Reference List by Annex Point

Section No. / Reference No.	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes / No)	Owner
A5.3.1/01	Behrenz, W.; Elbert, A.; Fuchs, R.	1983	Cyfluthrin (FCR 1272), a new pyrethroid with long-lasting activity for the control of public health and stored-product pests Journal: Bayer Pflanzenschutz-Nachrichten, Volume: 36, Pages: 127-176, Year: 1983 Report No.: M-075183-01-2 1983 Non GLP. Published	N	Public domain
A5.3.1/02	Michaelides, P. M.; Adams, A.; Welsh, J. L.; Bowron, M. J. ; Lucas, J. R.; Slatter, R. S.	1993	Comparative activity of beta-Cyfluthrin (Bulldock) Roussel Uclaf Environmental Health Ltd.; France Bayer CropScience AG Report No.: M-261596-01-1 30 June 1993 Non GLP. Unpublished	Y	Bayer Crop-Science AG
A5.3.1/03	Anon.	1982	Deltamethrin monograph - Applications of deltamethrin Bayer CropScience AG, Report No.: M-255452-01-2 18 October 1982 Non GLP. Unpublished	Y	Bayer Crop-Science AG
A5.7/01	Anon.	1987	Insecticide/acaricide resistance: survey and recommendations by industry FRAC/IRAC Newsletter Report No.: M-001507-01-1 December 1987 GLP n/a. Published	N	Public domain
A5.7/02	Anon.	1992	Vector Resistance to Pesticides Fifteenth Report of the WHO Expert Committee on Vector Biology and Control, TRS 818, 1992 Report No.: M-267730-01-1 1992 Non GLP. Published	N	Public domain
A5.7/03	Anon.	2000	Guidelines for preventing and managing insecticide resistance in the peach-potato aphid, *Myzus persicae* Insecticide Resistance Action Group Report No.: M-041872-01-1 February 2000 GLP n/a. Published	N	Public domain

Section No. / Reference No.	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes / No)	Owner
A5.7/04	Staetz	2004	Insecticide Mode of Action Classification: A Key to Insecticide Resistance Management (v.3.3.2) Insecticide Resistance Action Committee (IRAC International) Report No.: M-267712-01-1 2004 GLP n/a. Published	N	Public domain
A5.7/05	Brogdon and McAllister	1998	Insecticide Resistance and Vector Control Emerging Infectious Diseases; Vol. 4 No. 4, http://www.cdc.gov/ncidod/EID/vol4no4/brogdon.htm Report No.: M-267737-01-1 December 1998 GLP n/a. Published	N	Public domain

Reference List by Author

Author(s)	Section No. / Reference No.	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes / No)	Owner
Anon.	A5.3.1/03	1982	Deltamethrin monograph - Applications of deltamethrin Bayer CropScience AG, Report No.: M-255452-01-2 18 October 1982 Non GLP. Unpublished	Y	Bayer Crop-Science AG
Anon.	A5.7/01	1987	Insecticide/acaricide resistance: survey and recommendations by industry FRAC/IRAC Newsletter Report No.: M-001507-01-1 December 1987 GLP n/a. Published	N	Public domain
Anon.	A5.7/02	1992	Vector Resistance to Pesticides Fifteenth Report of the WHO Expert Committee on Vector Biology and Control, TRS 818, 1992 Report No.: M-267730-01-1 1992 Non GLP. Published	N	Public domain
Anon.	A5.7/03	2000	Guidelines for preventing and managing insecticide resistance in the peach-potato aphid, *Myzus persicae* Insecticide Resistance Action Group Report No.: M-041872-01-1 February 2000 GLP n/a. Published	N	Public domain
Behrenz, W.; Elbert, A.; Fuchs, R.	A5.3.1/01	1983	Cyfluthrin (FCR 1272), a new pyrethroid with long-lasting activity for the control of public health and stored-product pests Journal: Bayer Pflanzenschutz-Nachrichten, Volume: 36, Pages: 127-176, Year: 1983 Report No.: M-075183-01-2 1983 Non GLP. Published	N	Public domain
Brogdon and McAllister	A5.7/05	1998	Insecticide Resistance and Vector Control Emerging Infectious Diseases; Vol. 4 No. 4, http://www.cdc.gov/ncidod/EID/vol4no4/brogdon.htm Report No.: M-267737-01-1 December 1998 GLP n/a. Published	N	Public domain

Author(s)	Section No. / Reference No.	Year	Title Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes / No)	Owner
Michaelides, P. M.; Adams, A.; Welsh, J. L.; Bowron, M. J. ; Lucas, J. R.; Slatter, R. S.	A5.3.1/02	1993	Comparative activity of beta-Cyfluthrin (Bulldock) Roussel Uclaf Environmental Health Ltd.; France Bayer CropScience AG Report No.: M-261596-01-1 30 June 1993 Non GLP. Unpublished	Y	Bayer Crop-Science AG
Staetz	A5.7/04	2004	Insecticide Mode of Action Classification: A Key to Insecticide Resistance Management (v.3.3.2) Insecticide Resistance Action Committee (IRAC International) Report No.: M-267712-01-1 2004 GLP n/a. Published	N	Public domain

Competent Authority Report

According to Directive 98/8/EC

Deltamethrin

CAS 52918-63-5

Active substance in Biocidal Products, Product Type 18 (Insecticide)

