SECTION A5 Effectiveness against target organisms and intended uses

Subsection (Annex Point)		Official use only
5.1 Function (IIA5.1)	Insecticide in Wood Preservatives Main Group: 2 – Preservatives Product Type: 08 – Wood Preservatives	
5.2 Organism(s) to be controlled and products, organisms or objects to be protected (IIA5.2)		
5.2.1 Organism(s) to be controlled (IIA5.2)	Adult and larval wood pests (♂♀) such as *Hylotrupes bajulus* (House borer), *Reticulitermes santonensis* (European subterranean termite), *Anobium punctatum* (Furniture beetle) *Lyctus brunneus* (Powderpost beetle)	
5.2.2 Products, organisms or objects to be protected (IIA5.2)	Timber products (typically structural timber: roof beams, window frames) in HC 1-3	
5.3 Effects on target organisms, and likely concentration at which the active substance will be used (IIA5.3)	Efficacy data are tabulated below on the control of *Hylotrupes bajulus* (House borer; *Reticulitermes santonensis* (European subterranean termite) ; *Anobium punctatum* (Furniture beetle)	
5.3.1 Effects on target organisms (IIA5.3)	The effect on the target organism is death (knockdown). Efficacy data indicates effects on different species at different exposure scenarios at a concentration range in product of 0.01 to 0.5%. As lethality (knockdown) is the only recognised effect, concentration-dependence of the effect is demonstrable. The threshold concentration is species dependant. The toxic value for the *cis*-isomer is approximately 8 times lower than the *trans*-isomer, however different ratio isomer mixtures commercially available (typically 25:75 to 75:25) exhibit similar toxic values for wood-boring insects.	
5.3.2 Likely concentrations at which the A.S. will be used (IIA5.3)	From available efficacy data, and understanding of the loss of permethrin from wood as a function of time, product formulators consider a concentration range in product of 0.1 to 0.25% to be appropriate.	
PT08	0.25%	

SECTION A5 **Effectiveness against target organisms and intended uses**

5.4 Mode of action (including time delay) (IIA5.4)

5.4.1 Mode of action

Permethrin is an axonic poison, binding to protein in nerves (voltage-gated sodium channel). Normally, this protein opens causing stimulation of the nerve and closes to terminate the nerve signal. Pyrethroids bind to this gate and prevent it from closing normally which results in continuous nerve stimulation.

5.4.2 Time delay

Permethrin has a rapid knockdown, typically instantaneous

5.5 Field of use envisaged (IIA5.5)

MG02: Preservatives

Product type 8 Wood preservatives

5.6 User (IIA5.6)

Industrial

Manufacture of the Active Substance takes place outside the EU. Operations involving the preparation of a product will be reviewed on application for a product licence.

Professional

Type	User sector	Preservation process
Preventive	Industrial	vacuum-pressure process spraying dipping process (mechanised or manual)
Curative	Professional *in-situ* treatments	spraying injection brushing

General public

Type	User sector	Preservation process
Preventive	Amateurs and Do-it-yourself	• brushing, spraying
Curative	Do-it-yourself	• brushing, spraying

5.7 Information on the occurrence or possible occurrence of the development of resistance and appropriate management strategies (IIA5.7)

5.7.1 Development of resistance

There are no reported cases of development of resistance involving the use of permethrin in wood preservation.
However, due to extensive use in the agrochemical industry, pyrethroid resistance is emerging despite early optimism that

SECTION A5	Effectiveness against target organisms and intended uses
	because of its rapid toxicological action it would not produce resistance. Resistance is not evolving through unique new mechanisms; rather, existing mechanisms are being enhanced, and cross-resistance is occurring. Multiresistance (two or more resistance mechanisms in the same insect) is becoming widespread as control programs make sequential use of one chemical class after another. A more recent development in pyrethroid resistance is the appearance of target-site resistance (also termed knockdown resistance) to pyrethoids.
5.7.2 Management strategies	International and National systems are in place, and further programs are under development to control the development of resistance.
5.8 Likely tonnage to be placed on the market per year (IIA5.8)	Approximately 52 MT are imported by the Notifiers into the EU each year, of which 40 MT are used in PT08.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	30th November 2005
Materials and methods	The materials descriptions and the trials methodologies reported are acceptable.
Conclusion	The participant's conclusion is acceptable and the Directive's requirements on biological effectiveness have been proven. However, it is stated that there are no reported cases of development of resistance involving the use of permethrin in wood preservation but no mention is made as to the source of such a statement or of any literature search to substantiate such a statement
Reliability	1
Acceptability	Acceptable
Remarks	At the authorisation stage a comprehensive data set will be required for the resistance and biological effectiveness sectors
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Results and discussion	*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*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*

SECTION A5 Effectiveness against target organisms and intended uses

Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Summary of effects on target organisms and likely concentration at which the active substance will be used.

Section 5.3: Summary table of experimental data on the effectiveness of the active substance against target organisms at different fields of use envisaged, where applicable

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*
PT08	MG02	As prescribed	*Hylotrupes bajulus* (House borer)	As described in IUCLID entry	As described in IUCLID entry	Ageing Procedure g/100g / Treating solution / Mean Larvae surviving / Average mortality None / Toluene / 7.4 / 26 0.001 / 4.4 / 56 0.010 / 5.2 / 48 0.100 / 0 / 100 3 months / Toluene / 6.4 / 36 0.10 / 0 / 100 1.0 / 0 / 100 10 / 0 / 100 3 months / Toluene / 8 / 20 0.10 / 0.8 / 92 1.0 / 0 / 100 10 / 0 / 100	Berry, R.W (1977)
PT08	MG02	As prescribed	*Reticulitermes santonensis* (European subterranean termite)	As described in IUCLID entry	As described in IUCLID entry	The treatment with 5g/kg allowed only negligible surface abrasion. Treatments at 0.325 and 1.25 allowed perforation, but single discrete tunnels as opposed to general area damage. At 0.325, the veneer was perforated in large areas, at 1.25 and 5.0 the veneer was perforated in a few places.	Berry, R.W (1977)

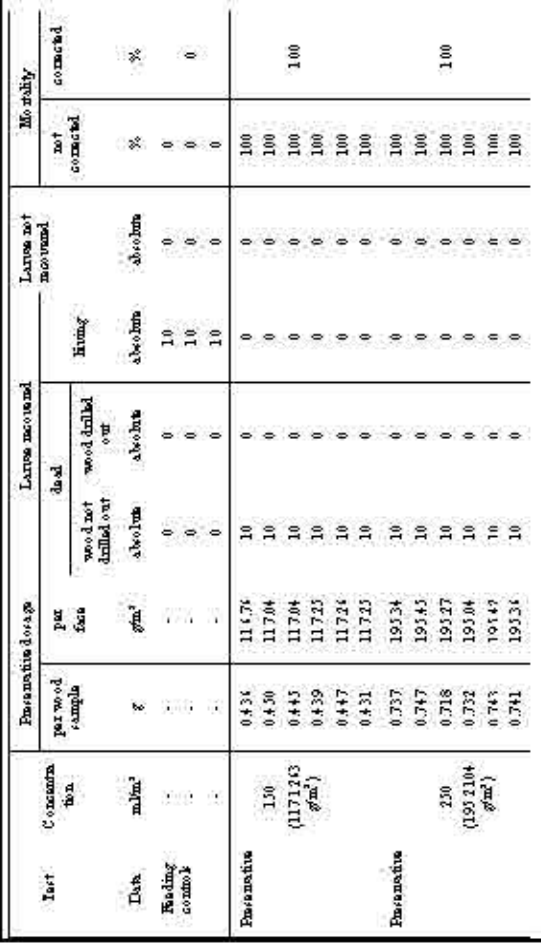
Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*
						Mean Termite survival was 55, 52, 54% at the three treatment levels (0.325, 1.25, 5.0 g/kg).	
PT08	MG02	As prescribed	*Anobium punctatum* (Furniture beetle)	As described in IUCLID entry	As described in IUCLID entry	Loading g/kg in solvent / Ageing period (weeks before) holes / Assessment (6mths) Exit larvae / Live Beetles / Dead Toluene 7 15 16 3 60 12 14 4 0.8 7 0 12 12 60 3 19 11 2.0 7 0 21 6 60 2 7 19 5.0 7 0 18 21 60 0 9 23	Berry, R.W (1977)
PT08	MG02	As prescribed	*Lyctus brunneus* (Powderpost beetle)	As described in IUCLID entry	As described in IUCLID entry	Treating solution (mg ai/kg solvent) / Number of blocks infested (/5) 12.5 5 50 1 200 0 800 0	Berry, R.W (1977)
PT08	MG02	As prescribed	*Hylotrupes bajulus* (House borer)	As described in IUCLID entry	As described in IUCLID entry	After 12 weeks exposure to larvae, the lowest treating solution concentration was effective, giving an upper toxic value of 75 kg/m3, equivalent to 0.09 kg permethrin/m3, achieved using a treating solution of 16.7% (m/m) equivalent to 0.02% (m/m) permethrin. When interpreted in accordance with EN 599-1, the biological reference value for permethrin was 0.09 kg permethrin/m3 for hazard classes 1 and 2	Carey, J.K., Lea, R.G., Reeves, N. (1999a)
PT08	MG02	As prescribed	*Hylotrupes bajulus* (House	As described in IUCLID entry	As described in IUCLID entry	After 12 weeks exposure to larvae, the lowest treating solution concentration was effective,	Carey, J.K., Lea, R.G.,

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*
			borer)			giving an upper toxic value of 25.9 kg/m3, equivalent to 0.14 kg permethrin/m3, achieved using a treating solution of 3.70% (m/m) equivalent to 0.02% (m/m) permethrin. When interpreted in accordance with EN 599-1, the biological reference values for permethrin are 0.14 kg permethrin/m3 for hazard classes 1 and 2, and 0.15 kg permethrin/m3 for hazard classes 3, 4 and 5	Reeves, N. (1999b)
PT08	MG02	As prescribed	*Hylotrupes bajulus* (House borer)	As described in IUCLID entry	As described in IUCLID entry	At the end of the test (12 weeks), the toxic values of the product tested was 5.51 - 11.95 g/m3.	No Author (1981)
PT08	MG02	As prescribed	*Anobium punctatum* (Furniture beetle)	As described in IUCLID entry	As described in IUCLID entry	At the end of the test (12 months), the toxic values of the product tested was 42.2 - 96.3 g/m3.	No Author (1980)
PT08	MG02	As prescribed	*Anobium punctatum* (Furniture beetle)	A solution of Xylamon wormwood killer N containing permethrin was tested according to EN48, BS5436:1977	No data	The application of Xylamon wormwood killer N at 300 ml/m2 gave a mortality of 87.5%	Berry, R.W (1980)
PT08	MG02	As prescribed	*Anobium punctatum* (Furniture beetle)	Solutions of Xylamon wormwood killer N, Xylamon wormwood killer	No data	Lowest loading preventing survival Xylamon wormwood killer N 3.18 kg/m3 Xylamon wormwood killer 6.53 kg/m3 Xylamon BV Special 0.41 kg/m3	Berry, R.W (1982)

<table>
<tr><th>Function</th><th>Field of use envisaged</th><th>Test substance</th><th>Test organism(s)</th><th>Test method</th><th>Test conditions</th><th>Test results: effects, mode of action, resistance</th><th>Reference*</th></tr>
<tr><td></td><td></td><td></td><td></td><td>and Xylamon BV special containing permethrin were tested according to EN49, BS5434:1977</td><td></td><td>Highest loading allowing survival
Xylamon wormwood killer N 1.56 kg/m3
Xylamon wormwood killer 3.53 kg/m3
Xylamon BV Special not established</td><td></td></tr>
<tr><td>PT08</td><td>MG02</td><td>As prescribed</td><td>Lyctus brunneus (Powderpost beetle)</td><td>DIN EN20</td><td>As described in IUCLID entry</td><td>Table 1: Summary of results of tests on the insect-controlling effect of "WTA-H-384" on Lyctus brunneus (Steph.) using a method based on DIN EN 20.
<table><tr><th>Amount of preservative</th><th>Sample no.</th><th>Number of beetles emerging*</th></tr><tr><td rowspan="5">0</td><td>K 1</td><td>10</td></tr><tr><td>K 2</td><td>32</td></tr><tr><td>K 3</td><td>21</td></tr><tr><td>K 4</td><td>3</td></tr><tr><td>K 5</td><td>21</td></tr><tr><td rowspan="5">200 ml per m²</td><td>P 1</td><td>0</td></tr><tr><td>P 2</td><td>0</td></tr><tr><td>P 3</td><td>0</td></tr><tr><td>P 4</td><td>0</td></tr><tr><td>P5</td><td>0</td></tr></table>* Beetles emerged from start of August to end of November 1981</td><td>Gersonde, M (1982)</td></tr>
<tr><td>PT08</td><td>MG02</td><td>As prescribed</td><td>Hylotrupes bajulus (House borer)</td><td>in accordance with EN 46 after previously washing out in accordance with EN 84.</td><td>As described in IUCLID entry</td><td>Table: Results of Iv test using FE-IB 2123 with a rate of application of 2.0 – 220 m/m² after washing out – duration of test: 4 weeks
<table><tr><th rowspan="2">Sample no.</th><th colspan="4">Number of house longhorn larvae</th></tr><tr><th>wood not gnawed dead</th><th>wood gnawed dead</th><th>living</th><th>missing</th></tr><tr><td>1</td><td>10</td><td>-</td><td>-</td><td>-</td></tr><tr><td>2</td><td>10</td><td>-</td><td>-</td><td>-</td></tr><tr><td>3</td><td>10</td><td>-</td><td>-</td><td>-</td></tr><tr><td>4</td><td>10</td><td>-</td><td>-</td><td>-</td></tr><tr><td>5</td><td>10</td><td>-</td><td>-</td><td>-</td></tr><tr><td>6</td><td>10</td><td>-</td><td>-</td><td>-</td></tr><tr><td>untreated controls</td><td></td><td></td><td></td><td></td></tr><tr><td>9 K</td><td>-</td><td>-</td><td>8</td><td>2</td></tr><tr><td>10 K</td><td>-</td><td>-</td><td>10</td><td>-</td></tr><tr><td>11 K</td><td>1</td><td>-</td><td>8</td><td>1</td></tr><tr><td>12 K</td><td>-</td><td>-</td><td>9</td><td>1</td></tr></table></td><td>Janotta, O (1993)</td></tr>
</table>

<table>
<tr><th>Function</th><th>Field of use envisaged</th><th>Test substance</th><th>Test organism(s)</th><th>Test method</th><th>Test conditions</th><th>Test results: effects, mode of action, resistance</th><th>Reference*</th></tr>
<tr><td>PT08</td><td>MG02</td><td>As prescribed</td><td>Hylotrupes bajulus (House borer)</td><td>In accordance with section 5.4 of the test principles of the IfBt and based in part on EN 46</td><td>As described in IUCLID entry</td><td>Results of testing the preventive effect of "VP FE-HI 1561, color: reddish brown" on freshly hatched larvae of the house longhorn beetle after being subjected to the conditions in a wind tunnel, without planing off any wood and when planing off a 1 mm and 2 mm layer of the treated wood surfaces before starting the animal trials.
<table>
<tr><th rowspan="2">%-age concentration of solution</th><th rowspan="2">Amount of preservative applied per m² of wood</th><th rowspan="2">Thickness of layer planed off in mm</th><th rowspan="2">Duration of trial in weeks</th><th colspan="4">Number and condition of larvae at end of trial</th></tr>
<tr><th colspan="2">dead</th><th colspan="2">living</th></tr>
<tr><th></th><th></th><th></th><th></th><th>wood not gnawed</th><th>wood gnawed</th><th>wood gnawed</th><th>not found</th></tr>
<tr><td rowspan="15">100</td><td rowspan="15">180 ml = 148.52 g</td><td rowspan="6">0</td><td rowspan="6">4</td><td>10</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td rowspan="5">1</td><td rowspan="5">4</td><td>10*</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10*</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10*</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10*</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td rowspan="5">2</td><td rowspan="5">4</td><td>10*</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10*</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10*</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10*</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>10*</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td colspan="2" rowspan="3">untreated control samples</td><td rowspan="3">-</td><td rowspan="3">4</td><td>1</td><td>1</td><td>8</td><td>0</td></tr>
<tr><td>0</td><td>0</td><td>9</td><td>1</td></tr>
<tr><td>0</td><td>0</td><td>10</td><td>0</td></tr>
</table>
* Some larvae had gnawed the wood, but not gnawed deeply.</td><td>Rudolph, D (1990)</td></tr>
</table>

