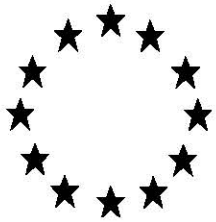
Competent Authority Report

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

Tagros Chemicals (India) Ltd.

Rapporteur: Ireland

August 2009

Permethrin PT8

Document IIIA A6

CONTENTS

Section A6.1 3
Section A6.2 44
Section A6.3 49
Section A6.4 63
Section A6.5 120
Section A6.6 121
Section A6.7 156
Section A6.8 174
Section A6.9 194
Section A6.10 196
Section A6.11 197
Section A6.12 198
Section A6.13 210
Section A6.14 212
Section A6.15 214
Section A6.16 216
Section A6.17 217
Section A6.18 218

Section A6.1.1 Acute Toxicity

Annex Point IIA6.1.1 **Acute oral toxicity in the rat: LD_{50} determination**

Reference

Official use only

Reference	[redacted] (1998a) Acute Oral Toxicity Study of Permethrin Technical in Rats. Department of Toxicology, [redacted], report No.: 1591 (unpublished).
	Dates of experimental work: July 16, 1998 – August 12, 1998.
Data protection	Yes
Data owner	Tagros Chemicals India Ltd.
Companies with letter of access	Not applicable
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/IA.

Comment [T1]: Confidential
Formatted: Highlight
Formatted: Highlight

Guidelines and Quality Assurance

Guideline study	Yes, the test method was based on OECD Guideline 401.
GLP	Yes
Deviations	No

Materials And Methods

Test material	As given in section 2 (Permethrin 40:60)
Lot/Batch number	PH 01
Specification	As given in section 2 (Permethrin 40:60)
Description	Light yellow colour, viscous liquid
Purity	92.50%
Stability	Not relevant (single dose)

Section A6.1.1 Acute Toxicity

Annex Point IIA6.1.1 **Acute oral toxicity in the rat: LD_{50} determination**

Test Animals	
Species	Rat (*Rattus norvegicus*)
Strain	Wistar
Source	[redacted]
Sex	Male and female
Age/weight at study initiation	12 weeks old at time of dosing 110 to 210 g
Number of animals per group	5 animals/sex/group
Control animals	Yes
Administration/ Exposure	Oral
Postexposure period	14 days
Type	Gavage
Concentration	0, 438, 500 and 571mg/kg bw
Vehicle	Peanut oil
Concentration in vehicle	Not documented
Total volume administered	10 ml/kg
Controls	Vehicle (Peanut oil)
Examinations	Clinical observations (Deaths and overt signs of toxicity): At 1, 2 and 3 hours after dosing, and once daily for 14 days thereafter. Necropsy: At animal sacrifice. The appearance of any macroscopic abnormalities was recorded. Histopathology: When deemed necessary. Body weights: Recorded prior to dosing and on days 7 and 14 after dosing.
Method of determination of LD_{50}	Probit analysis (Finney, 1971) was performed for male and female rats combined.
Further remarks	Not relevant

Comment [T2]: Confidential
Formatted: Highlight

Section A6.1.1 Acute Toxicity

Annex Point IIA6.1.1 **Acute oral toxicity in the rat: LD_{50} determination**

Results and Discussion

Clinical signs	Clinical signs in Permethrin technical treated groups were moribund state, lethargy, tremors, nostril discharge, exophthalmos, diarrhoea and piloerection. Such signs were observed for the first four days after dosing. Subsequently, no further abnormalities were detected in surviving animals. No abnormalities were detected in the control animals.
Pathology	No treatment related changes at necropsy.
Other	All surviving animals gained weight throughout the study.
	0% mortality for both sexes at 0 and 438 mg/kg bw 20% mortality for both sexes at 500 mg/kg bw 60% mortality for both sexes at 571 mg/kg bw/day
LD_{50}	The acute oral median lethal dose (LD_{50}) of Permethrin technical in Wistar rats was determined to be 554 mg/kg bw with 95% fiducial limits of 512 to 599 mg/kg bw.

Section A6.1.1 Acute Toxicity

Annex Point IIA6.1.1 **Acute oral toxicity in the rat: LD_{50} determination**

Applicant's Summary and conclusion

Materials and methods

The test substance Permethrin technical was dosed to 4 groups of Wistar rats (5/sex/group) at the following concentrations 0, 438, 500 and 571 mg/kg.

This study was conducted according to OECD guideline 401 and is described under point 3 with no deviations.

Results and discussion

The percent mortality observed for both sexes together were 0, 0, 20 and 60 at the dose levels of 0, 438, 500 and 571 mg/kg bw respectively. Results are summarised in Table A6.1.1-1.

Clinical signs in Permethrin technical treated groups were moribund state, lethargy, tremors, nostril discharge, exophthalmos, diarrhoea and piloerection. Such signs were observed for the first four days after dosing. Subsequently, no further abnormalities were detected in surviving animals. No abnormalities were detected in the control animals.

Animals from the treated groups showed normal body weight gain over the experimental period. Control group animals gained body weight over the duration of the experiment.

Some gross changes were noted on the lungs of control animals. As alterations were mild and sparse, they were taken as incidental findings.

Vascular changes were the predominant findings in the treated groups which were construed as terminal incidental changes. Enteritis was detected in three animals treated with 500 mg/kg bw. Hepatopathy was recorded in two animals treated with 500 mg/kg bw and two animals treated with 571 mg/kg bw.

Some minor changes in the uterus, spleen and heart were deemed not to be of toxicological significance.

Microscopic findings mostly corroborated gross alterations in the relevant organs.

Conclusion

The acute oral median lethal dose (LD_{50}) of Permethrin technical in Wistar rats was determined to be 554 mg/kg bw. In accordance with Council Directive 67/548/EEC, it is classified as "Harmful if swallowed", and assigned the symbol, Xn and the R phrase, R22.

Reliability 1

Deficiencies No

Section A6.1.1 Acute Toxicity

Annex Point IIA6.1.1 **Acute oral toxicity in the rat: LD_{50} determination**

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	Evaluation by Rapporteur Member State
Date	27/04/2009
Materials and Methods	Applicants version is acceptable
Results and discussion	Adopt applicant's version. The acute oral median lethal dose (LD_{50}) of Permethrin technical in Wistar rats was determined to be 554 mg/kg bw
Conclusion	In accordance with Council Directive 67/548/EEC, it is classified as "Harmful if swallowed", and assigned the symbol, Xn and the R phrase, R22.
Reliability	1
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 A6.1.1-1: Mortality data

Dose mg/kg bw	No. of animals used	Mortality after dosing at						Total Mortality		
		1-3 h	24 h	48 h	72 h	4-7 day	8-14 day	M	F	%
0	5 M + 5 F	0	0	0	0	0	0	0	0	0
438	5 M + 5 F	0	0	0	0	0	0	0	0	0
500	5 M + 5 F	0	2	0	0	0	0	0	2	20
571	5 M + 5 F	1	5	0	0	0	0	2	4	60

M = Male, F = Female, bw = body weight

Section A 6.1.2/1 **Acute Toxicity**

Annex Point IIA6.1.2 **Acute dermal toxicity in the rat: LD_{50} determination**

Official use only

Reference

Reference	[redacted] (1998b) Acute Dermal Toxicity Study of Permethrin Technical in Rats. Department of Toxicology, [redacted] unpublished report no.: 1593.
	Dates of experimental work: July 16, 1998 – August 12, 1998.
Data protection	Yes
Data owner	Tagros Chemicals India Ltd.
Companies with letter of access	Not applicable
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/IA.

Comment [T3]: Confidential
Formatted: Highlight
Formatted: Highlight

Guidelines and Quality Assurance

Guideline study	Yes, the test method was based on OECD Guideline 402.
GLP	Yes
Deviations	Yes, with the following deviation:
	The guideline states that the test substance should be held in contact with the skin with a porous gauze dressing and a non-irritating tape throughout a 24 hour exposure period, and that at the end of the exposure period, residual test substance should be removed, where practicable using water or an appropriate solvent. This procedure was not recorded in the study report.
	This deviation is considered to be major and may compromise the scientific validity of the study. However, an acute dermal study is currently underway, results of which will be submitted when available. This study should be available by July 2006.