Notifier: Bayer S.A.S. Bayer Environmental Science

DOCUMENT III-A

Section 6: Toxicological and Metabolism Studies

Rapporteur Member State: Sweden

Final CAR June 2011

KEMI
Kemikalieinspektionen
Swedish Chemicals Agency

Table of Contents; Doc III-A Section 6

Section A6 – Toxicological and Metabolic Studies

6.1 Acute toxicity

6.1.1 Acute oral

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1996) Acute Oral Toxicity Study of Deltamethrin in Albino Rats [redacted] Document A55812 6.1.1/01 6 August 1996 Unpublished See Monograph 91/414 from 1998 – Point B.5.2.1	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	Study follows OECD guideline 401	
2.2	**GLP**	Yes	
2.3	**Deviations**	Animals not fasted prior to test.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	4N0397B	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	98%	
3.1.2.3	Stability	Stable in its original container at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley Crl:CD® BR rat	
3.2.3	Source	Charles River Breeding Laboratories, USA	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	Age: 6 – 7 weeks Weight: Males: 187 – 254 g Females:144 – 213 g	X1

3.2.6	Number of animals per group	Five of each sex	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Postexposure period	14 days	
3.3.2	Type	Gavage	
3.3.3	Concentration	0, 50, 75, 100, 150 mg/kg	X2
3.3.4	Vehicle	Corn oil	
3.3.5	Concentration in vehicle	0, 10, 15, 20, 30 g/l	X2
3.3.6	Total volume applied	5 ml/kg	
3.3.7	Controls	No control	
3.4	**Examinations**	Clinical observations, mortality, body weights and macroscopic examination at necropsy.	
3.5	**Method of determination of LD_{50}**	Litchfield and Wilcoxon	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	All males (5/5) and females (5/5) in the 100 mg/kg group and 4/5 males and 5/5 females in the 150 mg/kg group were found dead within 24 hours of test article administration. The majority of these deaths occurred approximately 2 – 3 hours following dosing. Clinical findings noted for these animals prior to death included reduced or absent forelimb/hind limb grasp, impaired or absent righting reflex, writhing (lying down, wavelike movements of the abdomen, alternating limb movements), repetitive convulsions, repetitive jaw movement, gait alterations (animal rocked, lurched or swayed as it walked), vocalization, lacrimation, chromodacryorrhea, salivation and/or clear, yellow or red staining/matting on various body surfaces. One female in the 100 mg/kg group also appeared flattened with limbs extended and was observed with shallow respiration, hypothermia (body cool to touch), an absent pupillary response (bilateral), bilateral ocular opacity and hypoactivity. Single occurrences of popcorn seizures (animal repeatedly jumped or bounced in the air), walking with splayed forelimbs and gasping were noted for one female in the 100 mg/kg group, one male in the 100 mg/kg group and one female in the 150 mg/kg group, respectively. All other animals survived to the scheduled necropsy (day 14).	

		The predominant clinical signs noted in the 50 and 75 mg/kg groups and the surviving 150 mg/kg group male on day 0 were gait alterations, impaired righting reflex, reduced or absent forelimb/hind limb grasp, repetitive convulsions, writhing and walking with splayed hind limbs. Other clinical findings observed at lower frequencies in these groups included repetitive jaw movement, vocalization, animal appeared flattened with limbs extended, salivation, lacrimation and chromodacryorrhea. One female in the 50 mg/kg group was observed with hypothermia, pale extremities and gasping. Hindlimbs which were cool to touch and purple, hypersensitivity to touch and an absent pupillary response were noted for one male in the 75 mg/kg group. In general, these signs were initially observed at two hours following test article administration and did not persist beyond eight hours post-dosing. The only behavioural alterations persisting to day 1 (approximately 24 hours post-dosing) were reduced forelimb and hind limb grasp for the same male in the 75 mg/kg group. Other treatment-related clinical signs observed at the post-dosing (day 0) time points for the surviving animals consisted of red, clear and/or yellow matting/material on various body surfaces. In general, these signs were initially observed approximately one hour following administration of the test article and did not persist beyond day 2. Other findings noted in the 50, 75, 100 and/or 150 mg/kg groups, such as decreased defecation, decreased urination, soft stool, orange urine and dark eyes, occurred sporadically and could not be directly attributed to test article administration.	
4.2	**Pathology**	See Table A6.1.1-1 for mortality data. One female in the 150 mg/kg group had an ocular opacity. Red and/or yellow matting on various external surfaces was noted for 3/2 and 4/5 males/females in the 100 and 150 mg/kg groups, respectively. One male in the 150 mg/kg group had scabbing on the dorsal head. No other gross external or internal lesions were noted for males and females that died during the study. At the scheduled necropsy, scabbing on the neck was observed for two females in the 50 mg/kg group. No other gross external or internal lesions were noted.	
4.3	**Other**	-	
4.4	**LD_{50}**	92 mg/kg bw (combined)	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Deltamethrin (purity 98%) was dissolved in corn oil and administered orally by gavage as a single dose to nonfasted rats at levels of 50, 75, 100 and 150 mg/kg bw. Each group consisted of five male and five female rats (Sprague-Dawley Crl: CD BR).	

5.2	**Results and discussion**	The LD_{50} was estimated at 95 mg/kg bw for nonfasted male rats, and 87 mg/kg bw for nonfasted female rats (95% confidence limits were 74 – 122 mg/kg bw and 77 – 97 mg/kg bw for males and females, respectively). Mortality in the 50, 75, 100 and 150 mg/kg bw groups was 0/5, 0/5, 5/5 and 4/5, respectively for the males, and 0/5, 0/5, 5/5 and 5/5, respectively, for the females. All deaths occurred by day 1. The clinical observations in the 50 and 75 mg/kg bw groups and the surviving 150 mg/kg bw group male on day 0 included gait alterations, impaired righting reflex, reduced or absent forelimb/hind limb grasp, repetitive convulsions, writhing and walking with splayed hindlimbs, repetitive jaw movement, vocalization, animal appeared flattened with limbs extended, salivation, lacrimation and chromodacryorrhea. The only behavioural alteration persisting to day 1 were reduced forelimb and hind limb grasp for one male in the 75 mg/kg bw group. Other treatment-related clinical signs observed at the post-dosing time points for the surviving animals consisted of red, clear and/or yellow matting/material on various body surfaces. In general these signs did not persist beyond day 2. Scabbing on the neck was observed for two females in the 50 mg/kg bw group. No other gross external or internal lesions were noted. The acute oral LD_{50} values were as follows: Males: 95 mg/kg bw Females: 87 mg/kg bw Combined: 92 mg/kg bw	
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table A6.1.1-1 Table for Acute Toxicity/Mortality