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*
PT08	MG02	As prescribed	*Hylotrupes bajulus* (House borer)	EN46 after previous evaporation in accordance with EN73	As described in IUCLID entry	**Table:** Results of lv test using FE-IB 2123 with a rate of application of 210 – 220 ml/m² after evaporation – duration of test: 4 weeks Number of house longhorn larvae Sample no. / wood not gnawed dead / wood gnawed dead / living / missing 1: 10 / - / - / - 2: 10 / - / - / - 3: 10 / - / - / - 4: 10 / - / - / - 5: 10 / - / - / - 6: 10 / - / - / - untreated controls 9 K: - / - / 9 / 1 10 K: - / - / 10 / - 11 K: - / - / 10 / - 12 K: - / - / 8 / 2	Janotta, O (1993)
PT08	MG02	As prescribed	*Hylotrupes bajulus* (House borer)	DIN EN22	As described in IUCLID entry	Results of test on the controlling effect of "WTA-H-384" on large larvae of the house longhorn beetle after a 12-week animal trial. % conc. of solution / Amount of preservative applied per m² of wood / Number and condition of larvae and their distance (mm) from the treated surface: dead (number / mm) / living (number / mm) / not found 100 / 300 ml = 240 g: dead 10 / 1-1-5-11-15-15-16-19-20-? / living 1 / 20 / not found 1 100 / 300 ml = 240 g: dead 8 / 1-2-9-15-16-20-? / living 2 / 22-25 / not found 2 100 / 300 ml = 240 g: dead 10 / 1-1-1-3-5-6-8-9-13-17 / living 2 / 22-30 / not found 0 100 / 300 ml = 240 g: dead 11 / 1-1-1-1-2-3-3-11-12-12-? / living 0 / - / not found 1 untreated comparison wood: dead 0 / - / living 9+ 2 beetles / - / not found 1	BAM report (1980)

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*
PT08	MG02	As prescribed	*Hylotrupes bajulus* (House borer)	EN46	As described in IUCLID entry		Swiss Federal Laboratories for Materials Testing and Research (1983)

Function	Field of use envisaged	Test substance	Test organism(s)	Test method	Test conditions	Test results: effects, mode of action, resistance	Reference*

References:
Berry, R.W (1977) The evaluation of permethrin for wood preservation. Pestic. Sci, 8, 284-290
Berry, R.W (1980) Determination of Eradicant Action against Anobium punctatum larvae. EN 48& BS5436:1977 BRE Report PRL B 8002(2); PR 168/014
Berry, R.W (1982) Determination of Toxic values against Anobium punctatum by egg-laying and larval survival. EN 49 & BS5434:1977 BRE Report PJ 07 31; PR 168/014
Carey, J.K., Lea, R.G., Reeves, N. (1999a) Determination of Toxic Values against larvae of Hylotrupes bajulus. (Laboratory method) EN 47:1988 BRE Report No. TCR 32/99
Carey, J.K., Lea, R.G., Reeves, N. (1999b) Determination of Toxic Values against larvae of Hylotrupes bajulus. (Laboratory method) EN 47:1988 BRE Report No. TCR 33/99
No Author (1981) Determination of Toxic Values against Hylotrupes bajulus larvae. EN 47 & BS 5435:1977 Princes Risborough Laboratory Report No. 80/11
No Author (1980) Determination of Toxic Values against Anobium punctatum larvae. EN 21& BS5215:1975 Princes Risborough Laboratory Report
Janotta, O (1993) To determine the preventive effect of wood preservatives on freshly hatched larvae of Hylotrupes bajulus (L.), in accordance with EN 46 after previous evaporation in accordance with EN 73. Austrian Wood Research Institute Report No. 708/92/Iv-4
Gersonde, M (1982) To test the insect-controlling effect of the wood preservative "WTA-H-384" on Lyctus, using a method based on DIN EN 20 and a rate of application of 200 ml/m^2. BAM report Ref. No.: 5.1/3313 L
Janotta, O (1993) To determine the preventive effect of wood preservatives on freshly hatched larvae of Hylotrupes bajulus (L.), in accordance with EN 46 after previously washing out in accordance with EN 84. Austrian Wood Research Institute Report No. 708/92/Iv-3
BAM report (1980) To test the insect-controlling effect of the wood preservative "WTA-H-384" on large larvae of house longhorns beetles. Report No. 5.1/3313 A
Swiss Federal Laboratories for Materials Testing and Research (1983) To determine the preventive effect on freshly hatched larvae of the house longhorn (Hylotrupes bajulus L.) after aging in a wind tunnel for 24 week. Reference 23'10477.
Rudolph, D (1990) To test the preventive effect on freshly hatched larvae of the house longhorn beetle after being subjected to the conditions in a wind tunnel, without planing off any wood and when planing off a 1 mm and 2 mm layer of the treated wood surfaces before starting the animal trials. BAM report Ref. No.: 5.1/5307 B

APPENDIX 1 TO DOC III-A5

Reference List Doc. III-A5. sorted by reference no.

Section No/ Reference No	Author (s)	Year	Title. Source, Report No. GLP /(Un) Published	Data Protection Claimed (Yes/No)	Owner
5,2	Racey, P.A & Swift, S.M	1986	The residual effects of remedial timber treatments on bats. Biological conservation, 35, 215-214; Not GLP; Published	No	N/A
5,3,1	Berry, R.W	1977	The evaluation of permethrin for wood preservation. Pestic. Sci, 8, 284-290; Not GLP; Published	No	N/A
5,3,1	Berry, R.W	1980	Determination of Eradicant Action against Anobium punctatum larvae. EN 48& BS5436:1977 BRE Report PRL B 8002(2); PR 168/014; Not GLP; Unpublished	Yes	Sumitomo Chemical
5,3,1	Berry, R.W	1982	Determination of Toxic values against Anobium punctatum by egg-laying and larval survival. EN 49 & BS5434:1977 BRE Report PJ 07 31; PR 168/014; Not GLP; Unpublished	Yes	Sumitomo Chemical
5,3,1	Carey, J.K., Lea, R.G., Reeves, N.	1999a	Determination of Toxic Values against larvae of Hylotrupes bajulus. (Laboratory method) EN 47:1988 BRE Report No. TCR 32/99; Not GLP; Unpublished	Yes	Sumitomo Chemical
5,3,1	Carey, J.K., Lea, R.G., Reeves, N.	1999b	Determination of Toxic Values against larvae of Hylotrupes bajulus. (Laboratory method) EN 47:1988 BRE Report No. TCR 33/99; Not GLP; Unpublished	Yes	Sumitomo Chemical
5,3,1	No Author	1980	No Author; 1980; Determination of Toxic Values against Anobium punctatum larvae. EN 21& BS5215:1975 Princes Risborough Laboratory Report; Not GLP; Unpublished	Yes	Sumitomo Chemical
5,3,1	No Author	1981	Determination of Toxic Values against Hylotrupes bajulus larvae. EN 47 & BS 5435:1977 Princes Risborough Laboratory Report No. 80/11; Not GLP; Unpublished	Yes	Sumitomo Chemical
5,3,1	Janotta, O	1993	To determine the preventive effect c wood preservatives on freshly hatche larvae of Hylotrupes bajulus (L.), i accordance with EN 46 after previou evaporation in accordance with EN 7 Austrian Wood Research Institut Report No. 708/92/Iv-4	Yes	DESOWAG Gmbh

Section No/ Reference No	Author (s)	Year	Title. Source, Report No. GLP /(Un) Published	Data Protection Claimed (Yes/No)	Owner
5,3,1	Gersonde, M	1982	To test the insect-controlling effect c the wood preservative "WTA-H-384" o Lyctus, using a method based on DI EN 20 and a rate of application c 200 ml/m^2 . BAM report Ref. No 5.1/3313 L	Yes	DESOWAG Gmbh
5,3,1	BAM report	1980	To test the insect-controlling effect c the wood preservative "WTA-H-384" o large larvae of house longhorns beetle Report No. 5.1/3313 A	Yes	DESOWAG Gmbh
5,3,1	Swiss Federal Laboratories for Materials Testing and Research	1983	To determine the preventive effect o freshly hatched larvae of the hous longhorn (Hylotrupes bajulus L.) aft aging in a wind tunnel for 24 week Reference 23'10477.	Yes	DESOWAG Gmbh
5,3,1	Rudolph, D	1990	To test the preventive effect on freshly hatched larvae of the house longhorn beetle after being subjected to the conditions in a wind tunnel, without planing off any wood and when planing off a 1 mm and 2 mm layer of the treated wood surfaces before starting the animal trials. BAM report Ref. No.: 5.1/5307 B	Yes	DESOWAG Gmbh
5,3,2	Gruning, R., Pospischil, R., Cymorek, S., Metzner, W.	1986	Pyrethroids: Isomerism and efficacy. IRG/WP/1284; Not GLP; Published	Yes	Sumitomo Chemical
5,3,2	Orsler, R.J., Stone, M.W.S.	1984	The permanence of permethrin in wood preservation. IRG/WP/1284; Not GLP; Unpublished	Yes	Sumitomo Chemical
5,3,2	Powell, P.K., Robinson, W.H	1992	Penetration and permanence of permethrin in four softwoods. J. Economic Entomology, 85, 5, 1818 - 1821; Not GLP; Published	No	N/A
5,3,2	Rutherford, D., Reay, R.C, Ford, M.G.	1983	Loss of pyrethroids from treated wood. Biodeterioration 5, 144 - 153; Not GLP; Published	No	N/A

Section No/ Reference No	Author (s)	Year	Title. Source, Report No. GLP /(Un) Published	Data Protection Claimed (Yes/No)	Owner
5,4	Miller, T. A., Salgado, V.L.	1985	Chapter 2. The mode of action of pyrethroids on insects. In: The Pyrethroid Insecticides. Ed. J.P.Leahey. Published by Taylor & Francis; Not GLP; Published	No	N/A
5,6	Garrod, A.N.I., Guiver, R., Rimmer, D.A	2000	Potential exposure of Amateurs (Consumers) through painting Wood Preservative and Antifoulant preparations. Ann. Occup. Hyg., 44, 6, 421-426; Not GLP; Published	No	N/A
5,6	Rodes, C.E et al	2001	Experimental methodologies and preliminary transfer factor data for estimation of dermal exposure to particles. J. Exposure Analysis and Environmental Epidemiology, 11, 123-139; Not GLP; Published	No	N/A
5,7	Brogdon, W.G, McAllister, J.C	1998	Insecticide Resistance and Vector Control. Emerging Infectious Diseases, US CDC Publication, Vol.4 No.4; Not GLP; Unpublished	No	N/A
5,7	UNEP, FAO, WHO	2002	Reducing and Eliminating the Use of Persistent Organic Pesticides - Guidance on Alternative Strategies for Sustainable Pest and Vector Management, Chapter 3. Specific aspects of pest and vector management; Not GLP; Published	No	N/A

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 A6.1.1 6.1.1(1) Acute Oral Toxicity in Rats (LD_{50})

Annex Point IIA6.1.1

Key Study

			Official use only
		1 REFERENCE	
1.1	Reference	[redacted]; 1975a; Acute Oral Toxicity in Rats Compound No.: FMC 33297, LOT #C6725-57; [redacted]; unpublished Report (Project) No. 2739-75; 06.08.1975.	
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	
3.1.1	Lot/Batch number	C6725-57	
3.1.2	Specification	As given in section 2	X
Description		Yellow liquid	
Purity		As given in section 2	
Stability		Not applicable (single administration)	
3.2	Test Animals		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar	
3.2.3	Source	Not reported	
3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	200 to 300 g	
3.2.6	Number of animals per group	10	X
3.2.7	Control animals	No	
3.3	Administration/ Exposure	Oral	
3.3.1	Postexposure period	14 days	

Section A6.1.1 **6.1.1(1) Acute Oral Toxicity in Rats (LD_{50})**

Annex Point IIA6.1.1

		Key Study	
		Oral	
3.3.2	**Type**	Gavage	
3.3.3	**Concentration**	Gavage	400, 450, 500, 560, 630 mg/kg bw
3.3.4	**Vehicle**	Corn oil	
3.3.5	**Concentration in vehicle**	30% w/v	
3.3.6	**Total volume applied**	Not reported	
3.3.7	**Controls**	No	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	All animals that died did so on Day 1 (day of dosing considered Day 0); clinical signs were not specifically recorded.	
4.2	**Pathology**	Macroscopic observations included: urinary staining of the abdomen; chromodacryorrhea of both eyes; intestines filled with red or black or red and black fluid; mottled liver; bloody discharge around nose; liver has irregular surface.	
4.3	**Other**	Not applicable	
4.4	**LD_{50}**	LD_{50} males + females = 480 mg/kg (95% confidence limits of 440 to 520 mg/kg)	

Section A6.1.1 **6.1.1(1) Acute Oral Toxicity in Rats (LD_{50})**

Annex Point IIA6.1.1

Key Study

		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	Materials and methods	Albino rats, Wistar strain, weighing 200 to 300 grams were fasted for a minimum of 16 hours prior to administration of the test material. There were five males and five females per dose level. Dose levels were determined by a preliminary range finding study. Permethrin was administered by oral intubation as 30% w/v solution in corn oil. Following dosing the rats were returned to their cages and food and water made available *ad libitum*. Observations for mortality were made at 1 and 6 hours after dosing and daily thereafter for fourteen days. A gross necropsy was performed on each animal which died during the study.	
5.2	Results and discussion	All animals that died did so on Day 1 (day of dosing considered Day 0), with a clear dose-response relationship only apparent at doses above 500 mg/kg. Macroscopic observations included: urinary staining of the abdomen; chromodacryorrhea of both eyes; intestines filled with red or black or red and black fluid; mottled liver; bloody discharge around nose; liver has irregular surface. LD_{50} males + females = 480 mg/kg (95% confidence limits of 440 to 520 mg/kg).	
5.3	Conclusion		
5.3.1	Reliability	3	
5.3.2	Deficiencies	Yes. Deficiencies as compared to OECD Guideline 401 included clinical signs not recorded and only animals that died during the study were necropsied. Clinical sign characterisation is, however, possible from the results of other acute oral toxicity studies, and characterisation of necropsy findings is possible from the results of the necropsies conducted on the animals that died.	X

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*20/10/05*
Materials and Methods	***3.1.2*** *To what does this refer, specifically?* ***3.2.6*** *Five male/five female should be stated.*
Results and discussion	*Applicant's version adopted*
Conclusion	***5.3.2*** *No GLP. Otherwise, adopt applicant's version.*
Reliability	*2*
Acceptability	*Acceptable*
Remarks	***This study is very light on detail and lacks certain data which should be provided (see above). However, the information reported is sufficiently reliable to be used in risk assessment.***
	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. Table for Acute Oral Toxicity in Rats (LD_{50})