MATERIALS AND MethodS

Test material	As given in section 2 (Permethrin 40:60)

Lot/Batch number	PH 01	
Specification	As given in section 2 (Permethrin 40:60)	
Description	Light yellow colour, viscous liquid	
Purity	92.50%	
Stability	Not relevant (single dose)	
Test Animals		
Species	Rat (*Rattus norvegicus*)	
Strain	Wistar	
Source	[redacted]	
Sex	Male and female	
Age/weight at study initiation	Age not documented 200 - 287 g	
Number of animals per group	5 animals/sex/group	
Control animals	Yes	
Administration/ Exposure	Dermal	
Postexposure period	14 days	
Area covered	10 % of body surface was clipped for the application of the test substance	
Concentration	0 and 2000 mg/kg bw	
Occlusion	Not documented	X
Vehicle	Permethrin technical was applied undiluted	
Concentration in vehicle	Not relevant	

Comment [T4]: Confidential
Formatted: Highlight

Total volume applied	1.67 ml/kg
Duration of exposure	14 days
Removal of test substance	Not documented
Controls	Filtered water
Examinations	Clinical observations (Deaths and overt signs of toxicity): at 1, 2 and 3 hours after dosing, and once daily for 14 days thereafter. Necropsy: At animal sacrifice. The appearance of any microscopic abnormalities was recorded. Histopathology: When deemed necessary. Body weights: Recorded prior to dermal application and on days 7 and 14 after application.
Method of determination of LD_{50}	Statistical analysis was unnecessary as there were no mortalities.
Further remarks	None

Results and Discussion

Clinical signs	Clinical signs in groups treated with 2000 mg Permethrin technical/kg bw were lethargy, tremors, abdominal breathing, diarrhoea and piloerection, which were observed for the first three days after dermal application.
Pathology	No treatment related findings
Other	No mortalities in any groups Normal body weight gain in all groups during the experiment.
LD_{50}	The acute median lethal dose (LD_{50}) of Permethrin technical in Wistar rats was determined to be greater than 2000 mg/kg bw.

Applicant's Summary and conclusion

Materials and methods	The test substance Permethrin technical was dosed to 2 groups of Wistar rats (5 animals/ sex/group) at the following concentrations 0 and 2000 mg/kg bw. This study was conducted according to OECD guideline 402 and is described under point 3 with the following deviation: The guideline states that the test substance should be held in contact with the skin with a porous gauze dressing and a non-irritating tape throughout a 24 hour exposure period, and that at the end of the exposure period, residual test substance should be removed, where practicable using water or an appropriate solvent. This procedure was not recorded in the study report. This deviation is deemed to be major and may compromise the scientific validity of the study. However, an acute dermal study is currently underway, results of which will be submitted when available. This study should be available by July 2006.
Results and discussion	No mortalities were observed in the animals from the control or treatment groups. Results are summarised in Table A6.1.2/1-1. Clinical signs in groups treated with 2000 mg Permethrin technical/kg bw were lethargy, tremors, abdominal breathing, diarrhoea and piloerection, which were observed for the first three days after dermal application. Subsequently, no further abnormalities were detected in surviving animals. No abnormalities were detected in the control animals. Animals from the treated and control groups showed normal body weight gain during the experiment. Minor vascular alterations were observed in the lung and liver of control animals. One case of hydrometra was also observed in a control animal. In the treated group, gross vascular pathological changes, which were confirmed by microscopic examinations, were detected in the lung and liver. However these lesions were mild and sporadic and therefore were not deemed to be of toxicological significance.
Conclusion	The acute median lethal dose (LD_{50}) of Permethrin technical in Wistar rats was determined to be greater than 2000 mg/kg bw. In accordance with Council Directive 67/548/EEC it remains unclassified and requires no symbols or risk phrases.
Reliability	2
Deficiencies	One deviation was noted and is outlined under points 2.3 and 5.1. It may compromise the scientific validity of this study. However, an acute dermal study is currently underway, results of which will be submitted when available. This study should be available by July 2006.

Evaluation by Competent Authorities

Use separate "evaluation boxes" to provide transparency as to the comments and views submitted

Evaluation by Rapporteur Member State

Date	27/04/2009
Materials and Methods	3.3.4 The method and description of occlusion is not described. The RMS feels that for an acute dermal study this is a major reporting deficiency, therefore a reliability of 3 will be awarded.
Results and discussion	Adopt applicant's version or include revised version. If necessary, discuss relevant deviations from applicant's view referring to the (sub) heading numbers
Conclusion	Adopt applicant's version
Reliability	3
Acceptability	not acceptable In this case the study is not considered acceptable due to a poor reliability indicator. The description of occlusion is fundamental for an acute dermal toxicity study and is considered a major deficiency.
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 A6.1.2/1-1: Mortality data

Dose mg/kg bw	No. of animals used	Mortality at						Total Mortality		
		1-3 h	24 h	48 h	72 h	4-7 day	8-14 day	M	F	%
0 (Control)	5 M + 5 F	0	0	0	0	0	0	0	0	0
2000	5 M + 5 F	0	0	0	0	0	0	0	0	0

M = male, F = female, bw = body weight

Section A 6.1.2/2 **Acute Toxicity**

Annex Point IIA6.1.2 **Acute dermal toxicity in the rat: LD_{50} determination**

Official use only

Reference

Reference	[redacted] (2006), Acute Dermal Toxicity Study with Permethrin Technical in Wistar Rats. [redacted] unpublished report No.: 06019.
	Dates of experimental work: March 21, 2006 – April 4, 2006.
Data protection	Yes
Data owner	Tagros Chemicals India Ltd.
Companies with letter of access	Not applicable
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/IA.

Comment [T5]: Confidential
Formatted: Highlight
Formatted: Highlight

Guidelines and Quality Assurance

Guideline study	Yes, the test method was based on OECD Guideline 402.
GLP	Yes (certified by the Bundesinstitut für Risikobewertung/Federal Institute for Risk Assessment, Germany)
Deviations	None

MATERIALS AND MethodS

Test material	As given in section 2 (Permethrin 25:75)
Lot/Batch number	P-40
Specification	As given in section 2 (Permethrin 25:75)
Description	Light yellow to brown liquid
Purity	93.01%

Section A 6.1.2/2 **Annex Point IIA6.1.2**	**Acute Toxicity** **Acute dermal toxicity in the rat: LD_{50} determination**
Stability	Not relevant (single dose)
Test Animals	
Species	Rat (*Rattus norvegicus*)
Strain	Wistar
Source	[redacted]
Sex	Male and female
Age/weight at study initiation	10-12 weeks 200 - 300 g
Number of animals per group	Range finding experiment: One group of 1 animal/sex Main experiment (limit test): Two groups of 5 animals/sex/group
Control animals	Yes
Administration/ Exposure	Dermal
Postexposure period	14 days

Comment [T6]: Confidential

Formatted: Highlight

Section A 6.1.2/2 **Annex Point IIA6.1.2**	**Acute Toxicity** **Acute dermal toxicity in the rat: LD_{50} determination**
Area covered	Approximately 4x5 cm^2 dorsal skin area of each rat (clipped free of hair).
Occlusion	Not documented
Vehicle	Permethrin technical was applied undiluted
Concentration in vehicle	Not applicable
Total volume applied	Not documented
Duration of exposure	24 hours
Removal of test substance	The residual test substance was wiped from the skin using cotton soaked in water.
Controls	Animals in control group was similarly treated but without any test stubstance.
Examinations	All animals were observed for mortality and for any reaction at the application site, change in the fur, eyes, mucous membrane, respiratory, circulatory, autonomic and central nervous systems, somatomotor activity and any other overt clinical signs of toxicity including behavioural changes, daily for 14 days. Body weight of each animal was recorded just prior to application of dose (Day 0) and on Days 7 and 14 after treatment. All animals were sacrificed at the end of 14-day observation period for gross pathological examination. All organs and tissues of the animals were observed for gross pathological lesions if any.

Section A 6.1.2/2	**Acute Toxicity**
Annex Point IIA6.1.2	**Acute dermal toxicity in the rat: LD_{50} determination**
Method of determination of LD_{50}	Statistical analysis was unnecessary as there were no mortalities.
Further remarks	None

Results and Discussion

Clinical signs	No clinical signs of toxicity were observed in control and treated groups throughout the observation period. No signs of dermal reaction were observed at the application site.
Pathology	Gross pathology examination revealed lesions that were not related to test substance.
Other	No mortality was observed in control and treated groups throughout the observation period. Results are summarised in Table A6.1.2/2-1. No significant changes in body weight gain were observed in the treated group compared to the control group.
LD_{50}	The acute dermal LD_{50} of Permethrin technical in Wistar rats was determined to be greater than 2000 mg/kg bw.

Section A 6.1.2/2 **Acute Toxicity**

Annex Point IIA6.1.2 **Acute dermal toxicity in the rat: LD_{50} determination**

Applicant's Summary and conclusion

Materials and methods

The test substance Permethrin technical was dosed to 2 groups of Wistar rats (5 animals/sex/group) at the following concentrations 0 and 2000 mg/kg bw.

This study was conducted according to OECD guideline 402 and is described under point 3.

Results and discussion

No mortalities were observed in the animals from the control or treatment group. Results are summarised in Table A6.1.2/2-1.

Animals treated with 2000 mg Permethrin technical/kg bw did not show any clinical sign of toxicity throughout the observation period. Body weight gain observed in the treated group was similar to the control group. Gross pathology examination revealed lesions that were not considered to be treatment-related.

