points: days -14, -7, 0, 14, 56, 112 and 180 Parameters: packed cell volume (PCV), haemoglobin concentration (Hb), red blood cell count (RBC), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell count (WBC), differential white blood cell count, prothrombin.	

Section A6.13	6.13 Toxic effects on livestock and pets
Annex Point IIA6.13	

	Key Study
3.4.7 Clinical Chemistry	Yes number of animals: all animals time points: days -14, -7, 0, 14, 56, 112 and 180 Parameters: glucose, urea, sodium (Na^+), potassium (K^+), bilirubin (BILI), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), alkaline phosphatase (AP), creatine phosphokinase (CPK), total protein, albumin, α-, β_1-, β_2-, and γ-globulin.
3.4.8 Urinalysis	Yes number of animals: all animals time points: end of study Parameters: nitrite, pH, blood, glucose, ketones, urobilinogen, bilirubin, protein, appearance.
3.5 SACRIFICE AND PATHOLOGY	
3.5.1 ORGAN WEIGHTS	Yes organs: brain, liver, pituitary, spleen, heart, lungs, adrenals, testis, ovaries, thyroids, kidneys
3.5.2 Gross and histopathology	Yes **all dose groups; for nerve and muscle tissue, high dose group and controls, other dose groups only if effects** organs: pituitary, thyroid, heart, lungs, pyloric stomach, duodenum, colon, mesenteric lymph node, liver, spleen, pancreas, kidney, adrenal, urinary bladder, prostate, uterus, testis, ovaries, bone, gall bladder, tongue, salivary gland, thymus, trachea, abdominal skin, mammary gland, aortic arch, oesophagus, jejunum, ileum, caecum, skeletal muscle, costochondral junction, sternum, parathyroid, epididymis, vagina, cervical lymph node, ureter, oviduct, eyes, brain, trigeminal ganglia, dorsal root ganglia, posterior thigh muscle, lumbrical muscle and the following nerves - sciatic, ulnar, radial, posterior tibial, superficial fibular and plantar
3.5.3 OTHER EXAMINATIONS	
3.5.4 Statistics	Standard

Section A6.13 **6.13 Toxic effects on livestock and pets**

Annex Point IIA6.13

Key Study

3.6 Further remarks	Electrocardiography Yes number of animals: all animals time points: days -35, 91 and 174 Plasma antipyrine determinations Yes number of animals: all animals time points: end of study	
	4 RESULTS AND DISCUSSION	
4.1 Observations		
4.1.1 Clinical signs	Isolated cases of vomiting were seen in a few dose and control animals and one animal was treated for demodectic mange. No dose related signs of clinical toxicity were seen.	
4.1.2 Mortality	No mortalities at any dose.	
4.2 Body weight gain	No statistically significant changes were seen in the dosed groups compared with the controls.	
4.3 Food consumption and compound intake	Statistically significant changes in food consumption occurred on isolated occasions in the 50 mg/kg and 250 mg/kg groups but these were not considered to be of toxicological importance.	
4.4 Ophthalmoscopic examination	No toxicologically important changes were seen.	
4.5 Blood analysis		
4.5.1 Haematology	Statistically significant changes were seen in the following parameters: PCV (10 mg/kg), MCV (10 mg/kg), lymphocytes (50 and 250 mg/kg), neutrophils (50 and 250 mg/kg), band neutrophils (50 and 250 mg/kg). None of these changes were considered to be of toxicological importance.	
4.5.2 Clinical chemistry	Statistically significant changes occurred in the following parameters during the dosing period; glucose (10 mg/kg), urea (10 mg/kg), sodium (250 mg/kg), potassium (10 mg/kg), bilirubin (50 and 250 mg/kg), total protein (10, 50 and 250 mg/kg), albumin (250 mg/kg), β_1-globulin (10 mg/kg) and β_2-globulin (250 mg/kg). None of these changes appeared to be dose- or time-related or were of sufficient magnitude to be of toxicological importance. Similar significant but minor changes were occasionally observed before the animals were dosed.	X
4.5.3 Urinalysis	The only difference between the dosed and control groups was a slight lowering of the pH in the dosed groups.	
4.6 Sacrifice and pathology		