Dose [mg/kg]	*Number of dead / number of investigated*	*Time of death (range)*	*Observations*
400	5/10	Day 1	Pathology: urinary staining of the abdomen; chromodacryorrhea of both eyes; intestines filled with black or red or red and black fluid; mottled liver; bloody discharge around nose.
450	3/10	Day 1	Pathology: urinary staining of the abdomen; chromodacryorrhea of both eyes; intestines filled with black or red fluid; bloody discharge around nose.
500	4/10	Day 1	Pathology: urinary staining of the abdomen; chromodacryorrhea of both eyes; intestines filled with red fluid; mottled liver; bloody discharge around nose; liver has irregular surface.
560	8/10	Day 1	Pathology: urinary staining of the abdomen; mottled liver.
630	10/10	Day 1	Pathology: urinary staining of the abdomen; chromodacryorrhea of both eyes; intestines filled with black or red fluid; mottled liver; bloody discharge around nose.
LD_{50} value	480 mg/kg (95% confidence limits of 440 to 520 mg/kg)		

Section A6.1.1
Annex Point IIA6.1.1

6.1.1(2) Acute Oral Toxicity in Rats (LD_{50})

Key Study

		Official use only
	1 REFERENCE	
1.1 Reference	[redacted]; 1974a; Acute Oral Toxicity in Rats Compound No. FMC 33297; [redacted]; unpublished Report (Project) No. 2186-74; 15.10.1974.	
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	
3.1.1 Lot/Batch number	C 6514: 7 and C 6439: 112	
3.1.2 Specification	As given in section 2	X
3.1.3 Description	Clear liquid	
3.1.4 Purity	95.5%	
3.1.5 Stability	Not applicable (single administration)	
3.2 Test Animals		
3.2.1 Species	Rat	
3.2.2 Strain	Long-Evans	
3.2.3 Source	[redacted]	
3.2.4 Sex	Male and female	
3.2.5 Age/weight at study initiation	225 to 275 g	
3.2.6 Number of animals per group	10	X
3.2.7 Control animals	No	
3.3 Administration/ Exposure	Oral	
3.3.1 Postexposure period	14 days	
	Oral	

Section A6.1.1
Annex Point IIA6.1.1

6.1.1(2) Acute Oral Toxicity in Rats (LD_{50})

Key Study

3.3.2 Type	Gavage
3.3.3 Concentration	Gavage 590, 885, 1328, 1992, 2990
3.3.4 Vehicle	Wesson Corn Oil (Best Foods, Englewood Cliffs, N.J., USA)
3.3.5 Concentration in vehicle	30% w/v
3.3.6 Total volume applied	Not reported
3.3.7 Controls	No

4 RESULTS AND DISCUSSION

4.1 Clinical signs

Within 24 hours after dosing all animals died at the highest dose level of 2990 mg/kg, and convulsions were observed in over half of the animals that did not die at each of the two lower dose levels, 1328 and 1992 mg/kg. No other remarkable signs of pharmacological activity were observed during the study.

4.2 Pathology

The necropsy findings considered significant and possibly related to the administration of the test material are summarised below:

Observations	No. (%) of Rats in Which Sign was Observed: Dying during study (19 rats)	Sacrificed terminally (31 rats)
External urinary staining of ventral abdomen	9 (47%)	1 (3%)
Red, brown or black fluid in gastro-intestinal tract	11 (58%)	3 (10%)

No other gross necropsy findings were noted in dying animals or in the survivors which were considered uncommon for rats under laboratory conditions.

4.3 Other

Not applicable

4.4 LD_{50}

LD_{50} males + females = 1623 mg/kg (95% confidence limits of 1269 to 1977 mg/kg)

Section A6.1.1
Annex Point IIA6.1.1

6.1.1(2) Acute Oral Toxicity in Rats (LD_{50})

Key Study

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Individually housed Long-Evans rats (Blue Spruce Farms, Altamount, N.Y., USA), average body weight approximately 225 - 275 g, were fasted for a minimum of 16 hours prior to administration of permethrin. Five males and five females were dosed at each of five dose levels. The dose levels chosen were based on pilot range-finding tests. Permethrin was administered by oral intubation as a 30.0% w/w solution in Wesson Corn Oil (Best Foods, Englewood Cliffs, N.J., USA).

Following dosing, the rats were returned to their cages and food and water were made available *ad libitum*. Observations for pharmacological signs and mortality were made several times on the day of dosing and daily thereafter for a total of fourteen days. A gross necropsy was performed on each animal which died during the study. Animals surviving the observation period were sacrificed and necropsies were performed.

The LD_{50} and its 95% confidence limits were calculated from the incidence of animals dying at each dose level during the 14-day observation period.

5.2 Results and discussion

Within 24 hours after dosing all animals died at the highest dose level of 2990 mg/kg, and convulsions were observed in over half of the animals that did not die at each of the two lower dose levels, 1328 and 1992 mg/kg. No other remarkable signs of pharmacological activity were observed during the study.

The necropsy findings considered significant and possibly related to the administration of the test material are summarised below:

Observations	No. (%) of Rats in Which Sign was Observed	
	Dying during study (19 rats)	Sacrificed terminally (31 rats)
External urinary staining of ventral abdomen	9 (47%)	1 (3%)
Red, brown or black fluid in gastro-intestinal tract	11 (58%)	3 (10%)

No other gross necropsy findings were noted in dying animals or in the survivors which were considered uncommon for rats under laboratory conditions.

LD_{50} males + females = 1623 mg/kg (95% confidence limits of 1269 to 1977 mg/kg)

5.3 Conclusion

5.4 Reliability

2

Section A6.1.1
Annex Point IIA6.1.1

6.1.1(2) Acute Oral Toxicity in Rats (LD_{50})

Key Study

5.5 Deficiencies No X

Evaluation by Competent Authorities	
	Evaluation by Rapporteur Member State
Date	25/10/05
Materials and Methods	3.1.2 To what does this refer, specifically? 3.2.6 Five male/five female should be stated.
Results and discussion	Applicant's version adopted
Conclusion	5.3.2 No GLP.
Reliability	2
Acceptability	Acceptable
Remarks	*Very sketchy reporting, but given the age of the study and the fact that it was carried out pre GLP, the data can be deemed reliable.*
	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. Table for Acute Oral Toxicity in Rats (LD_{50})

Dose [mg/kg]	Number of dead / number of investigated	*Time of death (range)*	Observations
590	1/10	Day 5	Clinical signs: - Pathology: black fluid in gastrointestinal tract.
885	1/10	Day 0	Clinical signs: - Pathology: -
1328	3/10	Day 0	Clinical signs: convulsions. Pathology: external urinary staining of the abdomen; brown fluid in gastrointestinal tract; black fluid in gastrointestinal tract; red fluid in gastrointestinal tract.
1992	4/10	Day 0-Day 4	Clinical signs: convulsions. Pathology: red fluid in gastrointestinal tract; black fluid in gastrointestinal tract.
2990	10/10	Day 0	Clinical signs: - Pathology: external urinary staining of the abdomen; black fluid in gastrointestinal tract; black and red fluids in gastrointestinal tract; red fluid in gastrointestinal tract.
LD_{50} value	1623 mg/kg (95% confidence limits of 1269 to 1977 mg/kg)		

Section A6.1.2 **6.1.2 Acute Dermal Toxicity in Rabbits (Limit Test)**

Annex Point IIA6.1.2

		Key Study	Official use only
		REFERENCE	
1.1	**Reference**	[redacted]; Acute Dermal Toxicity in Rabbits Compound No. FMC 33297; [redacted]; unpublished Report (Project) No. 2908-75; 07.11.1975.	
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**	Yes; 16 CFR 1500.40.	
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	
3.1.1	**Lot/Batch number**	C-6699-65	
3.1.2	**Specification**	As given in section 2	X
3.1.2.1	**Description**	Amber liquid	
3.1.2.2	**Purity**	As given in section 2	
3.1.2.3	**Stability**	Not applicable (single administration)	
3.2	**Test Animals**		
3.2.1	**Species**	Rabbit	
3.2.2	**Strain**	New Zealand White	
3.2.3	**Source**	Not reported	
3.2.4	**Sex**	Not reported	
3.2.5	**Age/weight at study initiation**	1.45-2.40 kg	
3.2.6	**Number of animals per group**	5	X
3.2.7	**Control animals**	No	
3.3	**Administration/ Exposure**	Dermal	
3.3.1	**Postexposure period**	14 days	

Section A6.1.2 **6.1.2 Acute Dermal Toxicity in Rabbits (Limit Test)**

Annex Point IIA6.1.2

		Dermal	
3.3.2	**Area covered**	10 % of body surface	
3.3.3	**Occlusion**	Occlusive	
3.3.4	**Vehicle**	Not applicable	
3.3.5	**Concentration in vehicle**	Not applicable	
3.3.6	**Total volume applied**	Not reported	
3.3.7	**Duration of exposure**	24 h	
3.3.8	**Removal of test substance**	Not reported	
3.3.9	**Controls**	Not applicable	
		4 RESULTS AND DISCUSSION	
4.1	**Clinical signs**	There were no deaths and no remarkable signs of pharmacologic effect.	
4.2	**Pathology**	Necropsy not triggered (gross necropsy was only to be carried out on animals which died during the study).	X
4.3	**Other**	Very slight (barely perceptible) erythema was noted at 24 h in 2/5 abraded animals and 1/5 non-abraded animals; very slight (barely perceptible) oedema was noted at 24 h in 1/5 non-abraded animals.	
4.4	**LD_{50}**	> 2000 mg/kg; no lethal effect at maximal dose.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1 Materials and methods		Albino rabbits, New Zealand White strain, were prepared and dosed according to the method described in 16 CFR 1500.40. The hair of each rabbit was clipped from the trunk so as to expose 10% of the body surface area. The skin of half of the animals was abraded so as to penetrate the stratum corneum, but not to disturb the derma, longitudinally every two or three centimetres over the area of exposure.	X
		Permethrin was held in contact with the skin by a sleeve made of impervious plastic sheeting designed to contain the dose without leakage or undue pressure as described in 16 CFR 1500.40.	
		Following 24 hours of exposure the sleeves were removed and observations were made for oedema, erythema and eschar formation, and the exposed area was wiped free of excess test material. Observations for mortality were made daily for 14 days following treatment. A gross necropsy was to be performed on each animal which died during the study period.	

Section A6.1.2 **6.1.2 Acute Dermal Toxicity in Rabbits (Limit Test)**

Annex Point IIA6.1.2

5.1	**Results and discussion**	There were no deaths at the limit test dose of 2000 mg/kg, and no remarkable signs of pharmacologic effect were observed at any time during the 14-day study period. Very slight (barely perceptible) erythema was noted at 24 h in 2/5 abraded animals and 1/5 non-abraded animals; very slight (barely perceptible) oedema was noted at 24 h in 1/5 non-abraded animals. LD_{50} > 2000 mg/kg; no lethal effect at maximal dose.	
5.2	**Conclusion**		
5.3.1	**Reliability**	2	
5.3.2	**Deficiencies**	Yes. The sex of test animals was not reported (test guideline EC B.3 requires 5 males and 5 females in limit tests), however, no significant sex difference would be expected on the basis of acute oral toxicity data. The stratum corneum of half the animals was deliberately abraded (skin abrasion is to be specifically avoided under test guideline EC B.3), however, this only makes the test more severe than would otherwise have been the case. Permethrin was held in contact with the skin by a sleeve made of impervious plastic sheeting (test guideline EC B.3 requires a porous gauze dressing with a further cover), however this was designed to contain the dose without leakage or undue pressure. Surviving animals were not necropsied (as required by test guideline EC B.3), but given permethrin's low potential for dermal toxicity (and irritation), this deficiency is not considered critical.	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	*25/10/05*
Materials and Methods	***3.1.2*** *To what does this refer, specifically?* ***3.2.6*** *Five animals* ***per sex per dose group*** *should be used. The '5' here seems to refer to 5 abraded and 5 non-abraded animals. Skin should not be abraded for the purposes of increasing the irritation potential.*
Results and discussion	***4.2*** *Necropsy should be carried out on all animals.*
Conclusion	***5.1*** *It is not normal practice to abrade the skin.* ***5.3.2*** *No GLP.* *Adopt applicant's version otherwise.*
Reliability	*2*
Acceptability	*Acceptable*
Remarks	*This study is very light on detail and lacks certain data which should be provided (see above). However, the information reported is sufficiently reliable to be used in risk assessment.*
	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(6)-1. Table for Acute Dermal Toxicity in Rabbits

Dose [mg/kg]	*Number of dead / number of investigated*	*Time of death (range)*	*Observations*
2000 (abraded stratum corneum)	0/5	-	Clinical signs: no remarkable effects Pathology: not triggered Irritation: very slight (barely perceptible) erythema was noted at 24 h in 2/5 animals
2000 (intact stratum corneum)	0/5	-	Clinical signs: no remarkable effects Pathology: not triggered Irritation: very slight (barely perceptible) erythema was noted at 24 h in 1/5 animals; very slight (barely perceptible) oedema was noted at 24 h in 1/5 animals
LD_{50} value	> 2000 mg/kg		

Section A6.1.3 **6.1.3 Acute Inhalation Toxicity in Rats (Limit Test)**

Annex Point IIA6.1.3

	Key Study	Official use only
	1 REFERENCE	
1.1 Reference	[redacted]; Acute Inhalation Compound No. FMC 33297; [redacted]; unpublished Report (Project) No. 2911-75; 11.02.1976.	
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	
3.1.1 Lot/Batch number	C-6699-65	
3.1.2 Specification	As given in section 2	X
3.1.2.1 Description	Amber liquid	
3.1.2.2 Purity	As given in section 2	
3.1.2.3 STABILITY	Not applicable (short-term administration)	
3.2 Test Animals		
3.2.1 SPECIES	Rat	
3.2.2 Strain	Wistar albino	
3.2.3 Source	Not reported	
3.2.4 Sex	Male and female	
3.2.5 Age/weight at study initiation	Male - 217 to 229 g; female - 160 to 192 g	
3.2.6 NUMBER OF ANIMALS PER GROUP	10	X
3.2.7 Control animals	No	

Section A6.1.3 **6.1.3 Acute Inhalation Toxicity in Rats (Limit Test)**

Annex Point IIA6.1.3

	Key Study	
3.3 Administration/ Exposure	Inhalation	
3.3.1 Postexposure period	14 days	
	Inhalation	
3.3.2 Concentrations	Nominal concentration 23500..... [mg/m³]	
	Analytical concentration Not reported .... [mg/m³]	
3.3.3 Particle size	MMAD (mass median aerodynamic diameter) Not reported [µm] ± GSD (geometric standard deviation) Not reported [µm]	
3.3.4 Type or preparation of particles	For studies with particles	
3.3.5 Type of exposure	Whole body	
3.3.6 Vehicle	Not applicable	
3.3.7 Concentration in vehicle	Not applicable	
3.3.8 Duration of exposure	4 h	
3.3.9 Controls	No	
3.4 Examinations	Clinical observations, necropsy	
3.5 Method of determination of LD_{50}	Not applicable *Bliss, Litchfield and Wilcoxon, Finney, Weil, Thompson, Miller and Tainter*	X
3.6 Further remarks	Air was drawn through a flask in which permethrin was maintained in air suspension by means of an aerosol generator, and into the chamber at the rate of 25 litres/minute for four hours. The generating apparatus was weighed prior to and following exposure. A sum total of 141 g of permethrin was introduced into the chamber air supply during the four-hour exposure period, to effect an overall average chamber concentration of 23.5 mg/litre.	
	RESULTS AND DISCUSSION	
4.1 Clinical signs	None of the ten animals exposed to permethrin died during the fourteen-day study period. During the first two hours of exposure, all animals exhibited some degree of hyperactivity. By four hours, all animals exhibited severe whole-body tremors and marked hyperreflexia and hypersensitivity to external stimuli. These symptoms persisted unmitigated at 48 hours; at 72 hours eight of the ten animals were apparently normal, and by 96 hours all animals were free of signs.	
4.2 Pathology	No abnormalities were noted on gross necropsy of any animal.	
4.3 Other	At termination, one male animal had lost more than a quarter of its initial body weight.	