Dose [mg/kg bw]	Number of dead/number investigated		Time of death (range)
	M	F	
50	0/5	0/5	
75	0/5	0/5	
100	4/5	5/5	Before end of Day 1
100	1/5	-	Day 1
150	4/5	4/5	Before end of Day 1
150	-	1/5	Day 1
LD_{50} value	Males: 95 mg/kg bw; Females: 87 mg/kg bw; Combined: 92 mg/kg bw		

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted with the following corrections: X1: The weight of males was 187-234 g (not 187-254 g). X2: No controls were used in the study.
Results and discussion	The applicant's version is adopted.
Conclusion	The applicant's version is adopted. In this study it can be stated that the acute oral toxicity of deltamethrin is high when corn oil is used as vehicle. The acute oral LD_{50} of deltamethrin was found to be 95 mg/kg bw for nonfasted male rats and 87 mg/kg bw for nonfasted female rats (95% confidence limits were 74-122 mg/kg bw and 77-97 mg/kg bw for males and females, respectively). Based on this data a classification of deltamethrin in the category of danger Toxic is proposed and the risk phrase R25 ("Toxic if swallowed") is assigned. (Classification and hazard statements assigned under the new EU C&L Regulation: [Acute Tox. 3] [H301]).
Reliability	1
Acceptability	Acceptable. The deviation from OECD guideline 401 is considered not to compromise the scientific validity of the study.
Remarks	Results of acute oral toxicity studies with deltamethrin reported in the draft assessment report of deltamethrin (evaluation of deltamethrin during the procedure of inclusion into Annex I under Directive 91/414/EEC) have shown that the vehicle has a great influence on the LD_{50}. Aqueous suspensions are significantly less toxic than formulations in oils. The effect of two solubilisers, polyethylene glycol (PEG 200) or sesame oil has also been investigated herein (see point A6.11, Document A95064).

6.1.2 Acute dermal

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (2005) Acute Toxicity in the Rat after Dermal Application [redacted] Document M-258954-01-1 6.1.2/01 6 October 2005 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	OECD 402	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	EDDLTO038	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Light yellow powder	
3.1.2.2	Purity	99.9%	
3.1.2.3	Stability	Stable as stored at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Wistar Crl: (Wi)WU BR	
3.2.3	Source	Charles River, Sulzfeld, Germany	
3.2.4	Sex	Males and Females	
3.2.5	Age/weight at study initiation	Age: 9-13 weeks Body weight Males: 231 – 262 g Females: 197 – 209 g	
3.2.6	Number of animals per group	Five of each sex	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Dermal	
3.3.1	Postexposure period	14 days	

3.3.2	Area covered	24.75 cm^2 (10% of the body surface area)	
3.3.3	Occlusion	Semi-occlusive	
3.3.4	Vehicle	No. The test substance was applied pure.	
3.3.5	Concentration in vehicle	Not applicable	
3.3.6	Dose range	Male: 18.7 – 21.2 mg/cm^2 for a dose of 2000 mg/kg Female: 15.9 – 16.9 mg/cm^2 for a dose of 2000 mg/kg	
3.3.7	Duration of exposure	24h	
3.3.8	Removal of test substance	The treated area was rinsed with tepid water using soap and gently patting the area dry.	
3.3.9	Controls	No	
3.4	**Examinations**	Clinical signs and mortality, body weights, macroscopic examination at necropsy.	
3.5	**Method of determination of LD_{50}**	Finney, Sachs	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	No clinical signs were observed.	
4.2	**Pathology**	The necropsies performed at the end of the study revealed no particular findings.	
4.3	**Other**	There were no toxicological effects on body weight or body weight development in males and females.	
4.4	**LD_{50}**	> 2000 mg/kg bw	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The acute dermal toxicity of the test substance deltamethrin (purity 99.9%) was evaluated in Wistar rats. The test substance was administered by dermal route to a group of ten Wistar rats (five males and five females). The test substance was topically applied pure at the dose of 2000 mg/kg bw. The test site was then covered by a semi-occlusive dressing for 24 hours. The animals were checked for clinical signs, mortality and body weight gain for a period of 14 days following the single application of the test substance. A necropsy was performed on each animal.	
5.2	**Results and discussion**	No clinical signs were observed. There were no toxicological effects on body weight or body weight development in males and females. The necropsies performed at the end of the study revealed no particular findings Under the experimental conditions, the dermal LD_{50} of the test substance deltamethrin is higher than 2000 mg/kg bw in rats.	
5.3	**Conclusion**		
5.3.1	Reliability	1	

5.3.2	Deficiencies	No	

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted.
Results and discussion	The applicant's version is adopted.
Conclusion	The applicant's version is adopted. In this study it can be stated that the acute dermal toxicity of deltamethrin is low. The acute dermal LD_{50} of deltamethrin was found to be >2000 mg/kg bw in both male and female rats. Based on this data deltamethrin does not require EU classification with regard to acute dermal toxicity.
Reliability	1
Acceptability	Acceptable.
Remarks	