Conclusion

The acute dermal LD_{50} of Permethrin technical in Wistar rats was determined to be greater than 2000 mg/kg bw. In accordance with Council Directive 67/548/EEC it remains unclassified and requires no symbols or risk phrases.

Reliability

1

Deficiencies

No

Evaluation by Competent Authorities

Use separate "evaluation boxes" to provide transparency as to the comments and views submitted

Evaluation by Rapporteur Member State

Date

27/04/2009

Materials and Methods

applicants version is acceptable. Full description of occlusion procedure.

Results and discussion

Animals treated with 2000 mg Permethrin technical/kg bw did not show any clinical sign of toxicity throughout the observation period

Conclusion

The acute dermal LD_{50} of Permethrin technical in Wistar rats was determined to be greater than 2000 mg/kg bw. In accordance with Council Directive 67/548/EEC it remains unclassified and requires no symbols or risk phrases.

Reliability

1

Acceptability

Acceptable

Remarks

Section A 6.1.2/2 **Acute Toxicity**

Annex Point IIA6.1.2 **Acute dermal toxicity in the rat: LD_{50} determination**

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 A6.1.2/2-1: Mortality Data

Group/Dose (mg/kg bw)	No. of animals used	Sex	Percent mortality (up to 14 days)
0	5	Male	0
	5	Female	0
2000	5	Male	0
	5	Female	0

Section A6.1.3 **Acute Toxicity**

Annex Point IIA, VI.6.1.3 **Acute inhalation toxicity study in the rat**

Reference

Reference	[redacted] (1998) Acute Inhalation Toxicity Study of Permethrin Technical in Rats. Department of Toxicology, [redacted] unpublished report no.: 1595
	Dates of experimental work: August 28, 1998 – September 19, 1998.
Data protection	Yes
Data owner	Tagros Chemicals India Ltd.
Companies with letter of access	Not applicable
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/IA.

Comment [T7]: Confidential
Formatted: Highlight
Formatted: Highlight

Guidelines and Quality Assurance

Guideline study	Yes, the test method was based on OECD guideline 403.
GLP	Yes
Deviations	No

MATERIALS AND MethodS

Test material	As given in section 2 (Permethrin 40:60)
Lot/Batch number	PH 01
Specification	As given in section 2 (Permethrin 40:60)
Description	Yellow brown to brown liquid
Purity	92.50%
Stability	Not relevant (single dose)

Section A6.1.3 Acute Toxicity

Annex Point IIA, VI.6.1.3 **Acute inhalation toxicity study in the rat**

Test Animals	
Species	Rat
Strain	Wistar
Source	[redacted]
Sex	Male and female
Age/weight at study initiation	9 to 10 weeks at the start of the main study 124 – 150 g
Number of animals per group	5 animals/sex/group
Control animals	Yes
Administration/ Exposure	Inhalation
Postexposure period	14 days
Concentrations	Nominal concentration 12.631mg/l Analytical concentration 4.638 mg/l
Particle size	MMAD (mass median aerodynamic diameter): >4µm
Type of exposure	Head only
Vehicle	Dimethyl sulphoxide (DMSO)
Concentration in vehicle	12.63mg/l (nominal concentration) 4.638 mg/l (analytical concentration)
Duration of exposure	4 hours
Controls	DMSO (vehicle) only

Comment [T8]: Confidential
Formatted: Highlight

Section A6.1.3	Acute Toxicity
Annex Point IIA, VI.6.1.3	Acute inhalation toxicity study in the rat
Examinations	Gravimetric concentration analysis: To assess the breathing zone concentration, a measured volume of air was drawn from the inhalation chamber at the level of the breathing zone at every hour of exposure and determined by the gravimetric method. Particle size determination: Determined using a seven stage cascade impactor. Clinical observations (mortality and signs of toxicity): At hourly intervals during the 4 hour exposure period and daily thereafter. Necropsy: At animal sacrifice. The appearance of any macroscopic examinations was noted. Histopathology: When deemed necessary. Body weights: Recorded prior to exposure and on days 7 and 14 after exposure.
Method of determination of LD_{50}	Statistical analysis was not carried out.
Further remarks	Not relevant

Results and Discussion

Clinical signs	Abdominal breathing, nasal irritation and tremors were observed during the 3rd and 4th hour of exposure in the treatment group. The female animals that died during the study exhibited nostril discharge, one of these was found dead after the 4 hour exposure period. The other female showed signs of corneal opacity from day 1 to day 6 after exposure and was found dead on day 7 after exposure.
Pathology	An analysis of the pattern of gross visceral changes showed a high incidence of vascular alterations in lung from the treated group, which was considered to be treatment related.
Other	1 female was found dead after 4 hours exposure 1 female was found on day 7 after exposure Normal gain in body weight in all groups during the study.
LD_{50}	As only 20% mortality was observed in rats exposed to the maximum (limit) achievable aerosol concentration of Permethrin technical in air, it can be concluded that the LC_{50} of Permethrin technical is greater than 4.638 mg/l air.

Section A6.1.3 **Acute Toxicity**

Annex Point IIA, VI.6.1.3 **Acute inhalation toxicity study in the rat**

Applicant's Summary and conclusion

Materials and methods

2 groups of 5 rats/sex/group were exposed to Permethrin technical at the following concentrations 0 and 4.638 mg/L. Permethrin technical was administered as a liquid aerosol by the inhalation route.

The study was conducted according to OECD Guideline 403 and was described under point 3 with no deviations.

Results and discussion

The mean concentration of Permethrin technical in the air, at the breathing zone of the rats, was 4.638 mg/l air. Please see Table A6.1.3-1: Concentration of Permethrin technical in the Technical Chamber

20% mortality was observed in rats exposed to the maximum possible concentration of Permethrin technical aerosols (4.683 mg/l air). One female rat was found dead after 4 hour exposure and another female rat was found dead on day 7 after exposure. No mortalities were observed in the control group. Results are summarised in Table A6.1.3-2.

Abdominal breathing, nasal irritation and tremors were observed during the 3rd and 4th hour of exposure in the treatment group.

Two female animals exhibited nostril discharge, one of these was found dead after the 4 hour exposure period. The other female showed signs of corneal opacity from day 1 to day 6 after exposure and was found dead on day 7 after exposure.

No abnormalities were detected in control group animals during the 14 day observation period.

Animals in both the treated and control groups showed a normal gain in body weight during the study.

Minor changes in the lungs of control animals were mild and considered to be incidental to terminal sacrifice.

An analysis of the pattern of gross visceral changes showed a high incidence of vascular alterations in lungs from the treated group, which was considered to be treatment related.

Other minor changes in the kidney and thymus of the treated animals were considered mild and incidental to terminal sacrifice.

Microscopic observations corroborated these findings.

Conclusion

As only 20% mortality was observed in rats exposed to the maximum (limit) achievable aerosol concentration of Permethrin technical in air, it can be concluded that the LC_{50} of Permethrin technical is greater than 4.638 mg/l air. In accordance with Council Directive 67/548/EEC, Permethrin technical remains unclassified and requires no symbols or risk phrases.

Reliability 1

Section A6.1.3	Acute Toxicity
Annex Point IIA, VI.6.1.3	Acute inhalation toxicity study in the rat
Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	Evaluation by Rapporteur Member State
Date	27/04/2009
Materials and Methods	Applicants version is acceptable
Results and discussion	Adopt applicant's version. 20% mortality was observed in rats exposed to the maximum possible concentration of Permethrin technical aerosols (4.683 mg/l air).
Conclusion	Adopt applicant's version As only 20% mortality was observed in rats exposed to the maximum (limit) achievable aerosol concentration of Permethrin technical in air, it can be concluded that the LC_{50} of Permethrin technical is greater than 4.638 mg/l air. In accordance with Council Directive 67/548/EEC, Permethrin technical remains unclassified and requires no symbols or risk phrases.
Reliability	1
Acceptability	Acceptable
Remarks	Under 67/548 if the LC50 of a compound falls within the range of 1,LC50,5 mg/litre/4hr, it will be classified as Xn R20; Harmful by inhalation
	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 A6.1.3-1: Concentration of Permethrin technical in the technical chamber

Group	Number of animals exposed	Air flow Rate (1/min)	Infusion Rate (ml/h)	Calculated nominal concentration (mg/1)	Actual breathing zone concentration (mg/1)	
					Mean	SD
I	10 (5 M + 5 F)	10	12 (DMSO)	0	0	0
II	10 (5 M + 5 F)	10	12	12.631	4.638	0.084

M = Male, F = Female, SD = Standard deviation, DMSO = Dimethyl sulphoxide

Table A6.1.3-2: Mortality data

Group	Breathing zone conc. (mg/l of air)	No. of animals used	Mortalities						Mortality		
			During exposure (Day 0)	After exposure					Number		Per cent
			1-4 h	24h	48h	72h	4-7 day	8-14 day	M	F	
I	0	5 M + 5 F	0	0	0	0	0	0	0	0	0
II	4.638	5 M + 5 F	1	0	0	0	1	0	0	2	20

M = Male, F = Female

Section A6.1.4/1 **Acute Dermal Irritation**

Annex Point IIA6.1.4 **Acute dermal irritation in rabbits**

Official use only

Reference

Reference	[redacted] (1998d) Acute Dermal Irritation Study of Permethrin Technical in Rabbits. Department of Toxicology, [redacted] unpublished report no.: 1590.
	Dates of experimental work: July 13, 1998 – July 20, 1998.
Data protection	Yes
Data owner	Tagros Chemicals India Ltd.
Companies with letter of access	Not applicable
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/IA.