Section A6.1.3 **6.1.3 Acute Inhalation Toxicity in Rats (Limit Test)**

Annex Point IIA6.1.3

	Key Study	
4.4 LD_{50}	LD_{50} males > 23.5 mg/L (> 23500 mg/m^3); LD_{50} females > 23.5 mg/L (> 23500 mg/m^3); LD_{50} males + females > 23.5 mg/L (> 23500 mg/m^3)	X
	APPLICANT'S SUMMARY AND CONCLUSION	
5.1 Materials and methods	Five male and five female Wistar albino rats were placed in individual compartments separated by wire mesh in a 106 litre plexiglass chamber. Air was drawn through a flask in which permethrin was maintained in air suspension by means of an aerosol generator, and into the chamber at the rate of 25 litres/minute for four hours. The generating apparatus was weighed prior to and following exposure. A total of 141 g of test material was introduced into the chamber air supply during the four-hour exposure period, to effect an overall average chamber concentration of 23.5 mg/litre. The animals were observed for death or signs of toxic effect several times during the exposure period, hourly on the day of exposure, and daily thereafter for fourteen days. A gross necropsy was performed on each animal at the time of sacrifice.	
5.2 Results and discussion	None of the ten animals exposed to permethrin died during the fourteen-day study period. During the first two hours of exposure, all animals exhibited some degree of hyperactivity. By four hours, all animals exhibited severe whole-body tremors and marked hyperreflexia and hypersensitivity to external stimuli. These symptoms persisted unmitigated at 48 hours; at 72 hours eight of the ten animals were apparently normal, and by 96 hours all animals were free of signs. At termination, one male animal had lost more than a quarter of its initial body weight. No abnormalities were noted on gross necropsy of any animal. LD_{50} males > 23.5 mg/L (> 23500 mg/m^3); LD_{50} females > 23.5 mg/L (> 23500 mg/m^3); LD_{50} males + females > 23.5 mg/L (> 23500 mg/m^3)	
5.3 Conclusion		
5.3.1 Reliability	2	
5.3.2 Deficiencies	Yes. There was no analytical determination of the nominal dose level of 23.5 mg/L or of the MMAD (mass median aerodynamic diameter). It is likely, however, that the animals were exposed to a dose well in excess of the current guideline (EC B.2) limit dose of 5 mg/L for aerosols. Consequently, the study is considered adequate for purposes of classification and labelling, as well as for risk assessment.	X

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*26/10/05*
Materials and Methods	***3.1.2*** *To what does this refer, specifically?* ***3.2.6*** *Five male/five female should be stated.* ***3.5*** *Nowhere in the study submitted is this information on the calculation of LC_{50} given.* ***4.4*** *This should read LC_{50}.*
Results and discussion	*Adopt applicant's version*
Conclusion	***5.3.2*** *No GLP.* *Adopt applicant's version otherwise.*
Reliability	*2*
Acceptability	*Acceptable*
Remarks	*This study is very light on detail and lacks certain data which should be provided (see above). However, the information reported is reliable and from other studies submitted by the applicant, it appears that the TS is 95.5% pure.*
	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(7)-1. Table for Acute Inhalation Toxicity in Rats

Dose [mg/L]	*Number of dead / number of investigated*	*Time of death (range)*	*Observations*
23.5	0/10	-	Clinical signs: During the first two hours of exposure, all animals exhibited some degree of hyperactivity. By four hours, all animals exhibited severe whole-body tremors and marked hyperreflexia and hypersensitivity to external stimuli. These symptoms persisted unmitigated at 48 hours; at 72 hours eight of the ten animals were apparently normal, and by 96 hours all animals were free of signs. Pathology: No abnormalities were noted on gross necropsy of any animal. Other: At termination, one male animal had lost more than a quarter of its initial body weight.
LD_{50} value	> 23.5 mg/L		

Section A6.1.4 — 6.1.4(1) Acute Eye Irritation in Rabbits

Annex Point IIA6.1.4

	Key Study	Official use only
	1 REFERENCE	
1.1 Reference	[redacted]; Rabbit Eye Irritation Compound No. FMC 33297; [redacted]; unpublished Report (Project) No. 2910-75; 31.10.1975.	
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; a modification of that described in 16 CFR 1500.42 (formerly 21 CFR 191.12).	
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	
3.1.1 LOT/BATCH NUMBER	C-6699-65	
3.1.2 Specification	As given in section 2	X
3.1.2.1 Description	Amber liquid	
3.1.2.2 Purity	As given in section 2	
3.1.2.3 STABILITY	Not applicable (single administration)	
3.2 Test Animals	Non-entry field	
3.2.1 SPECIES	Rabbit	
3.2.2 Strain	New Zealand White	
3.2.3 Source	Not reported	
3.2.4 Sex	Not reported	
3.2.5 AGE/WEIGHT AT STUDY INITIATION	Not reported	
3.2.6 Number of animals per group	6, unwashed eyes group; 3, washed eyes group.	
3.2.7 Control animals	No	

Section A6.1.4 **6.1.4(1) Acute Eye Irritation in Rabbits**

Annex Point IIA6.1.4

	Key Study	
3.3 Administration/ Exposure		
3.3.1 PREPARATION OF TEST SUBSTANCE	Test substance was used as delivered	
3.3.2 Amount of active substance instilled	0.1 mL	
3.3.3 Exposure period	7 days, unwashed eyes group; 30 seconds, washed eyes group.	
3.3.4 Postexposure period	7 days	X
3.4 EXAMINATIONS		
3.4.1 Ophthalmoscopic examination	Yes	
3.4.1.1 Scoring system	Illustrated Guide for Grading Eye Irritation by Hazardous Substances (U.S. Government Printing Office, Washington, D.C.). Ocular reactions were scored at 1, 24, 48, and 72 hours and 4 and 7 days after administration.	
3.4.1.2 Examination time points	60 min, 24 h, 48 h, 72 h, 4 d, 7 d	
3.4.2 OTHER INVESTIGATIONS	Effect of rinsing at 30 seconds with 100 mL warm tap water.	
3.5 Further remarks		
	4 Results and Discussion	
4.1 Clinical signs	None reported	
4.2 Average score		
4.2.1 Cornea	Unwashed eyes group: average score for all animals at 24, 48, 72 h = 0 (stippling - appearance of pinpoint roughening: noted in one quarter or less of the area of the cornea in 2/6 animals) Washed eyes group: average score for all animals at 24, 48, 72 h = 0	
4.2.2 Iris	Unwashed eyes group: average score for all animals at 24, 48, 72 h = 0 Washed eyes group: average score for all animals at 24, 48, 72 h = 0	
4.2.3 Conjunctiva		
4.2.3.1 Redness	Unwashed eyes group: average score for all animals at 24, 48, 72 h = 0.17 Washed eyes group: average score for all animals at 24, 48, 72 h = 0.22	

Section A6.1.4 6.1.4(1) Acute Eye Irritation in Rabbits

Annex Point IIA6.1.4

	Key Study
4.2.3.2 CHEMOSIS	Unwashed eyes group: average score for all animals at 24, 48, 72 h = 0.22 Washed eyes group: average score for all animals at 24, 48, 72 h = 0
4.3 Reversibility	Unwashed eyes group: Yes, full recovery from conjunctival redness, chemosis and discharge, and corneal stippling, by 48 h. Washed eyes group: Yes, full recovery from conjunctival chemosis and discharge by 24 h, and full recovery from conjunctival redness by 48h.
4.4 Other	
4.5 Overall result	Permethrin demonstrated a low potential for eye irritation, resulting in temporary conjunctival redness, chemosis and discharge, and corneal stippling. All effects were completely reversible by 48 h. The effect of rinsing with water 30 seconds post-exposure was to prevent corneal stippling, and to reduce the full recovery time from conjunctival chemosis and discharge from 48 h to 24 h.
	5 APPLICANT'S SUMMARY AND CONCLUSION
5.1 Materials and methods	An eye irritation study, a modification of that described in 16 CFR 1500.42 (formerly 21 CFR 191.12) was performed on rabbits. Nine albino rabbits, New Zealand White strain, were individually housed and equilibrated in the laboratory prior to testing. Any animals considered unsuitable due to the presence of ocular abnormalities following pre-test examination were replaced before commencement of the test. One-tenth millilitre of permethrin was placed into the conjunctival sac of one eye of each rabbit, the contralateral eye serving as control. The eye was then held shut for one second. In three rabbits the treated eyes were washed at thirty seconds with 100 mL of warm tap water. Ocular reactions were scored according to the Illustrated Guide for Grading Eye Irritation by Hazardous Substances (U.S. Government Printing Office, Washington, D.C.) at 1, 24, 48, and 72 hours and 4 and 7 days after administration.

Section A6.1.4 **6.1.4(1) Acute Eye Irritation in Rabbits**

Annex Point IIA6.1.4

5.2 Results and discussion

Key Study

	Cornea	Iris	Conjunctiva	
			redness	chemosis
average score (unwashed eyes)	0 to 4	0 to 2	0 to 3	0 to 4
60 min	0	0	0.5	0.5
24 h	0 Stippling	0	0.5	0.67
48 h	0	0	0	0
72 h	0	0	0	0
24h, 48h, 72h	0	0	0.17	0.22

	Cornea	Iris	Conjunctiva	
			redness	chemosis
average score (washed eyes)	0 to 4	0 to 2	0 to 3	0 to 4
60 min	0	0	1	1
24 h	0	0	0.67	0
48 h	0	0	0	0
72 h	0	0	0	0
24h, 48h, 72h	0	0	0.22	0

Permethrin demonstrated a low potential for eye irritation, resulting in temporary conjunctival redness, chemosis and discharge, and corneal stippling. All effects were completely reversible by 48 h. The effect of rinsing with water 30 seconds post-exposure was to prevent corneal stippling, and to reduce the full recovery time from conjunctival chemosis and discharge from 48 h to 24 h..

5.3 Conclusion

Permethrin demonstrated a low potential for eye irritation, resulting in temporary conjunctival redness, chemosis and discharge, and corneal stippling. All effects were completely reversible by 48 h. The effect of rinsing with water 30 seconds post-exposure was to prevent corneal stippling, and to reduce the full recovery time from conjunctival chemosis and discharge from 48 h to 24 h.

Section A6.1.4 **6.1.4(1) Acute Eye Irritation in Rabbits**

Annex Point IIA6.1.4

Key Study

5.3.1 Reliability	2
5.3.2 Deficiencies	Yes; not GLP.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*26/10/05*
Materials and Methods	***3.1.2*** *To what does this refer, specifically?* ***3.3.4*** *From reading this, one would think that exposure was for 7 days and observation took place for a* ***further*** *7. This is not the case – exposure was for 7 days in the non-washed animals and during this time, examinations were made at the appointed times i.e. 1, 24, 48, and 72 hrs.*
Results and discussion	*Adopt applicant's version.*
Conclusion	*Adopt applicant's version.*
Reliability	*2*
Acceptability	*Acceptable*
Remarks	*A large number of other skin/eye irritancy studies were submitted (8). The TSs in these studies are different to that identified in the other key acute studies, where it has been identified as FMC 33297 (as is given in Section 2). FMC 30062, identified as a clear liquid with clumps of cotton-like material throughout (which is possibly due to contamination), causes persistent eye irritation (not resolved by termination on day 7) and is a skin irritant. FMC 30953 and FMC 30061, both identified as a clear liquid, similarly causes persistent eye irritation and, while not classifiable as skin irritants, show more potential to act as such. Assuming that all TSs are permethrin, then, omitting FMC 30062 due to the possibility of the TS being contaminated, it will classify as an eye irritant. No mention is made in Section 2 of these other coded substances listed above.*

	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	

Appendix

Table A6_1_4E-1. Results of eye irritation study

Use this table, if relevant effects occur.

	Cornea	Iris	Conjunctiva	
			redness	chemosis
score (average of animals in unwashed eyes group)	0 to 4	0 to 2	0 to 3	0 to 4
60 min	0	0	0.5	0.5
24 h	0 Stippling	0	0.5	0.67
48 h	0	0	0	0
72 h	0	0	0	0
Average 24h, 48h, 72h	0	0	0.17	0.22
Area affected	≤ 0.25	0	Not reported	Not reported
Maximum average score (including area affected, max 110)	Not reported	Not reported	Not reported	Not reported
Reversibility*	c	Not applicable	c	c
average time for reversion	48h	Not applicable	42h	42h
Give method of calculation maximum average score. * *c : completely reversible* *n c : not completely reversible* *n : not reversible*	-	-	-	-

Section A6.1.4 **6.1.4(2) Acute Dermal Irritation in Rabbits**
Annex Point IIA6.1.4

		Official use only
	Key Study	
	1 REFERENCE	
1.1 REFERENCE	[redacted]; Rabbit Primary Dermal Irritation Compound No. FMC 33297; [redacted]; unpublished Report (Project) No. 2909-75; 31.10.1975.	
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	Yes; 16 CFR 1500.41 (formerly 21 CFR 191.11).	
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	
3.1.1 Lot/Batch number	C-6699-65	
3.1.2 Specification	As given in section 2	X
3.1.2.1 Description	Amber liquid	
3.1.2.2 Purity	As given in section 2	
3.1.2.3 Stability	Not applicable (single administration)	
3.2 TEST ANIMALS		
3.2.1 Species	Rabbit	
3.2.2 Strain	New Zealand White	
3.2.3 Source	Not reported	
3.2.4 Sex	Not reported	
3.2.5 Age/weight at study initiation	1.9 to 2.3 kg	
3.2.6 Number of animals per group	6	
3.2.7 Control animals	No	
3.3 ADMINISTRATION/ EXPOSURE	Dermal	

Section A6.1.4 Annex Point IIA6.1.4	**6.1.4(2) Acute Dermal Irritation in Rabbits**	
3.3.1 Application		
3.3.1.1 Preparation of test substance	Test substance was prepared by mixing 1 gram of test substance with 1mL of water.	X
3.3.1.1 Test site and Preparation of Test Site	Rabbits were closely clipped over the back and sides with an electric clipper. There were two test sites per rabbit. Each site was 1" x 1" (2.54 cm x 2.54 cm) in area. A site to the left of the spinal column was abraded, while a site to the right of the spinal column was left intact. The abrasions were minor incisions throughout the stratum corneum, but not sufficiently deep to disturb the derma or produce bleeding. Skin cleaning not reported.	X
3.3.2 Occlusion	Occlusive	
3.3.3 Vehicle	Water	
3.3.4 Concentration in vehicle	1 g/mL	
3.3.5 Total volume applied	0.5 mL	
3.3.6 Removal of test substance	Not reported	
3.3.7 Duration of exposure	24h	X
3.3.8 Postexposure period	72h	
3.3.9 Controls	No	
3.4 Examinations		
3.4.1 Clinical signs	Yes	
3.4.2 Dermal examination	Yes	
3.4.2.1 Scoring system	As per EC B.4, except - Erythema and eschar formation: Severe erythema (beet redness) to slight eschar formation (injuries in depth)4	
3.4.2.2 Examination time points	24h, 72h	X
Other examinations	Not applicable	
3.5 Further remarks		
	4 RESULTS AND DISCUSSION	
4.1 Average score		

Section A6.1.4 **6.1.4(2) Acute Dermal Irritation in Rabbits**
Annex Point IIA6.1.4

4.1.1 Erythema	Intact/Abraded Skin	Hours	Mean Score
	Intact Skin	24h	0.5
	Abraded Skin	24h	0.5
	Intact Skin	72h	0
	Abraded Skin	72h	0
	Intact Skin	24h, 72h	0.25
	Abraded Skin	24h, 72h	0.25
4.1.2 Edema	Intact/Abraded Skin	Hours	Mean Score
	Intact Skin	24h	0
	Abraded Skin	24h	0
	Intact Skin	72h	0
	Abraded Skin	72h	0
	Intact Skin	24h, 72h	0
	Abraded Skin	24h, 72h	0

4.2 Reversibility Yes; recovery from very slight erythema (barely perceptible) by 72h.

4.3 Other examinations No signs of systemic toxicity were reported.

4.4 Overall result Primary Dermal Irritation Index = Sum of Mean Scores/4 = 0.25

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

A primary dermal irritation study, described in 16 CFR 1500.41 (formerly 21 CFR 191.11), was performed on rabbits.
Six albino rabbits, New Zealand White strain, 1.9 to 2.3 kg, were closely clipped over the back and sides with an electric clipper. There were two test sites per rabbit. Each site was 1" x 1" (2.54 cm x 2.54 cm) in area. A site to the left of the spinal column was abraded, while a site to the right of the spinal column was left intact. The abrasions were minor incisions throughout the stratum corneum, but not sufficiently deep to disturb the derma or produce bleeding.
Permethrin was administered as a 1 g/mL aqueous slurry. In all cases, 0.5 millilitre of the test mixture was applied beneath a surgical gauze square 1" x 1" (2.54 cm x 2.54 cm), two single layers thick, placed directly on the test site. The animals were then wrapped with plastic sheeting to keep the gauze in place and secured with adhesive tape. After 24 hours the sheeting and gauze patches were removed.