6.1.3 Acute Inhalation

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1978) RU 22974: Acute Inhalation Toxicity in Rats 6 Hour LC_{50} [redacted] Document A28960 6.1.3/01 15 May 1978 Unpublished See Addendum to the Monograph from 2002 – Point B.5.2.1	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	Study follows OECD guideline 403	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement, but was conducted in line with good scientific practice.	
2.3	**Deviations**	LC_{50} was based on combined values; purity of test substance not given.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	6E0861	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	Not specified	XI
3.1.2.3	Stability	Stable as stored at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague Dawley	
3.2.3	Source	Charles River, UK	
3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	Age: 7 – 8 weeks Weight: 172 – 240 g	
3.2.6	Number of animals per group	Seven of each sex	
3.2.7	Control animals	Seven of each sex	

3.3	**Administration/ Exposure**	Inhalation (single 6 hour whole body exposure period)	
3.3.1	Postexposure period	14 days	
3.3.2	Vehicle	None	
3.3.3	Concentration in vehicle	0, 0.049, 0.430, 0.540 and 0.720 g/m^3 of air	
3.3.4	Total volume applied	Not applicable	
3.3.5	Controls	Exposure to clean air only	
3.4	**Examinations**	Clinical observations, mortality, body weight, food consumption, temperature and humidity, necropsy, histopathology,	
3.5	**Method of determination of LD_{50}**	Miller and Tainter	X2
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Clinical signs which included skin and eye irritation, agitated grooming, ptyalism and diaphragmatic breathing, were noted in all groups exposed to deltamethrin. At the higher concentration of dust ataxia was observed. Stained fur, ataxia and hypersensitivity were noted during the 14 day observation period. The incidence and severity increased with increasing concentration of deltamethrin, but all reactions to exposure had disappeared by the end of the 14d observation period.. Five rats in Group 4 (0.54 g/m^3) and 12 rats in Group 5 (0.72 g/m^3) died as a result of exposure. There were no deaths in any other group. The behaviour of control rats was normal during exposure and over the 14 day post-exposure observation period.	
4.2	**Pathology**	***Lung to bodyweight ratios:*** Normal for rats in Groups 1 (Control) and 2 (0.049 g/m^3) killed immediately after exposure (0.44 – 0.50). Elevated in all rats in Groups 4 (0.54 g/m^3) and 5 (0.72 g/m^3) that died as a result of exposure (0.66 and 0.69 respectively). The rise was considered due to the presence of haemorrhage and oedema in the lungs of these rats. Normal for surviving rats in all groups killed at the end of the 14 day post-exposure observation period. ***Macroscopic pathology:*** Changes noted in those rats that died (from Groups 4 (0.54 g/m^3) and 5 (0.72 g/m^3)), considered a result of exposure to the dust of deltamethrin, included: gas filled stomachs; massive haemorrhage and oedema of the lungs; the test substance present as a white deposit in the larynx and trachea; mucus and blood within the lumen of the trachea.	

		No other treatment-related changes were seen in any other rats, killed either immediately after exposure or at the end of the 14 day observation period.	
4.3	**Other**	-	
4.4	**LC_{50}**	0.6 g/m³ of air	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The purpose of this study was to investigate the acute inhalation toxicity of the airborne dust of deltamethrin and to assess the LC_{50}. Groups of rats consisted of seven males and seven females. Three groups of rats were exposed continuously for 6 hours, each to a different concentration of the airborne dust generated from the powder sample of deltamethrin (0.43, 0.54 and 0.72 g/m³ of air). A fourth group of rats was exposed at a mean level of 0.049 g/m³ in order to investigate the effect of exposure at a low level, and to assess if possible the concentration at which no effects either irritant or toxic, are seen. A fifth group received clean air only for 6 hours and acted as a control. The percentage of particles below 5.5 µm in diameter (considered respirable) for each group: 0.049, 0.43, 0.54 and 0.72 g/m³ of air was 86.2%, 78.9%, 65.5-72.5% and 84 % respectively.	
5.2	**Results and discussion**	Clinical signs which included skin and eye irritation, agitated grooming, ptyalism and diaphragmatic breathing, were noted in all groups exposed to deltamethrin. At the higher concentration of dust ataxia was observed. Stained fur, ataxia and hypersensitivity were noted during the 14 day observation period. The incidence and severity increased with increasing concentration of deltamethrin, but all reactions to exposure had disappeared by the end of the 14d observation period. Five rats in Group 4 (0.54 g/m³) and 12 rats in Group 5 (0.72 g/m³) died as a result of exposure. There were no deaths in any other group. The behaviour of control rats was normal during exposure and over the 14 day post-exposure observation period. Low bodyweights were recorded after exposure for animals in Groups 3 (0.43 g/m³), 4 (0.54 g/m³) and 5 (0.72 g/m³). Bodyweight gain was normal in these Groups by day 4 or 5 of the 14 day observation period. Slight decreases in bodyweight were recorded in Group 2 (0.049 g/m³) the day after exposure. Thereafter bodyweight gain was normal. Food consumption was similar to the effect on bodyweight; a slight drop in food consumption by animals in Group 2 (0.049 g/m³) the day after exposure, thereafter normal, and a more significant drop in food consumption by animals in Groups 3 (0.43 g/m³), 4 (0.54 g/m³) and 5 (0.72 g/m³) for up to 6 days after exposure. This effect was treatment-related. ***Lung to bodyweight ratios:*** Normal for rats in Groups 1 (Control) and 2 (0.049 g/m³) killed immediately after exposure (0.44 – 0.50).	