Comment [T9]: Confidential
Formatted: Highlight
Formatted: Highlight

Guidelines and Quality Assurance

Guideline study	Yes, the test method was based on U.S. EPA Guideline 81-2, which is comparable to OECD guideline 404.
GLP	Yes
Deviations	No

MATERIALS AND MethodS

Test material	As given in section 2 (Permethrin 40:60)
Lot/Batch number	PH01
Specification	As given in section 2 (Permethrin 40:60)
Description	Light yellow colour, viscous liquid
Purity	92.50%
Stability	Stored at room temperature
Test Animals	
Species	Rabbit *(Oryctolagus cuniculus)*

Section A6.1.4/1 Acute Dermal Irritation

Annex Point IIA6.1.4 **Acute dermal irritation in rabbits**

Strain	New Zealand White
Source	[redacted]
Sex	Female
Age/Weight at study initiation	Age: Not documented 1.52 to 1.71 kg
Number of animals per group	3
Control animals	No (another site on same animal served as control)
Administration/ Exposure	Dermal
Application	
Preparation of test substance	Test substance was used as delivered.
Test site and Preparation of Test Site	Twenty-four hours prior to the treatment, hair from the dorso-lumbar region at two sites on each rabbit was closely clipped using a scissors. An area of approximately 6 cm^2 was clipped on both sides.
Occlusion	Occlusive The site was covered with a gauze patch of approximately 6 cm^2 and then covered with a gauze dressing not more than 8-ply, which was secured at the margins by hypo-allergic tape to prevent evaporation of Permethrin technical and to ensure that the animals did not ingest it.
Vehicle	None
Concentration in vehicle	100 %
Total volume applied	0.5 ml
Removal of test substance	The residual Permethrin technical was removed with cotton soaked in filtered water.
Duration of exposure	4 hours
Post exposure period	7 days

Comment [T10]: Confidential
Formatted: Highlight

Section A6.1.4/1 **Acute Dermal Irritation**

Annex Point IIA6.1.4 **Acute dermal irritation in rabbits**

Controls	A second clipped site on the animal was covered with a gauze patch without any application.
Examinations	
Clinical signs	Yes Individual clinical observations were made on the day of application of Permethrin technical, and then on days 1, 2, 3, 4, 5, 6 and 7 following application.
Dermal examination	Yes
Scoring system	The Draize method of scoring was applied.
Examination time points	The sites were examined at 1, 24, 48, 72 hours and on day 7 after patches were removed.
Other examinations	None
Further remarks	None

Results and Discussion

Average score	
Erythema	The average scores for all animals were: 1 at 1 hour, 0.33 at 24-72 and 0 at day 7.
Edema	The average value for all animals was 0 at all time points.
Reversibility	Yes Erythema noted at 72 hours was reverted by day 7.
Other examinations	None
Overall result	The mean score at 24-72 hours for Permethrin technical was 0.3, according to the Draize method.

Applicant's Summary and conclusion

Section A6.1.4/1	Acute Dermal Irritation
Annex Point IIA6.1.4	Acute dermal irritation in rabbits
Materials and methods	Permethrin technical was applied to the backs of a group of 3 White New Zealand rabbits. The test methods were based on US EPA Guidelines 81-5 and OECD Guidelines 404 and was described under point 3 with no deviations.
Results and discussion	The average scores for all animals were: 1 at 1 hour, 0.33 at 24-72 and 0 at day 7. Results are summarised in Table A6.1.4/1-1. Very slight redness of skin was observed in all treated sites at 1 hour after patches were removed. At 24, 48 and 72 hours after patch removal very slight redness of skin was noted in one rabbit. All treated sites were normal on day 7. No other abnormalities or reactions related to treatment were observed. According to the Draize method, the mean score at 24-72 hours for Permethrin technical was 0.3.
Conclusion	However, according to Council Directive 67/548/EEC, Permethrin technical remains unclassified as a skin irritant. Therefore, no symbols or risk phrases are assigned.
Reliability	1
Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	Evaluation by Rapporteur Member State
Date	28/04/2009
Materials and Methods	Applicant's version is acceptable
Results and discussion	Very slight redness of skin was observed in all treated sites at 1 hour after patches were removed. At 24, 48 and 72 hours after patch removal very slight redness of skin was noted in one rabbit. All treated sites were normal on day 7. According to the Draize method, the mean score at 24-72 hours for Permethrin technical was 0.3.
Conclusion	Therefore according to Council Directive 67/548/EEC, Permethrin technical is not a skin irritant and as a result no symbols or risk phrases are assigned.
Reliability	1
Acceptability	Acceptable

Section A6.1.4/1 Acute Dermal Irritation

Annex Point IIA6.1.4 Acute dermal irritation in rabbits

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 A6.1.4/1-1: Dermal irritation scores for Permethrin technical treated sites

	Erythema			Oedema		
Animal No.	1F	2F	3F	1F	2F	3F
Up to 1 hour	1	1	1	0	0	0
After 24 hours	0	0	1	0	0	0
After 48 hours	0	0	1	0	0	0
After 72 hours	0	0	1	0	0	0
After 7 days	0	0	0	0	0	0
Mean Score 24 – 72 hours	0.33			0		

F = Female

Section A6.1.4/2 **Acute Eye Irritation**

Annex Point IIA 6.1.4 **Acute eye irritation in rabbits**

Official use only

1 Reference

Reference	[redacted] (1998c) Acute Eye Irritation Study of Permethrin Technical in Rabbits. Department of Toxicology, [redacted] unpublished report no.: 1589.
	Dates of experimental work: July 13, 1998 – July 16, 1998.
Data protection	Yes
Data owner	Tagros Chemicals India Ltd.
Companies with letter of access	Not applicable
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/IA.

Comment [T11]: Confidential
Formatted: Highlight
Formatted: Highlight

Guidelines and Quality Assurance

Guideline study	Yes, the test method was based on OECD guideline 405.
GLP	Yes
Deviations	No

MATERIALS AND MethodS

Test material	As given in section 2 (Permethrin 40:60)
Lot/Batch number	PH01
Specification	As given in section 2 (Permethrin 40:60)
Description	Light yellow colour, viscous liquid
Purity	92.50%
Stability	Stored at room temperature

Section A6.1.4/2 Acute Eye Irritation

Annex Point IIA 6.1.4 **Acute eye irritation in rabbits**

Test Animals	
Species	Rabbit (*Oryctolagus cuniculus*)
Strain	New Zealand White
Source	[redacted]
Sex	Male
Age/Weight at study initiation	Age: Not documented 1.38 - 1.61 kg
Number of animals per group	3
Control animals	No (Contra lateral eye of each rabbit served as a control)
Administration/ Exposure	
Preparation of test substance	Test substance was used as delivered.
Amount of active substance instilled	0.1ml
Exposure period	24 hours
Post exposure period	3 days
Examinations	
Ophthalmoscopic examination	Yes
Scoring system	Scoring for ocular lesions was undertaken for the cornea, the iris and the conjunctiva using the method from Kwong and Hayes. For each observation occasion, scoring for ocular lesions was undertaken for the cornea, the iris and the conjunctiva (including lids and/ or nictitating membranes).
Examination time points	1, 24, 48 and 72 hours
Other investigations	One hour prior to treatment, both eyes of each rabbit were examined for ocular lesions.
Further remarks	Not relevant

Comment [T12]: Confidential

Formatted: Highlight

Section A6.1.4/2 **Acute Eye Irritation**

Annex Point IIA 6.1.4 **Acute eye irritation in rabbits**

Results and Discussion

Clinical signs	No abnormalities, other than eye irritation, were recorded in any of the three rabbits.
Average score	
Cornea	The average score for all animals was 0 at 24, 48, 72 hours. The mean score at 24-72 hours was 0.
Iris	The average score for all animals was 0 at 24, 48, 72 hours. The mean score at 24-72 hours was 0.
Conjunctiva	
Redness	The average score for all animals was 0 at 24, 48, 72 hours. The mean score at 24-72 hours was 0.
Chemosis	The average score for all animals was 0 at 24, 48, 72 hours. The mean score at 24-72 hours was 0.
Reversibility	Yes Two of the animals scored 1 for conjunctiva redness at 1-hour post application. This had reverted to a score of 0 at 24 hours.
Other	Examination of eyes with fluorescein dye showed partial (1/4) erosion of corneal epithelium in all treated eyes and 2 of 3 control eyes.
Overall result	The mean eye irritation scores (according to a modified Kay and Calandra interpretation of eye irritation) were 1.3, 0, 0 and 0, at 1, 24, 48 and 72 hours, respectively. The mean score at 24-72 hours was 0. A single installation of 0.1 ml Permethrin technical is non-irritant to rabbit eyes.