Section A6.1.4
Annex Point IIA6.1.4

6.1.4(2) Acute Dermal Irritation in Rabbits

Observations for signs of dermal irritation or systemic toxicity were recorded at 24 and 72 hours after application. At each observation, all treated sites were scored for erythema and eschar formation and oedema formation. The scores were used to calculate a primary dermal irritation index.

5.1 RESULTS AND DISCUSSION

Erythema

Intact/Abraded Skin	Hours	Mean Score
Intact Skin	24h	0.5
Abraded Skin	24h	0.5
Intact Skin	72h	0
Abraded Skin	72h	0
Intact Skin	24h, 72h	0.25
Abraded Skin	24h, 72h	0.25

Oedema

Intact/Abraded Skin	Hours	Mean Score
Intact Skin	24h	0
Abraded Skin	24h	0
Intact Skin	72h	0
Abraded Skin	72h	0
Intact Skin	24h, 72h	0
Abraded Skin	24h, 72h	0

Recovery from very slight erythema (barely perceptible) by 72h.

5.1 Conclusion

Reliability

2

Deficiencies

Yes.
No assessment of irritation was made at 60 minutes or 48 hours (as required by test guideline EC B.4), however, this deficiency is not considered critical in the context of the full reversibility of slight irritant effects by 72 hours.

The test material was applied as a 1 mg/mL aqueous slurry, rather than undiluted, as would generally be the case for test materials which are liquids. Provision is, however, made in EC B.4, 1.6.2.3 Dose Level, for administration of semi-solid test materials. Given permethrin's demonstrated low potential for irritation (even in the case of abraded skin, which test guideline EC B.4 recommends is avoided), and the relatively short time required for full reversibility of the slight irritating effects induced, it is considered that the results of the study adequately characterise the skin irritation potential of permethrin.

Section A6.1.4 **Annex Point IIA6.1.4**	**6.1.4(2) Acute Dermal Irritation in Rabbits**

The results are also in accordance with the current EC non-classification of permethrin with respect to skin irritation potential.

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	*26/20/05*
Materials and Methods	***3.1.2*** *To what does this refer, specifically?.* ***3.3.1.1*** *Liquid TSs are usually applied undiluted and not as a slurry.* ***3.3.1.2*** *It is not normal practice to abrade the skin.* ***3.3.7*** *The usual exposure period is 4 hours.* ***3.4.2.2*** *It is normally required to have 60 min, 24,* ***48*** *and 72 hour examinations.*
Results and discussion	*Adopt applicant's version.*
Conclusion	***5.3.2*** *No GLP. Otherwise, adopt applicant's version.*
Reliability	*2*
Acceptability	*Acceptable*
Remarks	*This study, like all the acute toxicity studies, is very light on detail and lacks certain data which should be provided (see above). However, the information reported is reliable and from other studies submitted by the applicant, it appears that the TS is 95.5% pure. Other discrepancies can be overlooked, given permethrin's low potential for irritation and its speed of reversibility.*
	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_1-4S-1. Table for skin irritation study

score (average animals investigated)	time	Erythema	Edema
average score Draize scores (0 to maximum 4)	60 min	-	-
	24 h	0.5	0
	48 h	-	-
	72 h	0	0
other times	*State time*	-	-
average score	24h, 72h	0.25	0
reversibility: *		c	not applicable
average time for reversibility		72h	not applicable

* c : completely reversible
n c : not completely reversible
n : not reversible

Section A6.1.5 6.1.5 Skin sensitisation (GPMT)

Annex Point IIA6.1.5

		Key Study	Official use only
		1 REFERENCE	
Reference		[redacted]; Skin Sensitisation in the Guinea-Pig of a Permethrin 25/75 *cis/trans* Isomer Ratio; [redacted]; unpublished Report No. 91626D/WLC 159/SS; 13.12.1991.	
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**	Yes; EPA FIFRA 81-6.	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	As given in section 2	X
3.1.1	**Lot/Batch number**	Not available	
3.1.2	**Specification**	As given in section 2	X
3.1.2.1	**Description**	Clear brown liquid	
3.1.2.2	**Purity**	As given in section 2	X
3.1.2.3	**Stability**	Not applicable (repeat acute administration)	
3.1.2.4	**Preparation of test substance for application**	a) <u>for induction:</u> used as delivered and in 50:50 mixture with Freund's complete adjuvant b) <u>for challenge:</u> used as delivered and in 50% v/v in corn oil	
3.1.2.5	**Pretest performed on irritant effects**	Yes	
3.2	**Test Animals**		
3.2.1	**Species**	Guinea pigs	
3.2.2	**Strain**	Dunkin/Hartley	
3.2.3	**Source**	[redacted].	
3.2.4	**Sex**	Female	

Section A6.1.5 6.1.5 Skin sensitisation (GPMT)

Annex Point IIA6.1.5

		Key Study	
3.2.5	Age/weight at study initiation	Approximately 6 to 7 weeks of age	
3.2.6	Number of animals per group	20	
3.2.7	Control animals	Yes	
3.3	Administration/ Exposure	State study type: Adjuvant	
3.3.1	Induction schedule	Day 0 – intradermal injection; day 7 – day 9, topical.	
3.3.2	Way of Induction	Intradermal and topical Occlusive	
3.3.3	Concentrations used for induction	As supplied and 50% v/v in corn oil (test material as supplied did not cause irritation)	X
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	50 % in water	
3.3.5	Challenge schedule	Day 21-22; see table in appendix.	
3.3.6	Concentrations used for challenge	As supplied and 50% v/v in corn oil (usually maximum non-irritant concentration)	
3.3.7	Rechallenge	No	
3.3.8	Scoring schedule	24h, 48h and 72h after challenge (after removal of patches)	
3.3.9	Removal of the test substance	Not reported	
3.3.10	Positive control substance	Formalin	
3.4	Examinations		
3.4.1	Pilot study	yes	
3.5	Further remarks	-	

4 RESULTS AND DISCUSSION

Section A6.1.5 **6.1.5 Skin sensitisation (GPMT)**

Annex Point IIA6.1.5

Key Study

4.1 Results of pilot studies

Intradermal injections
Vehicle: Corn oil

Concentration % v/v	Score		
	Hours	24	72
100	D	10	10
	E	2	2
	O	2	2
80	D	10	10
	E	2	2
	O	2	2
70	D	8	8
	E	2	2
	O	2	2
60	D	8	8
	E	2	2
	O	2	2
50	D	8	8
	E	2	2
	O	2	2
40	D	8	6
	E	2	2
	O	2	2
30	D	6	6
	E	2	2
	O	2	1
20	D	6	6
	E	2	2
	O	2	1
Vehicle control	D	4	3
	E	2	1
	O	1	1
Key: D Diameter (mm); E Erythema (0-4 numerical scores); O Oedema (0-4 numerical scores)			

Section A6.1.5 **6.1.5 Skin sensitisation (GPMT)**

Annex Point IIA6.1.5

Key Study

<u>Topical application</u>

Vehicle: -

Concentration % v/v	Score					
	0 Hours		24 Hours		48 Hours	
	E	O	E	O	E	O
100	0	0	0	0	0	0
75	0	0	0	0	0	0
60	0	0	0	0	0	0
Vehicle control	0	0	0	0	0	0
100	0	0	0	0	0	0
75	0	0	0	0	0	0
60	0	0	0	0	0	0
Vehicle control	0	0	0	0	0	0
100	0	0	0	0	0	0
75	0	0	0	0	0	0
60	0	0	0	0	0	0
Vehicle control	0	0	0	0	0	0
100	0	0	0	0	0	0
75	0	0	0	0	0	0
60	0	0	0	0	0	0
Vehicle control	0	0	0	0	0	0

Key: E Erythema (0-4 numerical scores); O Oedema (0-4 numerical scores)

4.2 Results of test

4.2.1	**24h after challenge**	0/20
4.2.2	**48h after challenge**	0/20
4.2.3	**Other findings**	-
4.3	**Overall result**	Negative

Section A6.1.5 6.1.5 Skin sensitisation (GPMT)

Annex Point IIA6.1.5

Key Study

5 Applicant's Summary and conclusion

5.1 MATERIALS AND METHODS

EPA FIFRA 81-6

Induction

Intradermal injections

A 4 x 6 cm area of dorsal skin on the scapular region of the guinea-pig was clipped free of hair with electric clippers. Three pairs of intradermal injections were made into a 2 x 4 cm area within the clipped area.

Injectables were prepared as follows:

Freund's complete adjuvant was diluted with an equal volume of water for irrigation (Ph. Eur.).

A permethrin 25/75 *cis/trans* isomer ratio, as supplied.

A permethrin 25/75 *cis/trans* isomer ratio, as supplied in a 50 : 50 mixture with Freund's complete adjuvant.

Topical application

The preliminary investigations indicated that permethrin, as supplied did not cause skin irritation. Therefore, six days after the injections, the same 4 x 6 cm interscapular area was clipped and shaved free of hair and the site was pre-treated by gentle rubbing with 0.2 mL per site of 10% w/w sodium lauryl sulphate in petrolatum. Twenty-four hours later a 2 x 4 cm patch of Whatman No. 3 paper was saturated with approximately 0.4 mL of a permethrin 25/75 *cis/trans* isomer ratio, as supplied. The patch was placed on the skin and covered by a length of impermeable plastic adhesive tape (5 cm width "Blenderm"). This in turn was firmly secured by elastic adhesive bandage (5 cm width "Elastoplast") wound round the torso of the animal and fixed with "Sleek" impervious plastic adhesive tape. The dressing was left in place for 48 hours.

Control animals

During the induction phase, the control animals were treated similarly to the test animals with the exception that the test substance was omitted from the intradermal injections and topical application.

Challenge

Control and test animals

The control and test animals were challenged topically two weeks after the topical induction application using a permethrin 25/75 *cis/trans* isomer ratio, as supplied and 50% v/v in corn oil.

Hair was removed by clipping and then shaving from an area on the left flank of each guinea-pig. A 2 x 2 cm patch of Whatman No. 3 paper was saturated with approximately 0.2 mL of a permethrin 25/75 *cis/trans* isomer ratio, as supplied and applied to an anterior site on the flank.

Section A6.1.5 **6.1.5 Skin sensitisation (GPMT)**

Annex Point IIA6.1.5

Key Study

	A permethrin 25/75 *cis/trans* isomer ratio, 50% v/v in corn oil was applied in a similar manner to a posterior site. The patches were sealed to the flank for 24 hours under strips of "Blenderm" covered by "Elastoplast" wound round the trunk and secured with "Sleek".The challenge sites were evaluated 24, 48 and 72 hours after removal of the patches. Give concise description of method; give test guidelines no. and discuss relevant deviations from test guidelines No signs of ill health or toxicity were recorded.
5.2 RESULTS AND DISCUSSION	**Induction** Intradermal injections Necrosis was recorded at sites receiving Freund's Complete Adjuvant in test and control animals. Irritation was seen in test animals at sites receiving a permethrin 25/75 *cis/trans* isomer ratio, as supplied and slight irritation was observed in control animals receiving corn oil. Topical application Slight erythema was observed in test animals following topical application with a permethrin 25/75 *cis/trans* isomer ratio, as supplied and similar signs of irritation were seen in the controls. **Challenge** There were no dermal reactions seen in any of the test or control animals.
5.3 CONCLUSION	In this test, performed in twenty albino guinea-pigs a permethrin 25/75 *cis/trans* isomer ratio did not produce evidence of skin sensitisation (delayed contact hypersensitivity)
5.3.1 Reliability	1
5.3.2 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	*27/10/05*
Materials and Methods	***3.1*** *This TS is not described in Section 2, code numbers given do not match.* ***3.1.2*** *To what does this refer, specifically?* ***3.1.2.2*** *Purity is unknown as the TS is not identified in Section 2.* ***3.3.3*** *TS, as supplied, was used alone in the induction phase.*
Results and discussion	*Applicant's version adopted*
Conclusion	*Applicant's version adopted*
Reliability	*1*

Section A6.1.5 **Annex Point IIA6.1.5**	**6.1.5 Skin sensitisation (GPMT)**
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. Detailed information including induction/challenge/scoring schedule for skin sensitisation test

state test applied, delete other (modify if necessary, i.e. day of treatment)

Inductions	GPMT		Buehler test	Observations/Remarks *give information on irritation effects*
	day of treatment	application	day of treatment	
Induction 1	0	intradermal		Necrosis was recorded at sites receiving Freund's Complete Adjuvant in test and control animals. Irritation was seen in test animals at sites receiving a permethrin 25/75 *cis/trans* isomer ratio, as supplied and slight irritation was observed in control animals receiving corn oil.
pretreatment for non-irritating substances	6	0.2 ml 10 % SLS in petrolatum		
Induction 2	7-9	topical		Slight erythema was observed in test animals following topical application with a permethrin 25/75 *cis/trans* isomer ratio, as supplied and similar signs of irritation were seen in the controls.
Induction 3	-	-		
challenge	21-22	topical		There were no dermal reactions seen in any of the test or control animals.
(rechallenge)	-	-		
scoring 1	23	0 / 20		There were no dermal reactions seen in any of the test or control animals.
scoring 2	24	0 / 20		There were no dermal reactions seen in any of the test or control animals.
scoring 3	25	0 / 20		There were no dermal reactions seen in any of the test or control animals.