		Elevated in all rats in Groups 4 (0.54 g/m³) and 5 (0.72 g/m³) that died as a result of exposure (0.66 and 0.69 respectively). The rise was considered due to the presence of haemorrhage and oedema in the lungs of these rats. Normal for all surviving rats in all groups killed at the end of the 14 day post-exposure observation period.	
		Macroscopic pathology: Changes noted in those rats that died (from Groups 4 (0.54 g/m³) and 5 (0.72 g/m³)), considered a result of exposure to the dust of deltamethrin, included: gas filled stomachs; massive haemorrhage and oedema of the lungs; the test substance present as a white deposit in the larynx and trachea; mucus and blood within the lumen of the trachea. No other treatment-related changes were seen in any other rats, killed either immediately after exposure or at the end of the 14 day observation period. LC_{50} (6 hour) for male and female rats combined was estimated at 0.6 g/m³ of air.	
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table A6.1.3-1 Table for Acute Inhalation Toxicity

Group/Dose (g/m³)	Number of dead/ number of investigated	Time of death (male/female)
1 (Control)	0/14	-
2 (0.049)	0/14	-
3 (0.43)	0/14	-
4 (0.54)	5/14	End of exposure (1m) 50 minutes after exposure (1f) 1 hour 20 minutes after exposure (1m) 1 hour 50 minutes after exposure (1m) Overnight after exposure (1f)
5 (0.72)	12/14	5 hours 55 minutes into exposure (1m) End of exposure (3f) Died within 2 hours 42 minutes following the end of exposure (4m, 3f) Overnight after exposure (1m)
LD50 value		0.6 g/m³ of air

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted with following comment: X1: The purity of the test substance was not specified in this study. However, according to Annex Confidential Data and Information it is stated by the applicant that the purity of batch no. 6E0861 is sufficient (i.e. 98%). The applicant's version is adopted with following corrections: X2: Method of determination of LC_{50} (not Method of determination of LD_{50}). Table A6.1.3-1: The same correction as above (LC_{50} instead of LD_{50}).
Results and discussion	The applicant's version is adopted.
Conclusion	The applicant's version is adopted. In this study it can be stated that the acute inhalation toxicity of deltamethrin is high. The acute inhalation LC_{50} (6 hrs, dust) for male and female rats combined was estimated at 0.6 g/m^3 of air (95% confidence limits were not specified). Based on this data a classification of deltamethrin in the category of danger Toxic is proposed and the risk phrase R23 ("Toxic by inhalation") is assigned. (Classification and hazard statements assigned under the new EU C&L Regulation: [Acute Tox. 3] [H331]).
Reliability	2
Acceptability	Acceptable. The deviations from OECD guideline 403 are considered not to compromise the scientific validity of the study.
Remarks	

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1990) Acute Inhalation Toxicity Evaluation of Deltamethrin in Rats [redacted] Document A70770 6.1.3/02 9 June 1990 Unpublished See Monograph 91/414 from 1998 – Point B.5.2.1	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	Study follows OECD guideline 403	
2.2	**GLP**	Yes	
2.3	**Deviations**	LD_{50} was based on combined values; purity of test substance not given.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	8N0701B2	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Not given	
3.1.2.2	Purity	By analogy with the batch number used in study A70869 (see Point 6.8.1), purity should be 99.4 %	
3.1.2.3	Stability	Not specified but deltamethrin is not known to decompose at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague Dawley CD	
3.2.3	Source	Charles River Laboratories, USA	
3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	Age: 50 – 56 days Body weight: Males: 220-282 g Females: 160-189 g	
3.2.6	Number of animals per group	Five of each sex	
3.2.7	Control animals	No	

3.3	**Administration/ Exposure**	Inhalation (single 4 hour whole body exposure period)	
3.3.1	Postexposure period	14 days	
3.3.2	Vehicle	None	
3.3.3	Concentration in vehicle	Not applicable	
3.3.4	Total volume applied	Nominal rates of 4.6, 9.3 and 9.8 mg/l Actual rates of 1.0, 1.8 and 2.3 mg/l	
3.3.5	Controls	None	
3.4	**Examinations**	Clinical observations, body weight and macroscopic examination at necropsy	
3.5	**Method of determination of LD_{50}**	Bliss	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	A number of pharmacotoxic signs were noted during the 14-day post-exposure observation period. However, the most significant were death and impaired hind limb function. All animals surviving the first 24 hours after exposure, except one male in group II, exhibited impaired hind limb function at some time during the post- exposure period. Generally the sign was first noted on the second or third day post-exposure and remained for about seven days. Deaths were observed over the whole study, from the day of exposure through 14 days post-exposure. Table A6.1.3-1 summarises the mortality data.	
4.2	**Pathology**	The following abnormalities were observed: enlarged inguinal and mandibular lymph nodes, pulmonary congestion, skin discoloration, and some minor abrasions. Pulmonary congestion was the most significant abnormality observed at necropsy with the following incidence: none in group III, three animals in group II and two animals in group I. All other abnormalities were considered incidental.	
4.3	**Other**	-	
4.4	**LC_{50}**	2.2 mg/l (combined)	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Groups of five male and five female Sprague Dawley derived albino rats (Charles River CD), were exposed (whole body) for a single four hour period to dust paniculate aerosol atmospheres of deltamethrin (purity not specified) at concentrations of 1.0, 1.8 and 2.3 mg/1. An aerosol of the test material was characterized by a mass median aerodynamic diameter (MMAD) of 3.7 microns with a geometric standard deviation of 1.87.	