Section A6.1.4/2 **Acute Eye Irritation**

Annex Point IIA 6.1.4 **Acute eye irritation in rabbits**

Applicant's Summary and conclusion

Materials and methods

Permethrin technical was instilled into the conjunctival sac of one eye of a group of 3 New Zealand White rabbits.

This study was conducted according to OECD guideline 405 and is described under point 3 with no deviation.

Results and discussion

The mean eye irritation scores (according to a modified Kay and Calandra interpretation of eye irritation) were 1.3, 0, 0 and 1, at 1, 24, 48 and 72 hours, respectively. The mean scores at 24-72 hours was 0, 0 and 0 for cornea, iris, redness and chemosis. A single installation of 0.1 ml Permethrin technical is non-irritant to rabbit eyes. Results are summarised in Table A6.1.4/2-1.

No abnormalities were detected in the control eyes of the rabbits during the course of this study, except at 24 hour treatment, partial (1/4) erosion of corneal epithelium was observed in two animals during examination with fluorescein dye and cobalt blue filter (corneal damage showing as green fluorescein staining).

No abnormalities, other than eye irritation were recorded in any of the three rabbits.

Conclusion

In accordance with Council Directive 67/548/EEC, Permethrin technical remains unclassified as an eye irritant and requires no symbols or risk phrases.

Reliability

1

Deficiencies

No

Section A6.1.4/2 Acute Eye Irritation

Annex Point IIA 6.1.4 Acute eye irritation in rabbits

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	Evaluation by Rapporteur Member State
Date	28/04/2009
Materials and Methods	Applicants version is acceptable
Results and discussion	The mean eye irritation scores (according to a modified Kay and Calandra interpretation of eye irritation) were 1.3, 0, 0 and 0, at 1, 24, 48 and 72 hours, respectively. The mean score at 24-72 hours was 0. A single installation of 0.1 ml Permethrin technical is non-irritant to rabbit eyes.
Conclusion	In accordance with Council Directive 67/548/EEC, Permethrin is not considered an eye irritant and requires no symbols or risk phrases.
Reliability	1
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 A6.1.4/2-1: Mean eye irritation scores

Rabbit No.	Sex	Individual total scores post installation			
		Hours			
		1	24	48	72
1	Male	2	0	0	0
2	Male	2	0	0	0
3	Male	0	0	0	0
Total score		4	0	0	0
Mean score (24-72 hours)			0		

Section A6.1.5 **Skin sensitisation**
Annex Point IIA6.1.5 **Buehler test**

Official use only

2 Reference

2.1	**Reference**	[redacted] (1998e) Skin Sensitisation Study of Permethrin Technical in Guinea Pigs [Buehler Test]. Department of Toxicology, [redacted] unpublished report no.: 1599. Dates of experimental work: November 10, 1998 – December 11, 1998
2.2	**Data protection**	Yes
2.2.1	Data owner	Tagros Chemicals India Ltd.
2.2.2	Companies with letter of access	Not applicable
2.2.3	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/IA.

3 Guidelines and Quality Assurance

3.1	**Guideline study**	Yes, the test method was based on OECD guideline 406.
3.2	**GLP**	Yes
3.3	**Deviations**	No

4 MATERIALS AND MethodS

4.1	**Test material**	As given in section 2 (Permethrin 40:60)
4.1.1	Batch number	PH 01
4.1.2	Specification	As given in section 2 (Permethrin 40:60)
4.1.2.1	Description	Light yellow colour, viscous liquid
4.1.2.2	Purity	92.50 %
4.1.2.3	Stability	Stored at room temperature

Comment [T13]: Confidential
Formatted: Highlight
Formatted: Highlight

Section A6.1.5 **Skin sensitisation**

Annex Point IIA6.1.5 **Buehler test**

4.1.2.4	Preparation of test substance for application	Induction: used as delivered Challenge: used as delivered
4.1.2.5	Pretest performed on irritant effects	Yes A volume of 0.5 ml of Permethrin technical was found to be non-irritant to the guinea pig when applied dermally in an irritancy screen test conducted in a few animals before the main study. Hence, 0.5 ml of Permethrin technical was selected for the main study.
4.2	**Test Animals**	
4.2.1	Species	Guinea pig *(Cavia porcellus)*
4.2.2	Strain	Hartley
4.2.3	Source	[redacted]
4.2.4	Sex	Male and Female
4.2.5	Age/Weight at study initiation	Age: Not documented 310 to 428 g
4.2.6	Number of animals per group	10 in control group and 20 in treated group
4.2.7	Control animals	Yes
4.3	**Administration/ Exposure**	Non-Adjuvant
4.3.1	Induction schedule	Day 0 – Day – 7 – Day 14
4.3.2	Way of Induction	Topical Occlusive
4.3.3	Concentrations used for induction	0.5 ml of undiluted Permethrin technical
4.3.4	Concentration Freunds Complete Adjuvant (FCA)	Not applicable

Comment [T14]: Confidential
Formatted: Highlight

Section A6.1.5 **Skin sensitisation**
Annex Point IIA6.1.5 **Buehler test**

4.3.5	Challenge schedule	Day 28
4.3.6	Concentrations used for challenge	0.5 ml of undiluted Permethrin technical
4.3.7	Rechallenge	No
4.3.8	Scoring schedule	24 h and 48 h after challenge
4.3.9	Removal of the test substance	Patches were removed after 6 hours
4.3.10	Positive control substance	2-mercaptobenzothiazole A.R.
4.4	**Examinations**	
4.4.1	Pilot study	Yes
4.4.2	Main study	The skin of guinea pigs were observed for the evaluation of challenge patch test reactions at 24 and 48 hours after patch removal, following the Magnusson and Kligman grading scale.
4.5	**Further remarks**	Body weight data were statistically analysed by Student 't' test and the degree of sensitising potential was assigned according to the percentage of animals giving a positive response in the test group, by following the classification of responses in the Buehler test.

5 Results and Discussion

5.1	**Results of pilot studies**	0.5 ml of undiluted Permethrin technical was found to be non-irritant to the guinea pig, and therefore was chosen for induction and challenge exposure.
5.2	**Results of test**	
5.2.1	24h after challenge	2 animals with signs of allergic reactions / 20 animals
5.2.2	48h after challenge	No response
5.2.3	Other findings	None

Section A6.1.5	Skin sensitisation
Annex Point IIA6.1.5	Buehler test
5.3 Overall result	Positive control: 2-mercaptobenzothiazole A.R, positive control, was found to be a moderate skin sensitiser (grade III) to guinea pigs as 55% of treated animals exhibited positive skin responses at 24 and 48 hours and 45% at 72 hours of the challenge phase. Main study: Two animals showed a positive response (grade 1) at 24 hours following removal of patch indicating a 10% positive skin response during the challenge phase. According to Directive 67/548/EEC a response of at least 15% of the animals is required in order to classify a compound as being a sensitiser. In this case, Permethrin technical is not deemed to be a sensitiser according to this directive. Therefore, no symbols or risk phrases are assigned.

Section A6.1.5 **Skin sensitisation**
Annex Point IIA6.1.5 **Buehler test**

6 Applicant's Summary and conclusion

6.1 Materials and methods

0.5 ml of Permethrin was applied to the skin of 20 Guinea pigs as supplied. The test was based on the Buehler method. X

This study was conducted according to OECD guideline 406 and is described under point 3 with no deviations.

6.2 Results and discussion

All animals showed body weight gain during the experimental period.

Positive control:
2-mercaptobenzothiazole A.R, positive control, was found to be a moderate skin sensitiser (grade III) to guinea pigs as 55% of treated animals exhibited positive skin responses at 24 and 48 hours and 45% at 72 hours of the challenge phase.

Main study:
Two animals showed a positive response (grade 1) at 24 hours following removal of patch indicating a 10% positive skin response during the challenge phase. According to Directive 67/548/EEC a response of at least 15% of the animals is required in order to classify a compound as being a sensitiser. Results are summarised in Tables A6.1.5-1 and A6.1.5-2.

6.3 Conclusion

In accordance with Council Directive 67/548/EEC, Permethrin technical remains unclassified as a skin sensitiser and requires no symbols or risk phrases.