Section A6.13 Annex Point IIA6.13	6.13 Toxic effects on livestock and pets	
	Key Study	
4.6.1 Organ weights	Absolute organ weights No statistically significant changes occurred between any of the dosed groups and the controls. Relative organ weights Statistically significant increases occurred in the heart weight for the 50 mg/kg group, liver weight for the 50 and 250 mg/kg groups and kidneys in all dosed groups. The magnitude of these changes does not increase with the dose level and in every case is not more than 17% above the control value and are therefore not considered to be of toxicological significance.	X
4.6.2 Gross and histopathology	No changes were found in any of the dosed groups which could be considered to be caused by dosing with permethrin.	
4.7 Other	Electrocardiography No toxicologically important changes were seen. Plasma antipyrine elimination A non-significant increase in the elimination rate of antipyrine was seen in the 50 and 250 mg/kg groups. This is probably due to inter-animal variation and is not considered to be important.	
	5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1 Materials and methods	Groups of 8 Beagle dogs were given an oral dose of 10, 50 or 250 mg/kg permethrin (94.5% w/v, *cis:trans* 25:75) daily for 6 months. The animals were weighed twice weekly and the dose of compound calculated according to bodyweight. The required quantity of compound was weighed into size 000 gelatin capsules, and administered orally once daily. A similar group of animals were kept as controls. Toxicological examinations included clinical signs, mortality, bodyweight, food consumption, ophthalmoscopy, electrocardiography, haematology, clinical chemistry, urinalysis, plasma antipyrine elimination, organ weights, gross pathology and histopathology.	

Section A6.13 Annex Point IIA6.13	6.13 Toxic effects on livestock and pets	
	Key Study	
5.2 Results and discussion	No toxicologically important changes were found in any of the following parameters: clinical signs, mortality, bodyweight, ophthalmoscopy, electrocardiography, plasma antipyrine elimination, absolute organ weights, gross pathology and histopathology. Statistically significant changes occurred in food intake (isolated occasions in the 50 mg/kg and 250 mg/kg groups), but these were not considered to be of toxicological importance. Statistically significant changes occurred in some haematological parameters (packed cell volume (10 mg/kg), mean corpuscular volume (10 mg/kg), lymphocytes (50 and 250 mg/kg), neutrophils (50 and 250 mg/kg), band neutrophils (50 and 250 mg/kg)), but none of the changes observed showed any time-related trends or were of sufficient magnitude to be of toxicological importance.	X
	Statistically significant changes also occurred in some clinical chemistry parameters (glucose (10 mg/kg), urea (10 mg/kg), sodium (250 mg/kg), potassium (10 mg/kg), bilirubin (50 and 250 mg/kg), total protein (10, 50 and 250 mg/kg), albumin (250 mg/kg), globulin fractions β_1 (10 mg/kg) and β_2 (250 mg/kg)), but none of these changes appeared to be dose- or time-related or were of sufficient magnitude to be of toxicological importance.	X
	Statistically significant changes occurred in relative organ weights for liver (50 and 250 mg/kg), heart (50 mg/kg) and kidneys (10, 50 and 250 mg/kg), but the magnitude of these changes does not increase with the dose level and in every case is not more than 17% above the control value. None of these changes were considered to be of toxicological importance.	
5.3 Conclusion		
5.3.1 LO(A)EL	> 250 mg/kg (highest dose tested)	X
5.3.2 NO(A)EL	250 mg/kg (highest dose tested)	X
5.3.3 Other		
5.3.4 Reliability	2	
5.3.5 Deficiencies	Yes; a few tissues were not found when the tissues were 'blocked' for histology or were damaged during histology preparation, however, no dose related abnormalities were seen in any of the examined tissues.	

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*24/11/05*
Materials and Methods	***3.1*** *Permethrin tech is the stated TS, however no code number is given to correspond to that which is described in Section 2.* ***3.1.2*** *What exactly does 'specification' refer to?* ***3.1.2.3*** *Stability is not given in Section 2.* ***3.3.4.6*** *What does this entry mean?* *Otherwise, the applicants version is acceptable.*
Results and discussion	***4.5.2*** *Bilirubin levels were decreased in the 10 mg/kg bw group also.* *Otherwise, adopt applicant's version.* ***4.6.1*** *The applicant considers that because the magnitude of the relative weight changes in liver, kidney and heart does not increase with the dose level and in every case is not more than 17% above the control value, that therefore these observations are not considered to be of toxicological significance. However, it cannot be ignored that data from other studies demonstrate that increased liver weight is a classic effect following permethrin administration and therefore changes such as these have toxicological significance.* ***5.2*** *As pointed out above, bilirubin levels were decreased in the 10 mg/kg bw group also.* *See comment at 4.6.1 above also.*
Conclusion	***5.3.1*** *LO(A)EL: 50mg/kg bw* ***5.3.2*** *NO(A)EL: 10 mg/kg bw*
Reliability	*2*
Acceptability	*Acceptable*
Remarks	*The authors of the report have omitted to include information on the 'Special Histopathological Examination of the Nervous System' which is to be found at the back of the report (P.81 – 88). In their results, they report that no evidence was found of damage to peripheral nerve fibres in proximal or distal trunks, or in motor and sensory endings, nor were lesions seen in the brain, spinal cord and trigeminal and dorsal root ganglia. This is useful information and should have been reported as part of the results in the main body of the text.* *In the data requirements, there is a stated requirement for studies to be* ***usually*** *conducted in 2 species, one rodent and one non-rodent. There are two 90 day rat studies submitted, as well as a 90 day, 6 month and 1 year study in the dog. As only the 6 month and 1 year* ***dog*** *studies are reported in the key study format, are we to presume that the applicant is making the case that the dog is the more sensitive species (which appears to be the case)? This should have been stated and explained by the applicant.*
	COMMENTS FROM ... ***(specify)***
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion. Discuss if deviating from view of rapporteur member state*

Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.14	6.14 Other tests related to the exposure of Humans	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	Technically not feasible [ ] Scientifically unjustified [ ]	
Limited exposure [ ]	Other justification [ ]	
Detailed justification:	Data on the toxicity of metabolites and the raw materials and intermediates used in the synthesis of permethrin have shown these materials to be moderately toxic to mice by oral administration ([redacted]; 1978). The results indicate the metabolites and the raw materials to be of similar or lower toxicity to permethrin, and as such data are not presented in Fraunhofer format. These data have been summarised in IUCLID Section 5.1.1 for review.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements.*	
Conclusion	*Applicant's justification is acceptable*	
Remarks	*There are no metabolites produced that merit individual testing. The toxicity of any raw materials or intermediates used in the synthesis of Permethrin are outside the scope of this evaluation.*	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.15	6.15 Food and Feedingstuffs	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	Technically not feasible [ ] Scientifically unjustified [ ]	
Limited exposure [ ]	Other justification [ ]	
Detailed justification:	The TGD 'Guidance on Data Requirements for Active Substances and Biocidal Products (Version 4.3.2, October 2000) states if an active substance is to be used in preparations for use where food for human consumption is prepared, consumed or stored or where feedingstuff for livestock is prepared, consumed or stored then the tests outlined in 6.15.1-6.15.6 are required. Wood preservative, Product Type 8 is not specified as one of the Product Types to which this requirement might apply. A potential point of contact may be grain storage barn treated with a wood preservative product containing permethrin, which may lead to amounts of permethrin entering the food and feedingstuffs at trace level. Historically permethrin has been used extensively as a crop protection product and the residues considered safe at levels considerably higher than those which might conceivably be achieved through leaching from wood. Therefore a justification for non-submission is suggested based upon limited exposure and historical precedent.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements.*	
Conclusion	*Applicant's justification is acceptable.*	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.16	6.16 Any other tests related to the exposure of Humans	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [X]	
Detailed justification:	The TGD 'Guidance on Data Requirements for Active Substances and Biocidal Products (Version 4.3.2, October 2000) states these data are only required should they be considered necessary. The data set for the assessment of human exposure and the effects of permethrin exposure through wood preservation is considered sufficient to allow a reasoned assessment of risk. Therefore a justification for non-submission of further data is suggested on the basis of a sufficiency of existing data.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements*	
Conclusion	*Applicant's justification is acceptable.*	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.17	6.17 Tests to assess the toxic effects of metabolites on plants	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] Limited exposure [X]	Technically not feasible [ ] Scientifically unjustified [ ] Other justification [ ]	
Detailed justification:	The TGD Guidance on Data Requirements for Active Substances and Biocidal Products (Version 4.3.2, October 2000) states these data are only required should the active ingredient be intended for use in a product for action against plants. Permethrin in wood preservative products is not intended for this use. Therefore a justification for non-submission of further data is suggested on the basis that there will be limited exposure.	
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*14/12/05*	
Evaluation of applicant's justification	*Applicant's justification for non-submission of data fulfils requirements.*	
Conclusion	*Applicant's justification is acceptable.*	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Appendix 1 to Doc III-A6

Bayer Environmental Science is a an affiliated company of Bayer CropScience, therefore the studies submitted by Bayer Environmental Science are owned by Bayer CropScience AG.

Reference List Doc. III-A6. sorted by reference no.