5.2	**Results and discussion**	The LC_{50} for male and female rats combined was estimated at 2.2 mg/l (95% confidence limits: 1.5-3.3 mg/l). The most significant clinical findings were impaired hind limb function, laboured breathing, increased salivation and hunched posture. Animals in all groups lost body weight during the first post-exposure week. Enlarged inguinal and mandibular lymph nodes and pulmonary congestion were observed.	
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table A6.1.3-2 Mortality Data

Group Number	Concentration (mg/l)	Number of Deaths/ Number on Study
I	2.3	5/10
II	1.8	4/10
III	1.0	1/10

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted.
Results and discussion	The applicant's version is adopted.
Conclusion	The applicant's version is adopted. In this study the acute inhalation LC_{50} (4 hrs, dust) for male and female rats combined was estimated at 2.2 mg/l of air (95% confidence limits: 1.5-3.3 mg/l).
Reliability	1
Acceptability	Acceptable. The deviations from OECD guideline 403 are considered not to compromise the scientific validity of the study.
Remarks	

6.1.4 Acute skin and eye irritation

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (2005a) Deltamethrin technical – Acute Skin Irritation/Corrosion on Rabbits [redacted] Document M-260123-01-1 6.1.4/01 27 October 2005 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	OECD 404	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	EDDLTO038	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	99.9%	
3.1.2.3	Stability	Stable as stored at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	Esd:NZW	
3.2.3	Source	Charles River Laboratories, France	
3.2.4	Sex	Females	
3.2.5	Age/weight at study initiation	Age: young adult Weight: 2100 – 2500 g	
3.2.6	Number of animals per group	Three	
3.2.7	Control animals	No, but the contra lateral skin area not treated with the test substance served as control	
3.3	**Administration/ Exposure**	Dermal	
3.3.1	Postexposure period	72 hours	

3.3.1.1	Preparation of test substance	0.5 g of pulverized test substance was moistened with Aqua p.i. (to ensure good contact with the skin)	
3.3.1.2	Test site and preparation of test site	On the day before the test, the fur was shorn on the right and felt side from the dorso-lateral area of the trunk of each of the rabbits	
3.3.2	Occlusion	Semi-occlusive	
3.3.3	Vehicle	None	
3.3.4	Concentration in vehicle	Not applicable (moistened only)	
3.3.5	Total volume applied	0.5 g	
3.3.6	Removal of test substance	The exposed skin area was carefully washed with water without altering the existing response, or the integrity of the epidermis.	
3.3.7	Duration of exposure	4 hours	
3.3.8	Postexposure period	72 hours	
3.3.9	Controls	The contra lateral skin area not treated with the test substance served as control	
3.4	**Examinations**		
3.4.1	Clinical signs	Yes	
3.4.2	Dermal examination	Yes	
3.4.2.1	Scoring system	Draize	
3.4.2.2	Examination time points	3 min. (animal 1) and 1, 24, 48 and 72 hours after patch removal.	
3.4.3	Other examinations	Body weight	
3.5	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Average score**		
4.1.1	Erythema	0	
4.1.2	Oedema	0	
4.2	**Reversibility**	Not applicable, as there was no irritation.	
4.3	**Other examinations**	There were no systemic intolerance reactions	
4.4	**Overall result**	There was no erythema, eschar or oedema observed in any of the animals at 3 minutes or at 1, 24, 48 and 72 hours after exposure. The score for erythema and eschar or oedema formation was 0.0. According to classification criteria deltamethrin technical is not an irritant to the skin. There were no systemic intolerance reactions.	

		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	A test was performed to assess potential irritant / corrosive effects of deltamethrin technical (purity 99.9%) on the skin of rabbits. 0.5 g of the test substance moistened with Aqua was applied on the intact skin of the dorso-lateral areas of the trunk of each of three female albino NZW rabbits for 4 h exposure. The Draize scale was used to assess the degree of erythema and oedema.	
5.2	**Results and discussion**	There was no erythema, eschar or oedema observed in any of the animals at 3 minutes or at 1, 24, 48 and 72 hours after exposure. The score for erythema and eschar or oedema formation was 0.0. According to classification criteria deltamethrin technical is not an irritant to the skin. There were no systemic intolerance reactions.	
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted.
Results and discussion	The applicant's version is adopted.
Conclusion	The applicant's version is adopted. In this study the primary irritation score was 0.0 indicating the test substance to be a non irritant to skin of rabbits. Based on this data deltamethrin does not require EU classification with regard to skin irritation.
Reliability	1
Acceptability	Acceptable.
Remarks	

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (2005b) Deltamethrin technical – Acute Eye Irritation on Rabbits [redacted] Document M-260858-01-1 6.1.4/02 18 November 2005 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	OECD 405	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	EDDLTO038	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	99.9%	
3.1.2.3	Stability	Stable as stored at room temperature.	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	Esd:NZW	
3.2.3	Source	Charles River Laboratories, France	
3.2.4	Sex	Females	
3.2.5	Age/weight at study initiation	Age: young adult Weight: 2500 – 2700 g	
3.2.6	Number of animals per group	Three	
3.2.7	Control animals	No, but the second eye of each rabbit, which remained untreated, serves as control.	
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 g of the pulverized test substance was placed into the conjunctival sac of one eye of each rabbit	
3.3.3	Exposure period	24 hours	
3.3.4	Postexposure period	72 hours (if eye irritations were observed, animals were monitored usually on day 7, 14 and 21 after application until the changes had completely subsided, however for not more than 21 days after application).	
3.4	**Examinations**		
3.4.1	Ophthalmoscopic examination	Yes	
3.4.1.1	Scoring system	Draize	
3.4.1.2	Examination time points	1, 24, 48 and 72 h	
3.4.2	Other investigations	-	
3.5	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Clinical signs**	Not recorded	
4.2	**Average score**		
4.2.1	Cornea	There were no effects on the cornea. The average score is 0.0 for corneal opacity for each rabbit.	
4.2.2	Iris	There were no effects on the iris. There average score is 0.0 for iritis for each rabbit.	
4.2.3	Conjunctiva	See Table A6.1.4-1.	
4.2.3.1	Redness	Yes. The average score is 1.3, 0.7 and 0.7 for redness conjunctivae for rabbit number 1, 2 and 3 respectively.	
4.2.3.2	Chemosis	Yes. The average score is 0.7, 0.0 and 0.3 for chemosis conjunctivae for rabbit number 1, 2 and 3 respectively.	
4.3	**Reversibility**	Yes, after 1 h to 3 days	
4.4	**Other**	-	
4.5	**Overall result**	According to classification criteria deltamethrin technical is not irritating to eyes. There were no systemic intolerance reactions.	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	A test was performed to assess the potential irritant effects of deltamethrin technical (purity 99.9%) on the eye of rabbit. 0.1 g of pulverized test substance was placed into the conjunctival sac of one eye of each of three female NZW rabbits. The Draize scale was used to assess the degree of irritation.	