6.3.1 Reliability

1

6.3.2 Deficiencies

No

Section A6.1.5 **Skin sensitisation**

Annex Point IIA6.1.5 **Buehler test**

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	Evaluation by Rapporteur Member State
Date	28/04/2009
Materials and Methods	5.1 Buehler is not the preferred skin sensitisation test for an active substance. The Guinea Pig Maximisation test would be more appropriate to test the active substance
Results and discussion	Two animals showed a positive response (grade 1) at 24 hours following removal of patch indicating a 10% positive skin response during the challenge phase. According to Directive 67/548/EEC a response of at least 15% of the animals is required in order to classify a compound as being a sensitiser.
Conclusion	In accordance with Council Directive 67/548/EEC, Permethrin technical remains unclassified as a skin sensitiser and requires no symbols or risk phrases.
Reliability	2 Due to the fact that the non-adjuvant Buehler method was used instead of M&K
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 A6.1.5-1: Summary of skin reactions at 24 and 48 hours following removal of challenge patch

Group	Observation time (Hours)	Number of animals showing response				Incidence (Grade 1 and above)	% Positive reaction
		Magnusson and Klingman grading scale					
		0	1	2	3		
Treated	24	18	2	0	0	2	10
	48	20	0	0	0	0	0
Control	24	10	0	0	0	0	0
	48	10	0	0	0	0	0

Skin response: 0 = No visible change; 1 = Discrete or patchy erythema; 2 = Moderate and confluent erythema; 3 = Intense erythema and swelling

Table A6.1.5-2: Summary of results of skin sensitisation test

	Number of animals with signs of allergic reactions / number of animals in group		
	Negative control	Test group (Permethrin technical)	Positive control
Scored after 24h	0 /10	2 /20	11 /20
Scored after 48h	0 /10	0 /20	11/ 20

Section A6.2 Annex Point IIA6.2	Metabolism studies in mammals	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	It is proposed that sufficient data is available in the literature to address the basic toxicokinetic data for Permethrin. Permethrin is an ester of the dichloro derivative of chrysanthemic acid and 3-phenoxybenzyl alcohol. A wide range of studies are reported in the literature in various mammalian species using single or repeated doses, low and high doses. ^{14}C-labelled Permethrin was orally administered to male Sprague Dawley rats at 0.5 to 4.8 mg/kg bw. Levels of the parent compound and metabolites were analysed in urine, faeces, expired air and in various tissues such as fat, liver, kidney and lung. Only 0.5% of the dose was found in the expired air as $^{14}CO_2$ while 76 to 96% of the radiocarbon from Permethrin or the derivatives was recovered in the excreta after 4 days, most being eliminated during the first 24 hours. This indicates that Permethrin and its metabolites are rapidly excreted and are not retained in the tissues. Furthermore a difference in the elimination of cis:trans Permethrin was noted. ^{14}C-labelled metabolites following the administration of ^{14}C-labelled-[*1R, trans*]-Permethrin were mainly detected in urine (84-91% of excreted radiocarbon) after 4 days. Radiocarbon compounds were mostly found in the faeces following the administration of ^{14}C-labelled-[*1R, cis*]-Permethrin (Pfau, 2005). The major routes of metabolism for both *trans* and *cis* isomers involved the hydrolysis of the ester moiety bond, oxidation at the *trans*- and *cis*-methyl of the geminal dimethyl groups of the acid moiety and oxidation the 2`- and 4`-positions of the phenoxy group. Conjugation of the resultant carboxylic acids, alcohols, and phenols with glucuronic acid, glycine, and sulphuric acid occurred to varying extent. ^{14}C-labelled Permethrin was administered to 4 groups of 4 Nubian and Nubian-Saanen-cross goats using repeated doses at 0.2-0.3 mg/kg bw/day. After the 10 consecutive daily oral doses of *trans* isomer, 72 to 79% of the radiolabel were excreted in urine and 12-15% in faeces. The *cis* isomer was found mostly in the faeces (52-68%). Only 0.7% of the dose was detected in the milk (Pfau, 2005). A similar pathway as described previously was identified. It involved the hydrolysis of the ester linkage, hydroxylation at the *cis*- or *trans*- methyl of the geminal dimethyl group at the cyclopropane ring, and hydroxylation at the 4`-position of the phenoxybenzyl moiety. Some of these metabolic products were further oxidised and/ or conjugated with glycine, glutamic acid and glucuronic acid. The major urinary metabolites derived from the alcohol moiety of both, *cis* and *trans*-isomers were glycine conjugates of 4-phenoxybenzoic acid (Pbacid) (66-89%) and 4`-OH-PB acid (4-12%). The major urinary metabolites	

Section A6.2 Annex Point IIA6.2	Metabolism studies in mammals
	derived from the acid moiety of both, *cis* and *trans*-isomers were Cl_2CA in the free form (2-47%) and as a glucuronide conjugate (27-71%). Low radioactivity was detected in the fat and was identified as the parent compound (59-80%). An *in vitro* study on mouse and rat liver microsomes was conducted to explain the metabolism pathway in the liver. It was concluded that both microsomal preparations hydrolised *trans*-Permethrin to a much greater extent than the *cis*-isomer. Please refer to the review (Pfau, 2005) for further details. Permethrin was administered to male Sprague Dawley rats at a single oral dose of 460 mg/kg bw or an intravenous dose of 46 mg/kg bw. The oral absorption was found to be slow. Peak plasma levels were observed 4 hours after dosing with elimination half-lives of 12.4 hour. Peak levels noted in the nervous system (central and peripheral) were higher than plasma concentrations. Levels of Permethrin and metabolites (such as m-phenoxybenzyl alcohol and 3-phenoxy benzoic acid) were determined in plasma and for the oral treatment group in nervous compartments. Accumulation of Permethrin was reported to be higher in the central nervous system than in plasma with maximum Permethrin levels 7.4-fold (sciatic nerve) and 4.8-fold (hypothalamus). Metabolites were also detected at similar or lower levels compared to the parent compound. Following surveillance of pest control operator using Permethrin, the metabolites (Cl_2CA and 3-phenoxy benzoic acid) were identified in the urine one day after application and had disappeared at the 3 months and 12 months checking. These metabolites were consistent with the metabolic pathways established in mammals (Pfau, 2005). Please refer to the literature review for the identified pathway. The literature review demonstrated that the relevant metabolites and their pathway have been clearly identified. Furthermore, Permethrin is rapidly and extensively excreted in urine and faeces. The *cis*-isomers appear to persist longer than the *trans*-isomers. However Permethrin supported for this submission contains mostly *trans*-isomers (25 *cis*: 75 *trans*). Therefore no studies are presented to address this point. In conclusion, there are no ethical grounds (that would not contravene the requirements of Directive 86/609/EC which advises against unnecessary testing using animals) for performing further studies on animals. It is therefore proposed that no additional investigations are required to address this point.
Undertaking of intended data submission [ ]	Not applicable

Section A6.2 Annex Point IIA6.2	Metabolism studies in mammals
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	23/6/09
Evaluation of applicant's justification	Applicant's justification is acceptable. There are numerous studies on ADME of permethrin in mammals and humans. In addition, several evaluations of this synthetic pyrethroid by international expert communities (JMPR, JECFA, EMEA) are based upon the data published from these studies. However, in paragraph 7, Sprague Dawley rats were dosed up to 460-mg/kg day and absorption was described as slow and it described how permethrin had the potential to accumulate in the CNS. This is in direct contrast to the opinion held in paragraph 2 and other sources in the literature. In addition it is near an LD_{50} of 480-mg/kg bw/day described by other sources. Therefore, the RMS will not be including this section of the literature search in the endpoints document.
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 A6.2/2 Annex Point IIA 6.2	Percutaneous absorption (*in vivo* test)	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [X]** **Other justification [ ]**	
Detailed justification:	It is proposed that sufficient information is available in the literature to address this point. In a dermal absorption study of Permethrin in mice, ^{14}C-cis-Permethrin was applied to the skin of mice at a level of 1 mg/kg bw in 0.1 mL of acetone. 40% of the applied Permethrin were rapidly distributed in the body. Eight hours later, ^{14}C was found mostly in the faeces (63.8%). The percentages of ^{14}C recovered in the carcass and in the intestine were 10.4 and 6.3%, respectively (Pfau, 2005). A dermal absorption was conducted *in vitro* and showed that little absorption occurred with DMSO and acetone by pig or rat skin (Pfau, 2005). In conclusion, there are no ethical grounds (that would not contravene the requirements of Directive 86/609/EC which advises against unnecessary testing using animals) for performing further studies on animals. It is therefore proposed that no additional investigations are required to address this point.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*24/06/2009*	
Evaluation of applicant's justification	*Under 98/8, it is acceptable for the RMS to take an endpoint from other sources of acceptable information*	
Conclusion	*In this circumstance the 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*	

Section A6.2/2 **Annex Point IIA 6.2**	**Percutaneous absorption (*in vivo* test)**
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.3.1 **Repeated dose toxicity**
Annex Point IIA6.3.1 **28-day oral toxicity study in the rat**

Official use only

7 Reference

Reference	[redacted] (2002) Permethrin: 28-Day Dietary Range Finding Study in Wistar Rats. [redacted] unpublished report no.: 3350/02
	Dates of experimental work: July 30, 2002 – August 28, 2002.
Data protection	Yes
Data owner	Tagros Chemicals India Ltd.
Letter of access	
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/IA.