Table A6_1_5-2. Result of skin sensitisation test

	Number of animals with signs of allergic reactions / number of animals in group		
	Negative control	**Test group**	**Positive control**
scored after 24h	0 / 20	0 / 20	10 / 10 (most recent)
scored after 48h	0 / 20	0 / 20	10 / 10 (most recent)

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

Annex Point IIA6.2

Key Study

Official use only

1 REFERENCE

1.1	Reference	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.
1.2	Data protection	No
1.2.1	Data owner	Public domain
1.2.2	Companies with letter of access	Not applicable
1.2.3	Criteria for data protection	No data protection claimed

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

X

3 MATERIALS AND METHODS

3.1 Test material

No.	Compound	mCi/mmol
1	[^{14}C-acid-1*R*,*t*]per	6.4
2	[^{14}C-alc-1*R*,*t*]per	4.6
3	[^{14}C-acid-1*R*,*c*]per	1.7
4	[^{14}C-alc-1*R*,*c*]per	4.6
5	[^{14}C-acid-1*RS*,*t*]per	58.2
6	[^{14}C-alc-1*RS*,*t*]per	55.9
7	[^{14}C-acid-1*RS*,*c*]per	58.2
8	[^{14}C-alc-1*RS*,*c*]per	55.9
9	[^{14}C-1*R*,*t*]Cl_2CA	6.4
10	[^{14}C]Pbalc	4.6

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

Annex Point IIA6.2

Key Study

Abbreviations for chemicals

Permethrin is a mixture of [1*RS*,*trans*] and [1*RS*,*cis*] isomers, designated as *t*-per and *c*-per, respectively. The system used to designate the hydroxylated per isomers is illustrated for example by 4′-HO,*t*-HO,*c*-per, which represents the *c*-per derivative hydroxylated at the 4′ position of the alcohol moiety and at the methyl group of the geminal dimethyl moiety which is *trans* to the carboxyl group. The hydrolysis products of the acid moieties of *t*- and *c*-per are *t*-Cl_2CA and *c*-Cl_2CA, respectively (Cl_2CA designating the dichloro analogue of chrysanthemic acid). The Cl_2CA isomers hydroxylated at the geminal dimethyl position are: *t*-HO,*t*-Cl_2CA; *c*-HO,*t*-Cl_2CA; *t*-HO,*c*-Cl_2CA; and *c*-HO,*c*-Cl_2CA. The *cis*-hydroxymethyl acids readily lactonise to form the corresponding lactones, *c*-HO,*t*-Cl_2CA-lactone and *c*-HO,*c*-Cl_2CA-lactone. Derivatives of phenoxybenzyl alcohol (PBalc) and phenoxybenzoic acid (PBacid) include those hydroxylated at the 2′ and 4′ positions (2′-HO-PBalc, 2′-HO-PBacid, 4′-HO-PBalc, and 4′-HO-PBacid). Several conjugates involving glycine, sulfate, and glucuronic acid (gluc) as the conjugating moieties are also considered, as are the lactones of the glucuronides.

3.1.1 Lot/Batch number Not available

3.1.2 Specification Deviating from specification given in section 2 as follows

3.1.2.1 Description Not reported

3.1.2.2 Purity Radiochemical purity >99%.

3.1.2.3 Stability Not applicable (single administration)

3.1.2.4 Radiolabelling ^{14}C

No.	Compound	Radiolabel
1	[^{14}C-acid-1*R*,*t*]per	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety
2	[^{14}C-alc-1*R*,*t*]per	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety
3	[^{14}C-acid-1*R*,*c*]per	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety
4	[^{14}C-alc-1*R*,*c*]per	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety
5	[^{14}C-acid-1*RS*,*t*]per	*C=O group of acid moiety
6	[^{14}C-alc-1*RS*,*t*]per	α-*CH_2 position of alcohol moiety
7	[^{14}C-acid-1*RS*,*c*]per	*C=O group of acid moiety
8	[^{14}C-alc-1*RS*,*c*]per	α-*CH_2 position of alcohol moiety
9	[^{14}C-1*R*,*t*]Cl_2CA	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety
10	[^{14}C]PBalc	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety

3.2 Test Animals Non-entry field

3.2.1 Species Rat

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

Annex Point IIA6.2

Key Study

3.2.2	**Strain**	Sprague-Dawley	
3.2.3	**Source**	*Horton Laboratories Inc., Oakland, California, USA*	
3.2.4	**Sex**	♂	
3.2.5	**Age/weight at study initiation**	160-200 g	
3.2.6	**Number of animals per group**	1	
3.2.7	**Control animals**	No	
3.3	**Administration/ Exposure**	Oral/Inhalation/dermal/intraperitoneal/intravenous/intratracheal	X
3.3.1	**Postexposure period**	4 or 12 days	
		Oral	
3.3.2	**Type**	Gavage	
3.3.3	**Concentration**	Gavage	

No.	Compound	Radiolabel
1	[^{14}C-acid-1*R*,*t*]per	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety
2	[^{14}C-alc-1*R*,*t*]per	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety
3	[^{14}C-acid-1*R*,*c*]per	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety
4	[^{14}C-alc-1*R*,*c*]per	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety
5	[^{14}C-acid-1*RS*,*t*]per	*C=O group of acid moiety
6	[^{14}C-alc-1*RS*,*t*]per	α-*CH_2 position of alcohol moiety
7	[^{14}C-acid-1*RS*,*c*]per	*C=O group of acid moiety
8	[^{14}C-alc-1*RS*,*c*]per	α-*CH_2 position of alcohol moiety
9	[^{14}C-1*R*,*t*]Cl_2CA	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety
10	[^{14}C]PBalc	Cl_2C*=CH position of acid moiety, uniform phenoxy labelling of alcohol moiety

3.2	**Test Animals**	Non-entry field
3.2.1	**Species**	Rat
3.2.2	**Strain**	Sprague-Dawley
3.2.3	***Source***	Horton Laboratories Inc., Oakland, California, USA
3.2.4	***Sex***	♂

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

Annex Point IIA6.2

Key Study

3.2.5 Age/weight at	160-200 g	
3.2.6 Number of animals per group	1	
3.2.7 Control animals	No	
3.3 Administration/ Exposure	Oral/Inhalation/dermal/intraperitoneal/intravenous/intratracheal	X
3.3.1 POSTEXPOSURE PERIOD	4 or 12 days	

Oral

3.3.2 Type Gavage

3.3.3 Concentration Gavage

^{14}C-Acid label				
t-Cl_2CA	*trans*-Permethrin		*cis*-Permethrin	
1*R*, 4 days	1*R*, 4 days	1*RS*, 12 days	1*R*, 4 days	1*RS*, 12 days
No. 9	No. 1	No. 5	No. 3	No. 7
Administered Dose, mg/kg				
0.5	2.0	4.8	2.9	4.8
^{14}C-Alcohol label				
	trans-Permethrin		*cis*-Permethrin	
PBalc, 4 days	1*R*, 4 days	1*RS*, 12 days	1*R*, 4 days	1*RS*, 12 days
No. 10	No. 2	No. 6	No. 4	No. 8
Administered Dose, mg/kg				
1.4	2.1	4.4	1.6	4.4

3.3.8 Vehicle Dimethyl sulphoxide (DMSO)

3.3.9 Concentration in vehicle Not reported

3.3.10 Total volume applied Not reported

3.3.11 Controls No

3.3.8 Samples Urine, faeces, [^{14}C]-carbon dioxide, tissues (blood, bone, brain, fat, heart, kidney, liver, lung, muscle, spleen, testes)

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

Annex Point IIA6.2

Key Study

4 RESULTS AND DISCUSSION

4.1 TOXIC EFFECTS, CLINICAL SIGNS Not reported

4.2 Recovery of labelled compound

^{14}C-Acid label				
t-Cl_2CA	*trans*-Permethrin		*cis*-Permethrin	
1*R*, 4 days	1*R*, 4 days	1*RS*, 12 days	1*R*, 4 days	1*RS*, 12 days
No. 9	No. 1	No. 5	No. 3	No. 7
% of Administered Radiocarbon Recovered				
> 90.1	> 83.1	> 98.5	> 87.3	> 99.5
^{14}C-Alcohol label				
	trans-Permethrin		*cis*-Permethrin	
PBalc, 4 days	1*R*, 4 days	1*RS*, 12 days	1*R*, 4 days	1*RS*, 12 days
No. 10	No. 2	No. 6	No. 4	No. 8
% of Administered Radiocarbon Recovered				
> 95.0	> 79.0	> 97.0	> 76.1	> 99.0

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

Annex Point IIA6.2

Key Study

4.3 ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

The compounds were rapidly metabolised and labels in the acid and alcohol fragments were almost completely eliminated from the body within a few days. The radiocarbon (alcohol or acid label) from the *cis* isomer was eliminated in the urine (52-54% of the dose) and the faeces (45-47%), whereas 79-82% of the radiocarbon from the *trans* isomer appeared in the urine and 16-18% in the faeces within 12 days after administration. The $^{14}CO_2$ contained in the expired air corresponded to less than 0.5% of the dose. The tissue residues were very low, although the *cis* isomer showed relatively higher residue levels (0.46-0.62 mg/kg tissue) in the fat.

The major metabolite from the acid moiety was Cl_2CA, which was mostly excreted in the urine, conjugated with glucuronic acid. This accounted for 50-63% of the dose from *trans*-permethrin and 15-22% from *cis*-permethrin. Oxidation at either of the geminal dimethyl groups occurred to the extent of 4.3-10.4% (*trans*) or 12.2-14.9% (*cis*), and these oxidised products were eliminated in the urine and faeces as such or as the lactone or glucuronide.

The major metabolite from the alcohol moiety was 3-(4'-hydroxyphenoxy)benzoic acid (4'-OH-PBacid) sulfate, accounting for 30.7-42.8% of the dose (*trans*) and 19.5-29.3% (cis). From *cis*-permethrin, 2'-OH-PBacid sulfate (about 3%) was identified. Another significant metabolite was PBacid, which occurred free and as glucuronide or glycine conjugates, and accounted for 25-31% (*trans*) and 5.7-10.1% (cis) of the dosed radiocarbon. Except for a trace of PBacid, all the above metabolites from the alcohol moiety were excreted entirely in the urine. However, the faeces of rats dosed with *trans*-permethrin contained 1-2% of the radioactive dose as PBalc. Thus substantial portions of the radioactive metabolites in the recovered excreta were identified.

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

Annex Point IIA6.2

Key Study

The five principal sites of metabolic attack in both permethrin isomers were ester cleavage, oxidation at the *trans*- and *cis*-methyl of the geminal dimethyl group of the acid moiety, and oxidation at the 2'- and 4'-positions of the phenoxy group. Conjugation of the resultant carboxylic acids, alcohols, and phenols with glucuronic acid, glycine and sulfuric acid occurred to varying extent. *cis*-Permethrin was more stable than *trans*-permethrin, and the *cis* isomer yielded four faecally excreted ester metabolites that resulted from hydroxylation at the 2'- or 4'-position of the phenoxy group or at the *trans*- or *cis*-methyl group on the cyclopropane ring. The ester-cleaved metabolites were extensively excreted into the urine whereas the metabolites retaining an ester bond were found only in the faeces. The major metabolite from the acid moiety of both isomers was Cl_2CA in free (1-8%) and glucuronide (14-42%) forms. Other significant metabolites were *trans*-OH-Cl_2CA (1-5%) and *cis*-OH-Cl_2CA in the free (3-5%), lactone (0-4%) and glucuronide (1-2%) forms. On the other hand, the alcohol moiety released after cleavage of the ester bond of both isomers was converted mainly to the sulfate of 3-(4'-hydroxyphenoxy)benzoic acid (4'-OH-PBacid) (29-43% of the dose) and PBacid in the free (1-10%) and glucuronide (7-15%) forms. Other significant metabolites of the alcohol moiety were PBalc, PBacid-glycine and the sulfate of 3-(2'-hydroxyphenoxy) benzoic acid (2'-OH-PBacid). [1*RS*, *trans*]- and [1*RS*, *cis*]-permethrin showed no significant differences in metabolic fate in the rat from [1*R*, *trans*]- and [1*R*, *cis*]-permethrin, respectively.

Applicant's Summary and conclusion

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

Annex Point IIA6.2

Key Study

5.1 Materials and methods

Male, albino Sprague-Dawley rats (160-200 g, Horton Laboratories Inc., Oakland, Calif.) were individually treated by stomach tube with ^{14}C-labelled compounds 1-10 in dimethyl sulphoxide.

No.	Compound
1	[^{14}C-acid-1*R*,*t*]per
2	[^{14}C-alc-1*R*,*t*]per
3	[^{14}C-acid-1*R*,*c*]per
4	[^{14}C-alc-1*R*,*c*]per
5	[^{14}C-acid-1*RS*,*t*]per
6	[^{14}C-alc-1*RS*,*t*]per
7	[^{14}C-acid-1*RS*,*c*]per
8	[^{14}C-alc-1*RS*,*c*]per
9	[^{14}C-1*R*,*t*]Cl_2CA
10	[^{14}C]PBalc

Key: per = Permethrin; *t* = *trans*; *c* = *cis*; alc = alcohol; CA = carboxylic acid; PB = phenoxybenzyl.

With compounds 5-8, the urine, faeces, and [^{14}C]carbon dioxide were collected for up to 12 days, while the treated rats were held in all-glass metabolism cages and provided ground rat chow and water ad libitum with [^{14}C]carbon dioxide collection in a monoethanolamine-methyl Cellosolve (2:1) mixture. Less efficient metabolism cages were used in the earlier studies with compounds 1-4, 9, and 10, resulting in lower overall recoveries than with compounds 5-8.

Tissue samples recovered on sacrifice after 4 or 12 days were analysed for total radiocarbon by combustion and liquid scintillation counting, with corrections for combustion efficiency and quench. Faeces were extracted with methanol, and the radiolabel in the extracts and in urine was determined by direct liquid scintillation counting. The concentrations in the insoluble faecal residue and in tissues were determined after combustion. Metabolites in urine and faeces were isolated and quantified by thin-layer chromatography; their identification was via co-chromatography with synthetic reference standards.

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

Annex Point IIA6.2

Key Study

5.2 RESULTS AND DISCUSSION

When a preparation of [1*RS*, *trans*]- or [1*RS*, *cis*]-permethrin (^{14}C-labelled in the alcohol or acid moiety) was administered orally to male rats at levels of 1.6-4.8 mg/kg, the compounds were rapidly metabolised and labels in the acid and alcohol fragments were almost completely eliminated from the body within a few days. The radiocarbon (alcohol or acid label) from the *cis* isomer was eliminated in the urine (52-54% of the dose) and the faeces (45-47%), whereas 79-82% of the radiocarbon from the *trans* isomer appeared in the urine and 16-18% in the faeces within 12 days after administration. The $^{14}CO_2$ contained in the expired air corresponded to less than 0.5% of the dose. The tissue residues were very low, although the *cis* isomer showed relatively higher residue levels (0.46-0.62 mg/kg tissue) in the fat.

The major metabolite from the acid moiety was Cl_2CA, which was mostly excreted in the urine, conjugated with glucuronic acid. This accounted for 50-63% of the dose from *trans*-permethrin and 15-22% from *cis*-permethrin. Oxidation at either of the geminal dimethyl groups occurred to the extent of 4.3-10.4% (*trans*) or 12.2-14.9% (*cis*), and these oxidised products were eliminated in the urine and faeces as such or as the lactone or glucuronide.

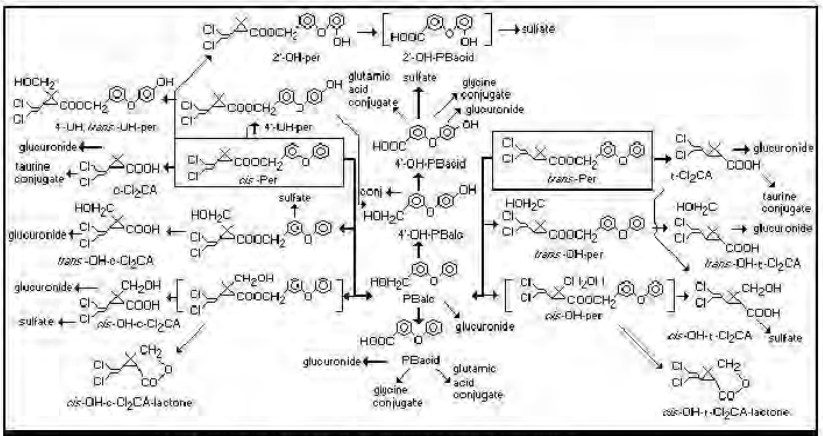
The major metabolite from the alcohol moiety was 3-(4'-hydroxyphenoxy)benzoic acid (4'-OH-PBacid) sulfate, accounting for 30.7-42.8% of the dose (*trans*) and 19.5-29.3% (*cis*). From *cis*-permethrin, 2'-OH-PBacid sulfate (about 3%) was identified. Another significant metabolite was PBacid, which occurred free and as glucuronide or glycine conjugates, and accounted for 25-31% (*trans*) and 5.7-10.1% (*cis*) of the dosed radiocarbon. Except for a trace of PBacid, all the above metabolites from the alcohol moiety were excreted entirely in the urine. However, the faeces of rats dosed with *trans*-permethrin contained 1-2% of the radioactive dose as PBalc. Thus substantial portions of the radioactive metabolites in the recovered excreta were identified.