Section No/ Reference No	AUTHOR (S)	Year	Title. Source, Report No. GLP /(Un) Published	Data Protection Claimed (Yes/No)	Owner
6,1,1(1)	[redacted]	1975	Acute Oral Toxicity in Rats with Compound FMC 33297. [redacted] Report No. 2739-75 (Unpublished)	Yes	Sumitomo Chemical
6,1,1(2)	[redacted]	1974	Comparative Acute Oral Toxicity in Mice with FMC 33297, FMC 37400, FMC 35171 and FMC 30960. [redacted] Report No. HEFG 79-C76 (Unpublished)	Yes	Sumitomo Chemical
6,1,2	[redacted]	1975	Acute Dermal Toxicity in Rabbits. Compound FMC 33297. [redacted] Report No. 2908-75 (Unpublished)	Yes	Sumitomo Chemical
6,1,3	[redacted]	1976	Acute Inhalation. Compound No. FMC 33297. [redacted]. Report No. 2911-75 (Unpublished)	Yes	Sumitomo Chemical
6,1,4(1)	[redacted]	1975	Rabbit Eye Irritation. Compound No. FMC 33297. [redacted]. Report No. 2910-75 (Unpublished)	Yes	Sumitomo Chemical
6,1,4(2)	[redacted]	1975	Rabbit Primary Dermal Irritation. Compound No. FMC 33297. [redacted]. Report No. 2909-75 (Unpublished)	Yes	Sumitomo Chemical
6,1,5	[redacted]	1991	Skin Sensitisation in the Guinea Pig of a Permethrin 25/75 cis/trans Isomer RatioThe [redacted]. Report No. 91626D/WLC 159/SS	Yes	Sumitomo Chemical
6,2 (1)	Gaughan LC, Unai T & Casida JE	1977	Permethrin Metabolism in Rats; Department of Entomological Sciences, University of California, Berkeley, California 94720, USA; J. Agric. Food Chem., Vol. 25, No. 1, pp 9-17; 1977.	No	
6,2	Bartelt, N. & Hubbell, J.	1987	Percutaneous Absorption of Topically Applied 14C-Permethrin in Volunteers. Final Medical ReportBurroughs Wellcome Co. Report No. THRD/86/0047	Yes	Sumitomo Chemical

6,3,3	[redacted]	1980	Permethrin Technical. Inhalation Study in Rats – 16 x 6 Hour Exposures Over a 3 Week Period. [redacted]. Report No. WLC34/80323.	Yes	Sumitomo Chemical
6,4,1 (1)	[redacted]	1975	21z73, Rat Oral 90 Day Study. [redacted]. Report No. HEFG 76-1 (Unpublished)	Yes	Sumitomo Chemical
6,4,1 (2)	[redacted]	1978	Permethrin Oral Administration to Dogs for 6 Months. [redacted]. Report No. HEFG 78-14	Yes	Sumitomo Chemical
6,5 (1)	[redacted]	1980	21z: Potential Toxicity and Oncogenicity in Dietary Administration to Rats for a Period of 104 weeks. [redacted]. Report No. 80/WRL003/283 (Unpublished)	Yes	Sumitomo Chemical
6,5 (2)	Ishmael, J. & Litchfield, M.H.	1988	Chronic Toxicity and Carcinogenic Evaluation of Permethrin in Rats and Mice. Fundamental and Applied Toxicology. Vol. 11. pp308-322	No	N/A
6,6,1	Haworth SR	1979	Salmonella/Mammalian-Microsome Plate Incorporation and Pre-Incubation Mutagenesis Assays of Burroughs Wellcome Compound Permethrin Tech BW 0021Z73 #8E8026 and 8I8012; EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland 20852, USA; unpublished Report (Study) No. 015-560-150A-1 and 015-560-150A-2; 16.10.1979.	Yes	Sumitomo Chemical
6,6,2	Barrueco, C. et al	1994	Induction of structural chromosomal aberrations in human lymphocyte cultures and CHO cells by permethrin. Teratogenesis, Carcinogenesis, and Mutagenesis 14:31-38.	No	N/A
6,6,3	Clive, D.	1977	Mutagenicity of BW 21z73 in L5178Y/TK+/- Mouse Lymphoma Cells With and Without Exogenous Metabolic ActivationThe Wellcome Foundation Ltd. Report No. TTEP/77/0001	Yes	Sumitomo Chemical
6,6,4	[redacted]	1997	Micronucleus Test of Permethrin Technical in Mice. [redacted] Report No. 1270/JRF/TOX/97. (Unpublished)	Yes	Bayer CropScience AG
6,6,5	[redacted]	1997	Chromosomal Aberration Study of Permethrin Technical in Mice	Yes	Bayer CropScience AG
6,6,6	[redacted]	1975	21z73 Dominant Lethal Study in Male Mice. [redacted]. Report No. HEFG 75-10 (Unpublished)	Yes	Sumitomo Chemical