5.2	**Results and discussion**	There were no effects on the cornea and the iris of the rabbits. The average score is 0.0 for corneal opacity and iritis for each rabbit. The average score is 1.3, 0.7 and 0.7 for redness conjunctivae for rabbit number 1, 2 and 3 respectively. The average score is 0.7, 0.0 and 0.3 for chemosis conjunctivae for rabbit number 1, 2 and 3 respectively. Reversibility was observed after 1 h to 3 days. According to classification criteria deltamethrin technical is not irritating to eyes. There were no systemic intolerance reactions.	
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table 6.1.4-1 Summary of Irritant Effects (Score)

Animal	Effects	24 h	48 h	72 h	Mean scores	Response	Reversible (days)
1	Corneal opacity	0	0	0	0.0	-	na
	Iritis	0	0	0	0.0	-	na
	Redness conjunctivae	2	2	0	1.3	-	3
	Chemosis conjunctivae	1	1	0	0.7	-	3
2	Corneal opacity	0	0	0	0.0	-	na
	Iritis	0	0	0	0.0	-	na
	Redness conjunctivae	2	0	0	0.7	-	2
	Chemosis conjunctivae	0	0	0	0.0	-	1*
3	Corneal opacity	0	0	0	0.0	-	na
	Iritis	0	0	0	0.0	-	na
	Redness conjunctivae	2	0	0	0.7	-	2
	Chemosis conjunctivae	1	0	0	0.3	-	2

Response:
- corneal opacity: mean scores < 2 = -, ≥ 2 < 3 = +, ≥ 3 = ++
- iritis: mean scores < 1 = -, ≥ 1 < 2 = +, = 2 = ++
- conjunctival redness: mean scores < 2.5 = -, ≥ 2.5 = +
- conjunctival oedema: mean scores < 2 = -, ≥ 2 = +

na: not applicable
*: in respect of the result 1 h post application

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted.
Results and discussion	The applicant's version is adopted.
Conclusion	The applicant's version is adopted. In this study redness conjunctivae (mean score <2.5) and chemosis conjunctivae (mean score <2.0) was noted in rabbits at 24 and 48 hrs after exposure of the test substance. The irritation noted in the study was not considered significant for a classification of deltamethrin as an eye irritant according to EC criteria.
Reliability	1
Acceptability	Acceptable.
Remarks	

6.1.5 Acute skin sensitisation

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1977) RU 22974 – Decamethrine Decis Technical Roussel UCLAF – Sensitisation Test in the Guinea Pig [redacted] Document A28978 6.1.5/01 28 September 1977 Unpublished See Monograph 91/414 from 1998 – Point B.5.2.4	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	Study follows OECD guideline 406 (M + K)	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement, but the study was conducted in line with good scientific practice.	
2.3	**Deviations**	No controls, no individual body weights, no details on housing conditions.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	7B0205	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	powder practically white	
3.1.2.2	Purity	100 %	X1
3.1.2.3	Stability	Not specified but deltamethrin is not known to decompose at room temperature.	
3.1.2.4	Preparation of test substance for application	Applied neat	
3.1.2.5	Pretest performed on irritant effects	Yes	
3.2	**Test Animals**		
3.2.1	Species	Guinea pigs	
3.2.2	Strain	Albino Hartley	
3.2.3	Source	Not given	

3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	Age not given Weight: 300 – 400 g	
3.2.6	Number of animals per group	Ten of each sex	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**	Guinea Pig Maximisation Test	
3.3.1	Induction schedule	10 topical applications of the test substance: three/week with a 2 day interval for three weeks and one at the start of the fourth week. 2 intradermal injections of Freund's complete adjuvant on day 1 and 10.	
3.3.2	Way of induction	Topical occlusive (for 48 hours) and intradermal injection	
3.3.3	Concentrations used for induction	0.5 g test substance	
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	50% in physiological saline	
3.3.5	Challenge schedule	Day 36 from induction	
3.3.6	Concentrations used for challenge	0.5 g test substance	
3.3.7	Rechallenge	No	
3.3.8	Scoring schedule	1 h, 7h, 24 h, 48 h after patch removal	
3.3.9	Removal of test substance	Not given	
3.3.10	Positive control substance	None	
3.4	**Examinations**		
3.4.1	Pilot study	Yes	
3.5	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Results of pilot studies**	Reported as not causing irritation	
4.2	**Results of test**		
4.2.1	24h after challenge	No sensitisation	
4.2.2	48h after challenge	No sensitisation	
4.2.3	Other findings	None	
4.3	**Overall result**	Not sensitising	