The proposed metabolic pathways for *cis*- and *trans*-permethrin are shown overleaf.

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

Annex Point IIA6.2

Key Study



Metabolic pathways of permethrin in mammals.

The five principal sites of metabolic attack in both permethrin isomers were ester cleavage, oxidation at the *trans*- and *cis*-methyl of the geminal dimethyl group of the acid moiety, and oxidation at the 2'- and 4'-positions of the phenoxy group. Conjugation of the resultant carboxylic acids, alcohols, and phenols with glucuronic acid, glycine and sulfuric acid occurred to varying extent. *cis*-Permethrin was more stable than *trans*-permethrin, and the *cis* isomer yielded four faecally excreted ester metabolites that resulted from hydroxylation at the 2'- or 4'-position of the phenoxy group or at the *trans*- or *cis*-methyl group on the cyclopropane ring. The ester-cleaved metabolites were extensively excreted into the urine whereas the metabolites retaining an ester bond were found only in the faeces.The major metabolite from the acid moiety of both isomers was Cl_2CA in free (1-8%) and glucuronide (14-42%) forms. Other significant metabolites were *trans*-OH-Cl2CA (1-5%) and *cis*-OH-Cl_2CA in the free (3-5%), lactone (0-4%) and glucuronide (1-2%) forms. On the other hand, the alcohol moiety released after cleavage of the ester bond of both isomers was converted mainly to the sulfate of 3-(4'-hydroxyphenoxy)benzoic acid (4'-OH-PBacid) (29-43% of the dose) and PBacid in the free (1-10%) and glucuronide (7-15%) forms. Other significant metabolites of the alcohol moiety were PBalc, PBacid-glycine and the sulfate of 3-(2'-hydroxyphenoxy) benzoic acid (2'-OH-PBacid). [1RS, *trans*]- and [1RS, *cis*]-Permethrin showed no significant differences in metabolic fate in the rat from [1R, *trans*]- and [1R, *cis*]-Permethrin, respectively.

Section A6.2 **6.2(1) Metabolism (in vivo test – rat, oral)**

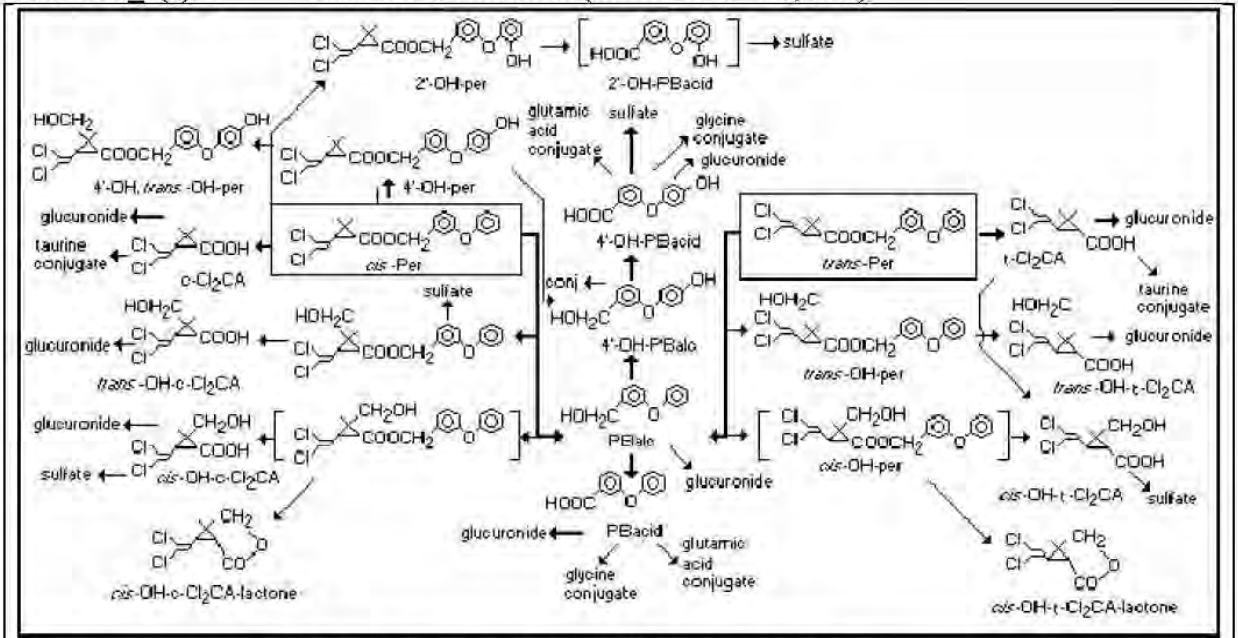
Annex Point IIA6.2

	Key Study	
5.3 Conclusion	When administered orally to male rats at 1.6 to 4.8 mg/kg, the [1R, *trans*], [1RS, *trans*], [1R, *cis*], and [1RS, *cis*] isomers of Permethrin are rapidly metabolised, and the acid and alcohol fragments are almost completely eliminated from the body within a few days. *cis*-Permethrin is more stable than *trans*-permethrin and the *cis* compound yields four faecal ester metabolites which result from hydroxylation at the 2′-phenoxy, 4′-phenoxy, or 2-*trans*-methyl position or at both of the latter two sites. Other significant metabolites are 3-phenoxybenzoic acid (free and glucoronide and glycine conjugates), the sulfate conjugate of 4′-hydroxy-3-phenoxybenzoic acid, the sulfate conjugate of 2′-hydroxy-3-phenoxybenzoic acid (from *cis*-permethrin only), the *trans*- and *cis*-dichlorovinyldimethylcyclopropane-carboxylic acids (free and glucoronide conjugates), and the 2-*trans*- and 2-*cis*-hydroxymethyl derivatives of each of the aforementioned *trans* and *cis* acids (free and glucoronide conjugates)	
5.1.1 Reliability	2	
5.1.2 Deficiencies	Yes. Less efficient metabolism cages were used in the earlier studies with compounds 1-4, 9, and 10, resulting in lower overall recoveries than with compounds 5-8. Nevertheless, recoveries for compounds 1-4, 9, and 10, were still relatively high and in the range > 76.1% to > 95.0% of administered radiocarbon. Dose levels did not extend into the range at which toxic effects would have been expected to occur, however, the dose levels used did allow an acceptable characterisation of uptake, depletion and metabolism of the test substances as required by test guideline EC B.36.	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	*16/11/05*
Materials and Methods	***2.3*** *This should, more correctly, read 'not applicable', as it has already been stated that no GLP has been adhered to.* ***3.3*** *Notifier should have inserted 'oral' here to indicate method of administration. Otherwise, adopt applicant's version.*
Results and discussion	***4.3*** *Slight discrepancies are noted in some of the % values given for metabolites. However, they are minor and do not affect the interpretation of the data overall.* *Otherwise, adopt applicant's version*
Conclusion	**5.3.2** *The correct % recoveries are between 76 and 99.0 for compounds 1 – 4 and 9 and 10; for compounds 5 – 8, the range of % recoveries is 79.0 and 99.5. Otherwise, adopt applicant's version.*

Reliability	*2*
Acceptability	*Acceptable*
Remarks	*Accepting the age of the study and bearing in mind that it was not done according to GLP (and therefore there are many deviations from a newer GLP compliant study), the data extracted is nonetheless reliable and can be used.*
	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_2(1)-1. Table for Metabolism (in vivo test – rat, oral)



Metabolic pathways of permethrin in mammals.

Section A6.2 6.2(2) Percutaneous absorption (in vivo test - human)

Annex Point IIA6.2

Key study

Official use only

		1 REFERENCE
1.1	Reference	Bartelt, N & Hubbell, J; 1987; Percutaneous Absorption of Topically Applied 14C-Permethrin in Volunteers. Final Medical Report. (Protocol 16-01).; Burroughs Wellcome Co., Research Triangle Park, North Carolina, USA; unpublished Report (Doc.) No. THRS/86/0047; 08.01.1987. Allsup TL, Otto VR & Hubbell, J. (1986) The Percutaneous Absorption of Topically Applied 14C-Permethrin in Normal Volunteers. (Clinical Protocol No P31-16-01). Report No. TBZZ/86/0044
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	^{14}C- Permethrin
3.1.1	Lot/Batch number	B.W. Co. Reference No. E. 35276; ICI Reference No. X263/5; Preparation No. L.C. 2/4.
3.1.2	Specification	Deviating from specification given in section 2 as follows
3.1.2.1	Description	Not reported
3.1.2.2	Purity	Radiochemical purity not reported; specific activity of ^{14}C *cis*-permethrin 38.3 mCi/mmole.
3.1.2.3	Stability	Not applicable (short-term administration)
3.1.2.4	Radiolabelling	^{14}C-labeled in the carbonyl moiety
3.2	Test Animals	
3.2.1	Species	Human

Section A6.2 **6.2(2) Percutaneous absorption (in vivo test - human)**
Annex Point IIA6.2

		Key study		
3.2.2	**Strain**	Caucasian		
3.2.3	**Source**	General population of Baltimore, Maryland, USA		
3.2.4	**Sex**	Male		
3.2.5	**Age/weight at study initiation**	Volunteer No.	Age	Weight (kg)
		1	22	67.3
		2	24	84.5
		3	21	69.4
		4	26	53.9
		5	51	62.5
		6	42	70.5
3.2.6	**Number of animals per group**	Pilot study - 2; main study - 4.		
3.2.7	**Control animals**	No		
3.3	**Administration/ Exposure**	**Dermal**		
3.3.1	**Preparation of test site**	Shaved skin two days prior to treatment. Immediately before application, the skin was washed with soap and water, rinsed and towel dried. A Teflon block which outlined the treatment area and acted as a reservoir for the dosing solution was placed at each treatment site.		
3.3.2	**Concentration of test substance**	637.5 µg/mL		
3.3.3	**Specific activity of test substance**	38.3 mCi/mmole		
3.3.4	**Volume applied**	0.8 mL of an isopropanol formulation containing 510 µg (6.25 µCi; 8.0 µg/cm^2) ^{14}C-Permethrin was applied slowly until a total dose of 2040 µg (25 µCi) was applied to the back of each volunteer.		
3.3.5	**Size of test site**	Four areas, approximately 8 cm x 8 cm, total 256 cm^2		
3.3.6	**Exposure period**	5 days (120 h)		

Section A6.2 **6.2(2) Percutaneous absorption (in vivo test - human)**
Annex Point IIA6.2

		Key study
3.3.7	**Sampling time**	Plasma: 0, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96 and 120 h post-treatment. **Urine: 0, 0-2, 2-4, 4-6, 6-8, 8-16 and 16-24 h post-treatment on Day 1; 0-8, 8-16 and 16-24 h on Days 2-5.** Faeces: through 120 h post-treatment. Skin: 24 h, 48 h, 72 h, 96 h, 120 h post-treatment. Non-occlusive dressings: 24 h, 48 h, 72 h, 96 h, 120 h post-treatment. Skin washes: 120 h post-treatment.
3.3.8	**Samples**	Plasma, urine, faeces, skin, non-occlusive dressings, skin washes.
		4 RESULTS AND DISCUSSION
4.1	**Toxic effects, clinical signs**	No effects reported.
4.2	**Dermal irritation**	No effects reported.
4.3	**Recovery of labelled compound**	46-76% (the total recovery of applied radiocarbon in the non-occlusive gauze dressings averaged about 53% in the first two volunteers (pilot study) and approximately 72% in volunteers 3-6 (main study)).
4.4	**Percutaneous absorption**	1.24 ± 0.73% (mean ± S.D.), range < 0.3-2.08%
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	^{14}C-Permethrin labelled in the carbonyl moiety was applied to four small washed, shaved areas on the back (total 256 cm^2) of each of six male volunteers (two in a pilot segment, four in a subsequent period) and covered with a non-occlusive dressing which was changed at a specified schedule. The sites remained unwashed for 5 days. A portion of the skin at each site was sequentially stripped with 20 pieces of tape at each dressing change. Plasma, urine and faecal samples and the stripping tapes were obtained at specified intervals and shipped frozen for analysis.

Section A6.2 **6.2(2) Percutaneous absorption (in vivo test - human)**
Annex Point IIA6.2

Key study

5.2	Results and discussion	Each volunteer received 2040 µg ^{14}C-permethrin applied to 256 cm^2 (8 µg/cm^2) and the total amount absorbed from these sites was < 0.3-2.08% of the dose applied. The plasma levels were extremely low (≤ 0.31 ng/mL) and of the samples in which activity was detectable, a peak was noted at 24 hours and declined rapidly thereafter. Primary excretion occurred in the urine with a maximum of 42.4 µg (≤ 2% applied dose) excreted in the urine and faeces combined. Faecal excretion accounted for < 4% of the total excreted radiocarbon. The total recovered radiocarbon represented 46-76% of the applied dose and the majority was recovered in the non-occlusive dressings. By 5 days post-treatment, little permethrin remained at the treatment site as indicated by very low level activity in skin strippings and washings.
5.3	Conclusion	Following application of 8 µg/cm^2 of radiolabelled permethrin to a 256 cm^2 site on the back of volunteers with normal skin, a mean of 1.24 ± 0.73% of the applied dose (range 0.30 to 2.08%) was absorbed and excreted almost entirely in urine after dosing. At 120 hr post-treatment, little (< 0.7%) permethrin remained in the skin for further absorption and the recovery of excreted radiocarbon in faeces was virtually complete. Pharmacokinetic analysis using a zero-order input and first-order output one-compartment model adequately described the curves for the rate of urinary excretion of radiocarbon versus time. Slow dermal absorption of permethrin (3.4 to 7.4 ng/hr/cm), independent of the topical dose applied was observed. Based on the urinary excretion rate data, it was concluded that the dermal absorption of permethrin and urinary excretion of permethrin metabolites was rate limited by penetration through the skin. The data from this study suggest that a portion of the topical dose accumulated in skin appendages such as hair follicles, apocrine glands, and sebaceous glands and was removed in the dressings.
5.3.1	Reliability	2
5.3.2	Deficiencies	Yes. Recovery of labelled compound was lower than would normally be considered ideal at 46-76%. However, the non-occlusive dressings covering the treatment sites were used to obtain information on the loss of radiocarbon from the skin and were not intended to allow quantitative recovery of all applied radiocarbon. The total recovery of applied radiocarbon in the non-occlusive gauze dressings averaged about 53% in the first two volunteers (pilot study) and approximately 72% in volunteers 3-6 (main study).