Comment [T15]: Confidential
Formatted: Highlight
Formatted: Highlight

Guidelines and Quality Assurance

Guideline study	Yes, the test method was based on OECD Guideline 407.
GLP	Yes
Deviations	Yes, the following deviations: X

1. No haematological, clinical biochemical analysis or histopathology was carried out as is recommended in the guideline.
2. The guideline recommends conducting sensory reactivity to stimuli, however this was not carried out.

These deviations are not considered to compromise the scientific validity of the study.

MATERIALS AND MethodS

Test material	Permethrin technical
Lot/Batch number	143

Section A6.3.1 Repeated dose toxicity
Annex Point IIA6.3.1 28-day oral toxicity study in the rat

Specification	As given in section 2 (Permethrin 25:75)
Description	Yellow to pale brown coloured viscous liquid, with a mild characteristic odour, which tends to crystallize partly at room temperature.
Purity	92.4%
Stability	An in-house stability study (Study No: 3349/02) was carried out on both 50 and 10000 ppm doses. Results of this showed that the test item was stable at these concentrations for 30 days, with a loss of 6.0% and 5.1%, respectively from the concentration recorded on day 0, when stored at room temperature within polyethylene bags placed inside a stainless steel drum.
Test Animals	
Species	Rat (HsdCpd: WR rats conventionally bred)
Strain	Wistar
Source	[redacted]
Sex	Male and female
Age/weight at study initiation	8 weeks at start of treatment Males: 297 g – 299 g Females: 178 g – 180 g
Number of animals per group	12 (6 males and 6 females)
Control animals	Yes
Administration/ Exposure	
Duration of treatment	Oral
Frequency of exposure	28 days
Postexposure period	Daily (in food)

Oral

Comment [T16]: Confidential
Formatted: Highlight

Section A6.3.1 Annex Point IIA6.3.1	Repeated dose toxicity 28-day oral toxicity study in the rat	
Type	In food	
Concentration	0, 200, 800, 3000 and 10000 ppm (equivalent to 0, 17.15, 68.6, 257.25 and 857.5mg/kg bw) On treatment day 4, the 10000 ppm group was reduced to 5000 ppm (equivalent to 428.75 mg/mg bw) and the 3000 ppm group was reduced to 2400 ppm (equivalent to 205.8 mg/kg bw)	
Vehicle	Acetone	
Concentration in vehicle	Not applicable	
Total volume applied	None	
Controls	Not applicable	
Examinations		
Observations		
Clinical signs	Yes, once daily	
Mortality	Yes, twice daily	
Body weight	Yes, before treatment and weekly thereafter	
Food consumption	Weekly food consumption was recorded. The weekly consumption per rat was divided by the number of days (7) to obtain food consumption (g)/rat/day.	
Water consumption	Not recorded	
Ophthalmoscopic examination	Before treatment and at the end of the treatment period, prior to sacrifice. Mydriasis was induced before examination using a solution of 1% Tropicamide.	
Haematology	No	X
Clinical Chemisty	No	X
Urinalysis	No	X
Sacrifice and pathology		
Organ Weights	Yes	
	Organs: adrenals, gonads, epididymides, spleen, liver, kidneys, thymus, brain and heart	

Section A6.3.1 **Repeated dose toxicity**
Annex Point IIA6.3.1 **28-day oral toxicity study in the rat**

	Organ weight ratios as percentage of body weights were determined.
Gross and histopathology	Yes All rats were fasted overnight and subjected to gross necropsy at study termination.
Other examinations	Body weight, net weight gain, food consumption, organ weight and organ weight ratio values were compared by Bartlett's test for homogeneity of intra-group variances. When the variances proved to be heterogeneous, the data was transformed using appropriate transformation. The data with homogeneous intra-group variances were subjected to one-way analysis of variance (ANOVA – Snedecor and Cochran, 1987). Following ANOVA, when the 'F' value was significant, Dunnett's pairwise comparison (Scheffe, 1953) of means of treated groups with the control mean was carried out individually. Dose response correlation was estimated and tested by 't' test analysis where significant differences were noted between test and control groups. All analysis and comparisons were evaluated at the 5% level.
Statistics	Yes Organs: adrenals, gonads, epididymides, spleen, liver, kidneys, thymus, brain and heart Organ weight ratios as percentage of body weights were determined.

Further remarks

Results and Discussion

Observations

Clinical signs

Males:

Treatment related signs of tremors (moderate to severe) with hypersensitivity were observed on treatment days 3 and 4 in all rats at 10000 ppm

Treatment related tremors (mild moderate) with hypersensitivity were observed at various stages from days 7 to 29 in 4 rats at 5000 ppm

Females:

Treatment related clinical signs of tremors (moderate to severe) associated with hypersensitivity were observed on days 3 and 4 in all rats, except for 1 rat, which exhibited clinical signs of tremors and also died on day 3 at 10000 ppm.

Treatment related tremors (mild moderate) with hypersensitivity were observed in 4 rats at various stages, from days 5 to 29

Signs of dullness and discharge from both eyes were observed in one female from days 8 to 10. On day 10 the animal was noted to be weak and was found dead on day 11.

Section A6.3.1 Annex Point IIA6.3.1	Repeated dose toxicity 28-day oral toxicity study in the rat
Mortality	Two females died on treatment days 3 and 11 at 10000 ppm One female was sacrificed moribund on day 4.
Body weight gain	Males: No treatment related changes in mean body weights and in cumulative net weight gains. Females: No treatment related changes in mean body weights and in cumulative net weight gains Increase in the cumulative net weight gains during weeks 1 and 2 at 10000 ppm.
Food consumption and compound intake	No statistically significant differences in any of the tested doses were noted with the exception of the high dose male group (10000 ppm) for which a statistically significant decrease in food intake during week 1 was noted.
Ophtalmoscopic examination	No eye abnormalities were noted at any dose level.
Blood analysis	
Haematology	Not conducted
Clinical chemistry	Not conducted
Urinalysis	Not conducted
Sacrifice and pathology	
Organ weights	Males: Treatment related increase in absolute liver weights at high intermediate and high doses. Treatment related increase in the relative weights of livers at the high intermediate and high doses. Females: Treatment related increase in absolute weights of livers at the high intermediate and high doses.
Gross and histopathology	No treatment related gross changes were noted.
Other	None
	Applicant's Summary and conclusion
Materials and methods	Permethrin technical was administered for 28 days to 5 groups of Wistar rats (6 animals/sex) at the following dose: 0, 200, 800, 3000 and 10000 X

Section A6.3.1 Repeated dose toxicity
Annex Point IIA6.3.1 28-day oral toxicity study in the rat

ppm (equivalent to 0, 17.15, 68.6, 257.25 and 857.5mg/kg bw). On treatment day 4, the 10000 ppm group was reduced to 5000 ppm (equivalent to 428.75 mg/mg bw) and the 3000 ppm group was reduced to 2400 ppm (equivalent to 205.8 mg/kg bw)

This study was conducted according to OECD guideline 407 and is described under point 3 with the following deviations:

1. No haematological, clinical biochemical analysis or histopathology was carried out as recommended in the guideline.
2. The guideline recommends conducting sensory reactivity to stimuli, however this was not carried out.

This study was carried out as a range finding test for a subsequent 90 day study in which these parameters were measured and is still considered to contain scientifically valid information.

Results and discussion

No treatment related clinical signs were observed in either sex, at the low, mid and high intermediate dose levels except for two incidental findings of hair thinning with regrowth, which was observed in 2 female rats of the mid dose group.

At the high dose (10000 ppm), treatment related clinical signs of tremors associated with hypersensitivity were observed on treatment days 3 and 4 in all male rats. These tremors were of moderate severity. When the dose was reduced to 5000 ppm, from day 4, mild to moderate tremors which were associated with hypersensitivity were observed at various stages from days 7 to 29 in 4 male rats.

At the high dose (10000 ppm), treatment related clinical signs of tremors associated with hypersensitivity were observed on days 3 and 4 in all female rats, except for 1, which exhibited clinical signs of tremors and also died on day 3. These tremors ranged from moderate to severe. When the dose was reduced to 5000 pmm, from day 4 mild to moderate tremors which were associated with hypersensitivity were observed in 4 female rats at various stages. One such female rat exhibited clinical signs of dullness and discharge from both eyes. This was observed from days 8 to 10. On day 10 the animal was noted to be weak and was found dead on day 11.

At the high dose, two female rats died on treatment days 3 and 11. A third animal was sacrificed moribund on day 4.

No statistical inter-group differences in mean body weights were noted in any of the male tested groups. The cumulative net weight gains were comparably lower at the high dose and statistical significance was achieved during week 1. In all other male treatment groups, cumulative net weight gains were similar to the controls.