Section A6.2 **6.2(2) Percutaneous absorption (in vivo test - human)**
Annex Point IIA6.2

Key study

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	28th April 2009
Materials and Methods	Applicants version is acceptable.
Results and discussion	Adopt applicant's version
Conclusion	Other conclusions: Adopt applicant's version
Reliability	2
Acceptability	Acceptable
Remarks	This study is a clinical trial in humans rather than a animal study. This makes it difficult to evaluate using normal evaluation criteria. However, it appears to have been well conducted and bar the low recovery (72%), is acceptable. The applicants explanation for the low recovery appears plausible. In addition, the fact the the substance was applied in an isopropanol formulation may have contributed to the low recovery.
	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	

Section A6.2 6.2(2) Percutaneous absorption (in vivo test - human)

Annex Point IIA6.2

Key study

Table A6_2(2). Table for Percutaneous absorption (in vivo test - human)

Percent Recovery of Radiocarbon following Topical Dosing of Volunteers with ^{14}C-permethrin

Volunteer No.	Urine	Faeces	Nonocclusive Dressings	Final Skin Washing
1	0.40	< 0.02	59.6	0.012
2	0.29	< 0.01	46.1	0.0004
3	1.28	< 0.02	75.6	0.01
4	2.00	0.08	74.4	0.005
5	1.82	0.06	68.6	0.01
6	1.39	< 0.05	70.2	0.04

Section A6.3.1	A6.3.1 Repeated dose toxicity (oral)	
	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 data requirement is for a repeat dose oral toxicity test according to OECD Guideline 407 (rat, 28 days). A 28 day rat repeat dose test is not available for review. However, 90 and 180 day repeat dose toxicity (rat and dog) data are available which negate the requirement for a 28 day repeat dose test, since an accurate and realistic determination of sub-acute toxicity can be derived from available sub-chronic oral exposure studies. A variety of sub-acute repeat dose toxicity data on other species are available for review, and are summarised in IUCLID Section 5.4.	X
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*22/11/05*	
Evaluation of applicant's justification	*The applicant refers to the availability of 90 and 180 day repeat dose toxicity (rat and dog) data (IUCLID section 5.4?), which, in this case, is indeed justification for non-submission of the shorter 28d study.*	
Conclusion	*Accept applicant's justification.*	
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 A6.3.2	A6.3.2 Repeated dose toxicity (dermal)	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] Limited exposure [ ]	Technically not feasible [ ] Scientifically unjustified [X] Other justification [ ]	
Detailed justification:	This study is usually required when the dermal route of exposure is significant and the compound is known to be toxic by the dermal route and can penetrate through intact skin. This study with permethrin is not required on the following basis; • Although the dermal route of exposure is the most significant route of exposure in professional wood preservation use, there is evidence to indicate that significant amounts of permethrin can not pass through intact skin (1.24% dermal adsorption). • Acute dermal toxicity studies showed no toxic effects up to and including the highest dose tested (See Section 6.1.2). • It is also possible to calculate the route-to-route exposure from available oral toxicity studies and using dermal penetration studies (Section 6.2) as there are no specific effects observed following dermal exposure in animals. Therefore an accurate and realistic determination of dermal toxicity can be derived from available sub-chronic oral exposure studies and *in vitro* dermal penetration studies.	X
Undertaking of intended data submission [ ]		
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	*22/11/05*	
Evaluation of applicant's justification	*Where are the **in vitro** dermal penetration studies referred to here?*	
Conclusion	*Applicant's version accepted, taking into account the remarks made below.*	
Remarks	*Is there an **actual** requirement for a multiple dose study for Biocides (unlike PPPs)? A repeated dermal dose study cannot be located. There is a human volunteer study (single dose) submitted at 6.2, and the 1.24% dermal absorption value seems to emanate from here. However, no **in vitro** dermal penetration studies can be located. Will there be a problem using values derived from human studies for the purposes of establishing dermal absorption values?*	
	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 A6.3.3 **6.3.3 Repeated dose toxicity (Inhalation)**

Annex Point IIA6.3

Key Study

		Official use only
	1 REFERENCE	
1.1 Reference	[redacted]; 1980; Permethrin Technical Inhalation Study in Rats 15 x 6 Hour Exposures Over a 3 Week Period; [redacted]; GLP; unpublished Report No. WLC 34/80323; 11.11.1980.	
1.2 Data protection	Yes	
1.2.1 Data owner	Sumitomo Chemicals (UK) Ltd	
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	X
3.1.1 Lot/Batch number	Lot ZJ	
3.1.2 Specification	As given in section 2	X
3.1.2.1 Description	Brown viscous liquid	
3.1.2.2 Purity	94.7% (25.2% *cis*, 69.5% *trans*)	
3.1.2.3 Stability	Not reported	
3.2 Test Animals		
3.2.1 Species	Rat	
3.2.2 Strain	Charles River CD	
3.2.3 Source	[redacted]	
3.2.4 Sex	Male and female	
3.2.5 AGE/WEIGHT AT STUDY INITIATION	Group mean bodyweights varied from 122 – 125 g	
3.2.6 Number of animals per group	5 male, 5 female	
3.2.7 Control animals	Yes - control animals were not exposed to aerosol	
3.3 ADMINISTRATION/ EXPOSURE	Inhalation	
3.3.1 DURATION OF TREATMENT	15 × 6 hour exposure periods over a 21 day period	

Section A6.3.3 **6.3.3 Repeated dose toxicity (Inhalation)**

Annex Point IIA6.3

Key Study

3.3.2 FREQUENCY OF EXPOSURE	2 consecutive days week 1, no exposure on weekend 5 consecutive days week 2, no exposure on weekend 5 consecutive days week 3, no exposure on weekend 3 consecutive days week 4
3.3.3 POSTEXPOSURE PERIOD	None
3.3.4 Inhalation	
3.3.4.1 Concentrations	Nominal concentration [mg/m³] 5, 50, 500 Analytical concentration [mg/m³] 6.1, 42.2, 583
3.3.4.2 Particle size	The respirability of chamber aerosol was determined once during each exposure using a cascade multi-stage impactor. Mean results are given in Table 6.3.3_3.3.4.2.
3.3.4.3 TYPE OR PREPARATION OF PARTICLES	Permethrin technical was delivered via atomisers at a controlled rate using syringes mounted on slow infusion pumps.
3.3.4.4 Type of exposure	Whole body
3.3.4.5 Vehicle	None
3.3.4.6 Concentration in vehicle	Not applicable
3.3.4.7 Duration of exposure	6 h per day except the 14th exposure which was of 4 hours duration due to time taken in obtaining blood samples and to enable a degree of recovery before exposure
3.3.4.8 Controls	Exposed to clean dry air only
3.4 Examinations	
3.4.1 Observations	
3.4.1.1 Clinical signs	All signs associated with abnormal behaviour were recorded for individual animals. Each animal was examined at least twice a day. During exposure all animals were observed at least every 30 minutes. Response to external stimulus was also recorded.
3.4.1.2 Mortality	Each animal was examined at least twice a day.
3.4.2 Body weight	All animals were weighed individually commencing the day following arrival and weekly thereafter up to and including the day on which they were killed
3.4.3 Food consumption	The weight of food eaten by the animals in each cage (5 rats per cage) was measured weekly commencing the day following arrival and up to and including the day on which they were killed

Section A6.3.3	6.3.3 Repeated dose toxicity (Inhalation)	
Annex Point IIA6.3		
	Key Study	
3.4.4 WATER CONSUMPTION	Water was supplied ad libitum, but consumption was not recorded	
3.4.5 Ophthalmoscopic examination	Macroscopic and microscopic examination of the eyes was performed post mortem	X
3.4.6 Haematology	Yes number of animals: all animals time points: Blood samples were taken prior to the 14th exposure Parameters: Packed cell volume, Haemoglobin, Red cell count, Mean corpuscular haemoglobin, Mean corpuscular haemoglobin concentration, Total white cell count, Differential count (neutrophils, lymphocytes, eosinophils, basophils, monocytes), thrombotest, platelet count	
3.4.7 Clinical Chemistry	Yes number of animals: all animals time points: Blood samples were taken prior to the 14th exposure Parameters: sodium, potassium, chloride, calcium, inorganic phosphorus, glutamic-pyruvic transaminase, glucose, total cholesterol, urea, total protein, albumin, alkaline phosphatase	
3.4.8 Urinalysis	Yes number of animals: all animals time points: Urine samples were taken between the 13th and 14th exposures Parameters: volume, specific gravity, pH, protein, glucose, reducing substances, ketone, bile pigments, urobilinogen, haemoglobin, microscopy of spun deposit	
3.5 SACRIFICE AND PATHOLOGY		
3.5.1 ORGAN WEIGHTS	Yes organs: liver, kidneys, adrenals, testes, adrenals, lungs, pituitary, prostate, thyroid, uterus, ovaries, thymus, spleen, brain, heart	
3.5.2 Gross and histopathology	Yes high dose group and controls, other dose groups only if marked with * organs: brain, sciatic nerve, pituitary, thyroid, larynx*, thymus, oesophagus, nasal passages*, stomach, small and large intestines, liver*, pancreas, kidneys, adrenals, spleen, heart, trachea*, lungs*, gonads, uterus, prostate, urinary bladder, gall bladder (mouse), skeletal muscle tissue, skin, eyes	
3.5.3 OTHER EXAMINATIONS	None	

Section A6.3.3	6.3.3 Repeated dose toxicity (Inhalation)	
Annex Point IIA6.3		
	Key Study	
3.5.4 Statistics	For all parameters other than organ weights, ♂♀ animals analysed separately. One way analysis of variance was performed on each parameter and treated groups compared with control group using students t test based on residual variance For organ weights, analysis of variance was performed after adjustment for final bodyweight as covariate where appropriate and where the regression coefficient describing the linear relationship between organ weight and body weight were significantly different from zero at the 10% level. If heterogeneity of variance at 1% of significance existed, a logarithmic transformation was performed on the data to stabilise the variance. Group means were compared using the Williams test for contrasting increasing dose levels of compound with the control. Significance testing was carried out at the 5% and 1% levels.	
3.6 Further remarks	None	
	RESULTS AND DISCUSSION	
4.1 Observations		
4.1.1 Clinical signs	**Control**: Considered normal **Low dose**: Similar to control group, licking inside of mouth was considered normal for inhalation exposures. **Intermediate dose**: Appeared more alert than control and low dose, and adopted a hunched position. More extensive licking of the inside of the mouth. The fur was observed to be slightly oily, due to deposition of test material. **High dose**: Demonstrated less exploratory behaviour and grooming. More extensive licking of the inside of the mouth. Other clinical signs observed included; body tremors, hypersensitivity, laboured respiration, rales, poor grooming, crusty brown staining around the snout. The timing and occurrence of the hypersensitivity and body tremors appeared to indicate increased tolerance by the rats.	
4.1.2 Mortality	No mortalities at any dose	
4.2 Body weight gain	No effects	
4.3 Food consumption and compound intake	No effects	
4.4 OPHTALMOSCOPIC EXAMINATION	Macroscopic and microscopic examination of the eyes was performed post mortem and indicated no observed effects	X
4.5 Blood analysis		
4.5.1 Haematology	Results are given in Table 6.3.3_4.5.1 Several significant differences were observed, but in the absence of dose-related changes, these were considered to be not biologically significant.	

Section A6.3.3 **6.3.3 Repeated dose toxicity (Inhalation)**

Annex Point IIA6.3

Key Study

4.5.2 Clinical chemistry	Results are given in Table 6.3.3_4.5.2 Reduced plasma glucose levels were demonstrated in all exposure groups. The reduction was treatment related in the females, but less so in the males. The values obtained statistical significance in the intermediate and high doses. Several other significant differences were observed, but in the absence of dose-related changes, these were considered to be not biologically significant.
4.5.3 Urinalysis	Results are given in Table 6.3.3_4.5.3 Two values (protein levels in male high dose rats and SG in female high dose rats) were significantly different from the controls. In the absence of consistent differences between both sexes, these were considered to be not biologically significant.
4.6 SACRIFICE AND PATHOLOGY	
4.6.1 Organ weights	Results are given in Table 6.3.3_4.6.1 Statistically significant differences from the control (*) were observed in several instances, but only the increased liver weight was considered to be biologically significant.

Section A6.3.3 **6.3.3 Repeated dose toxicity (Inhalation)**

Annex Point IIA6.3

Key Study

4.6.2 GROSS AND HISTOPATHOLOGY	**Lungs**: the frequency and severity of areas of inflammatory changes, characterised by interstitial pneumonitis, perivascular and peribronchial lymphoid cuffing and occasional macrophage aggregation in the lungs of the majority of rats exposed to permethrin aerosol was considered to be more pronounced than the control animals. **Turbinates**: An increased incidence of rhinitis was seen in the nasal turbinates of treatment groups compared to the control group. No difference between the treatment groups was observed. No other biologically significant changes were observed. Incidental findings include; Lungs; a small area of epithelialisation (1♂ control) Trachea: small subepithilial inflammatory foci in the trachea of 14♂, 15♂, 31♀ intermediate dose. Turbinates: Free blood in turbinates of 8♂ low dose Cervical lymph nodes: A degree of sinus histiocytosis and lymphoid hyperplasia in rat 10♂ low dose Liver: Occasional parenchymal mononuclear cell foci, fat deposition and reduced glycogen content of hepatocytes were variously observed Urinary tract: Dystrophic mineralisation was seen in occasional tubules of rat 23♀ (control) and 38♀ (high dose) Prostate: Prostatis in 20♂ (high dose) Adrenals: Fine vacuolation of cortical cells in rat 18♂ (high dose) Brain: Focal gliosis in rats 5♂ (control) and 20♂ (high dose)
4.7 Other	None
	APPLICANT'S SUMMARY AND CONCLUSION
5.1 MATERIALS AND METHODS	No guidelines were followed. Rats were exposed to an aerosol generated from permethrin technical for 15 6-hour periods over a 21 day period. No vehicle was used. Rats were housed in plastic cages with mesh tops and floors, until the exposure period, when they were placed in inhalation chambers for 6 hours.

Section A6.3.3 **6.3.3 Repeated dose toxicity (Inhalation)**

Annex Point IIA6.3

Key Study

5.2 RESULTS AND DISCUSSION

No deaths occurred during the study.

Clinical signs:

Marked clinical signs considered to be related to exposure to an aerosol of permethrin technical were limited to the high dose (583 mg/m3).

Whole body tremors reached a maximum incidence of 9/10 rats during the fifth exposure. Tremors persisted for up to 24 hours following exposure.

Evidence of tolerance to exposure to permethrin technical aerosol was manifest as a reduced incidence and severity of tremors during exposures subsequent to the 5th exposure.

Hypersensitivity to noise or touch was first observed following the second exposure (10/10 rats) and persisted intermittently in some animals until 24 hours after the 7th exposure.

Female rats were more severely affected than males.

Bodyweight gain: Nothing abnormal detected.

Food consumption: Nothing abnormal detected.

Haematology: Nothing abnormal detected.

Blood chemistry: Reduced plasma glucose concentrations were detected in all permethrin technical exposed groups. Statistically significant separation from the control group occurred in intermediate dose (42.2 mg/m3) females and in the high dose (583 mg/m3).

An increase which was not statistically significant, but was treatment related was observed in the serum cholesterol concentrations of high dose (583 mg/m3) male rats.

Urinalysis: Nothing abnormal detected.

Macroscopic pathology: No treatment-related abnormalities were detected.

Organ weight analysis: Significantly increased group mean liver weights in the high dose (583 mg/m3) group.

Microscopic pathology:

The frequency and severity of inflammatory changes in the lungs of the majority of the rats exposed to permethrin technical aerosol was considered to be more pronounced than in control animals.

Increased incidence of rhinitis was observed in the nasal turbinates of rats exposed to permethrin technical aerosol compared to control animals. No differences between the various treatment groups could be detected.

5.3 Conclusion

5.3.1 LO(A)EL 42.2 mg m^{-3}

5.3.2 NO(A)EL 6.1 mg m^{-3}

5.3.3 Other

5.3.4 Reliability 2

5.3.5 Deficiencies No