No statistical inter-group differences in mean body weights were noted

Section A6.3.1 **Repeated dose toxicity**

Annex Point IIA6.3.1 **28-day oral toxicity study in the rat**

in any of the female tested groups except for one incidence of significantly lower mean body weights during week 1 in the high dose group. The cumulative net weight gains were comparably lower at the high dose, statistical significance was achieved during weeks 1 and 2. In all other female treatment groups, cumulative net weight gains were similar to the controls.Please see Tables A6.3.1-1 and A6.3.1-2.

There were no significant inter-group differences in terminal fasting body weights.

No statistical inter-group differences in any of the tested doses were noted with the exception of the high dose male group, for which significantly lower food intake during week 1 was noted. Please refer to Table A6.3.1-3.

No eye abnormalities were noted at any dose level.

In males, analysis of organ weights and their ratios showed treatment related significantly higher absolute weights of livers at the high intermediate (17.6%) and high doses (28.9%), and the relative weights of livers at the high intermediate (17.1%) and high dose (32.5%). At the mid dose, the relative weights of livers was significantly higher (9.2%) than controls. This slight increase was not considered biologically adverse. A dose-response relationship was noted between the increase in absolute and relative liver weights.

In females, analysis of organ weights and their ratios showed treatment related, significantly higher absolute weights of livers at the high intermediate (12.9%) and high doses (22.5%), and the relative weights of liver at the high intermediate (11.6%) and high dose (27.6%). The increase in absolute weights of livers displayed a dose response relationship.

Three female rats from the high dose group died during the course of the study. However gross changes, such as lung abscesses and an enlarged bilateral adrenal gland, were not considered to be treatment related. No other gross changes noted for any other animal, as examined at study end, were deemed to be treatment related. Please refer to Table A6.3.1-4.

Conclusion Based on findings of increases in absolute and relative liver weights noted in the 2400 ppm treatment group, an NOEL of 800 ppm (equivalent to 61.9, 75.3 and 68.6 mg/kg bw/day) for males, females and combined sex was established for Permethrin technical in this study.

LO(A)EL 2400 ppm (equivalent to 205.8 mg/kg bw day)

NO(A)EL 800 ppm (61.9, 75.3 and 68.6 mg/kg bw/day for males, females and combined sex)

Section A6.3.1 **Annex Point IIA6.3.1**	**Repeated dose toxicity** **28-day oral toxicity study in the rat**	
Other	None	
Reliability	2	X
Deficiencies	Two deviations were noted and were outlined under point 2.3 and 5.1. However, they will not compromise the scientific validity of this study.	X

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	Evaluation by Rapporteur Member State
Date	01/07/2009
Materials and Methods	5.1, 5.3.4. 5.3.5, Applicants version is not acceptable. 3.4.6 However haematology examinations should be conducted on animals at the end of the test period. 3.4.7 Clinical chemistry determinations are essential in elucidating toxic effects in tissues and organs. Finally histopathology is also required under guideline 407. 3.4.8 Urinalysis is optional Functional observations are not deemed necessary as the study was conducted as a preliminary study to the 90-day subchronic study.
Results and discussion	Throughout the results clinical observations are described as 'unaffected by treatment' when at times they clearly are affected by treatment. The SD are large which would mask statistical significance. Though there is no statistical significant recorded in this study the body weights are biologically significantly different as a result of treatment. There is also evidence of a neurotoxic effect which is observed in animals at the high dose suffering from tremors.
Conclusion	LO(A)EL: 2400 ppm NO(A)EL: 800 ppm Other conclusions: This study is not acceptable
Reliability	*3*
Acceptability	Not acceptable OECD guideline 407 clearly states that clinical biochemistry, haematology and histopathology should be conducted. In fact these tests are fundamental and essential for a 28-day study. According to the Technical Guidance on 98/8, "at least the following data should be obtained from a repeated dose toxicity test:……haematology and clinical biochemical examinations and the finding of gross and histopathology". Therefore a reliability score of 3 is given and the study is not considered acceptable and will not be considered for risk assessment. The observations and gross pathology may be useful as supportive data to other studies.
Remarks	

Section A6.3.1 **Repeated dose toxicity**

Annex Point IIA6.3.1 **28-day oral toxicity study in the rat**

	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	

Table A6.3.1-1: Summary of Cumulative Weekly Net Body Weight Gains (g)- Males

Group no. Dose (ppm)	No. of rats	Weeks			
		1	**2**	**3**	**4**
G1 0	6	24 6.4	52 7.2	66 9.0	84 11.9
G2 200	6	28 4.3	58 8.4	69 12.7	89 11.4
G3 800	6	23 5.0	51 6.6	66 8.2	83 8.1
G4 2464@	6	29 7.0	56 3.8	68 6.1	90 6.5
G5 5536@	6	10* 11.4	37 19.7	54 23.2	71 23.3

*: Significantly lower (-) than the control group

@: Weighted average dose

Values: Mean ± SD

Table A6.3.1-2: Summary of Cumulative Weekly Net Body Weight Gains (g)- Female

Group no. Dose (ppm)	No. of rats	Weeks			
		1	2	3	4
G1 0	6	12 2.4	20 6.9	25 5.9	31 6.4
G2 200	6	9 3.5	15 7.1	22 4.0	29 3.4
G3 800	6	9 4.4	16 7.6	22 3.9	28 2.9
G4 2464@	6	9 5.2	17 5.1	20 4.7	27 5.6
G5 5536@	4	-11* # 18.4	1*^ 17.1	15^ 10.6	19^ 15.3

*: Significantly lower (-) than the control group
@: Weighted average dose
#: mean of 4 rats
^: Mean of 3 rats
Values: Mean ± SD

Table A6.3.1-3: Summary of Mean Food and Test Item Intake

Group no. Dose(ppm)	G1 0	G2 200	G3 800	G4 2464@	G5 5536@
MALES					
FOOD INTAKE					
g/animal/28 days	794.7	818.1	763.9	769.1	748.8
g/animal/day	28.4	29.2	27.3	27.5	26.7
g/kg Bwt/28 days	2249.2	2292.7	2166.2	2156.7	2207.1
g/kg Bwt/day	80.3	81.9	77.4	77.0	78.8
TEST ITEM INTAKE					
mg/kg Bwt/28 days	0.0	458.5	1733.0	5314.0	12218.3
Mg/kg Bwt/day	0.0	16.4	61.9	189.8	436.4
FEMALES					
FOOD INTAKE					
g/animal/28 days	524.3	529.9	522.2	523.6	519.6
g/animal/day	18.7	18.9	18.7	18.7	18.6
g/kg Bwt/28 days	2626.7	2668.5	2634.9	2651.9	2820.3
g/kg Bwt/day	93.8	95.3	94.1	94.7	100.7
TEST ITEM INTAKE					
mg/kg Bwt/28 days	0.0	533.7	2107.9	6534.3	15613.4
Mg/kg Bwt/day	0.0	19.1	75.3	233.4	557.6
COMBINED SEX					
FOOD INTAKE					
g/animal/28 days	659.5	674.0	643.1	646.3	634.2
g/animal/day	23.6	24.1	23.0	23.1	22.7
g/kg Bwt/28 days	2437.9	2480.6	2400.6	2404.3	2513.7
g/kg Bwt/day	87.1	88.6	85.7	85.9	89.8
TEST ITEM INTAKE					
mg/kg Bwt/28 days	0.0	496.1	1920.5	5924.1	13915.9
mg/kg Bwt/day	0.0	17.7	68.6	211.6	497.0

@: Weighted average dose

Table A6.3.1-4: Summary of Gross Necropsy Findings

PARAMETERS	Sex	Males					Females				
	Group No.	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5
	Dose(ppm)	0	200	800	2464@	5536@	0	200	800	2464@	5536@
	No. of rats	6	6	6	6	6	6	6	6	6	6
No. dead during treatment		0	0	0	0	0	0	0	0	0	2
No. of moribund sacrifice		0	0	0	0	0	0	0	0	0	1
No. finally sacrificed		6	6	6	6	6	6	6	6	6	3
No. examined for gross pathology		6	6	6	6	6	6	6	6	6	6
No. showing gross pathology		0	0	0	0	1	0	0	2	1	2
A. No. showing external pathology		0	0	0	0	0	0	0	2	0	0
i. Skin – hair thinning with hair regrowth multifocal		0	0	0	0	0	0	0	2	0	0
B. No. showing visceral organ pathology		0	0	0	0	1	0	0	0	1	2
i. Kidney – unilateral pelvis dilated		0	0	0	0	1	0	0	0	1	0
ii. Lungs abscess – various sizes multiple (0.1 – 0.3 cm)		0	0	0	0	0	0	0	0	0	1
iii. Lungs left lobe – abscess (1.1 cm)		0	0	0	0	0	0	0	0	0	1
iv. Adrenal bilateral enlarged (0.7 cm)		0	0	0	0	0	0	0	0	0	1

@ Weighted average dose