		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The sensitizing potential of deltamethrin (100%) was investigated in twenty albino (Hartley) guinea pigs (10 males and 10 females). The method used derived from the Guinea Pig Maximisation test. The induction comprised 10 closed-patch topical applications of the test substance (0.5 g undiluted deltamethrin, placed under occlusive patches for 48 h) and two intradermal injections of Freund's complete Adjuvant. The test substance was applied 3 times per week with a 2 day interval, for 3 weeks, and once at the start of the 4th week. The animals were challenged with the test article (0.5 g undiluted deltamethrin) two weeks after the induction phase by closed-patch topical application.	
5.2	**Results and discussion**	None of the animals responded following challenge with undiluted deltamethrin.	
5.3	**Conclusion**		
5.3.1	Reliability	2	
5.3.2	Deficiencies	No	

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted with following comment: X1: The purity of the test substance is not specified in the study. There is no certificate of analysis in the study. It is stated in the study that the *concentration* of deltamethrin is 100% but since there may be some impurities in the composition, the purity might be slight less than 100%.
Results and discussion	The applicant's version is adopted.
Conclusion	The applicant's version is adopted. None of the animals responded following challenge with undiluted deltamethrin. Based on this data, deltamethrin is considered to be a non sensitising agent according to the Guinea Pig Maximisation test.
Reliability	2
Acceptability	Acceptable. The deviations from OECD guideline 406 are considered not to compromise the scientific validity of the study.
Remarks	Using data from this study and a Buehler Patch test (Vohr 2005) deltamethrin is considered to be a non sensitising agent according to EC criteria.

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (2005) Deltamethrin technical – Study for the Skin Sensitization Effect in Guinea Pigs (Buehler Patch Test) [redacted] Document M-261562-01-1 6.1.5/02 18 November 2005 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	OECD 406	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	EDDLTO038	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	99.9%	
3.1.2.3	Stability	Stable in the vehicle (polyethylene glycol)	
3.1.2.4	Preparation of test substance for application	The test item was formulated in polyethylene glycol 400 to yield a suspension or a paste (83.3%; 500 mg test item mixed with 0.1 ml vehicle)	
3.1.2.5	Pretest performed on irritant effects	Yes	
3.2	**Test Animals**		
3.2.1	Species	SPF-bred guinea pigs	
3.2.2	Strain	Crl:HA	
3.2.3	Source	Charles-River Laboratory Animal Breeders, Kißlegg, Germany	
3.2.4	Sex	Females	
3.2.5	Age/weight at study initiation	Age: 5 – 6 weeks Weight: 333 – 425 g	
3.2.6	Number of animals per group	20	
3.2.7	Control animals	10	

3.3	**Administration/ Exposure**	Buehler patch test (3 induction treatments)	
3.3.1	Induction schedule	Days 1, 8 and 15	
3.3.2	Way of induction	Topical Semi-occlusive	
3.3.3	Concentrations used for induction	83.3% (500 mg test item mixed with 0.1 ml vehicle: polyethylene glycol)	
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	None	
3.3.5	Challenge schedule	Day 29 (2 weeks after the last dermal induction)	
3.3.6	Concentrations used for challenge	83.3% (500 mg test item mixed with 0.1 ml vehicle: polyethylene glycol)	
3.3.7	Rechallenge	No	
3.3.8	Scoring schedule	30 and 54 h after the beginning of the challenge	
3.3.9	Removal of test substance	The remaining test item was rinsed away with sterile physiological saline solution.	
3.3.10	Positive control substance	No	X1
3.4	**Examinations**		
3.4.1	Pilot study	Yes	
3.5	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Results of pilot studies**	Not irritating	
4.2	**Results of test**		
4.2.1	30h after challenge	No reactions	
4.2.2	54h after challenge	No reactions	
4.2.3	Other findings	By the end of the study the mean body weight of the treatment group animals was in the same range than that of the control group.	
4.3	**Overall result**	There were no skin effects in the animals of the test item group and the control group during the three induction treatments (83.8% test item). The challenge with the 83.3% test item paste let to no skin effects in the animals of the test item group and no skin effects in the control group. Thus deltamethrin technical under the conditions of this test is not considered to be a dermal sensitizer and labelling for deltamethrin technical should not be required.	

	5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The Buehler epicutaneous patch test was performed on 30 female guinea pigs (20 animals for the test item group and 10 control animals) to determine whether deltamethrin technical (purity: 99.9%) exhibits skin-sensitizing properties. Additional two animals were used for dose-finding for the challenge concentration. The test item was formulated in polyethylene glycol 400 to yield a suspension or a paste (83.3%). This 83.3% paste was used for the three induction treatment and the challenge.
5.2	**Results and discussion**	There were no skin effects in the animal of the test item group and the control group during the three induction treatments. The challenge with the 83.3% test item paste led to no skin effects in the animals of the test item group and no skin effects in the control group. In summary, by comparing the effects in the test item group and in the control group it can be concluded that under the conditions of the Buehler Patch Test and with respect to the evaluation criteria deltamethrin technical exhibits no skin-sensitization potential.
5.3	**Conclusion**	
5.3.1	Reliability	1
5.3.2	Deficiencies	No

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted with following comment: X1: No positive control substance was used in this study. However, the Buehler patch test methodology was checked for reliability in a test on female guinea pigs previously conducted using alpha hexyl cinnamic aldehyde formulated in polyethylene glycol 400. The positive controls in this study gave expected results. The sensitivity as well as the reliability of the experimental technique is thus confirmed by this study.
Results and discussion	The applicant's version is adopted.
Conclusion	The applicant's version is adopted. None of the animals responded following challenge with the 83.3% test item paste. Based on this data, deltamethrin is considered to be a non sensitising agent according to the Buehler Patch Test.
Reliability	1
Acceptability	Acceptable.
Remarks	Using data from this study and a Guinea Pig Maximisation Test ([redacted] 1977) deltamethrin is considered to be a non sensitising agent according to EC criteria.

6.2 Metabolism studies in mammals

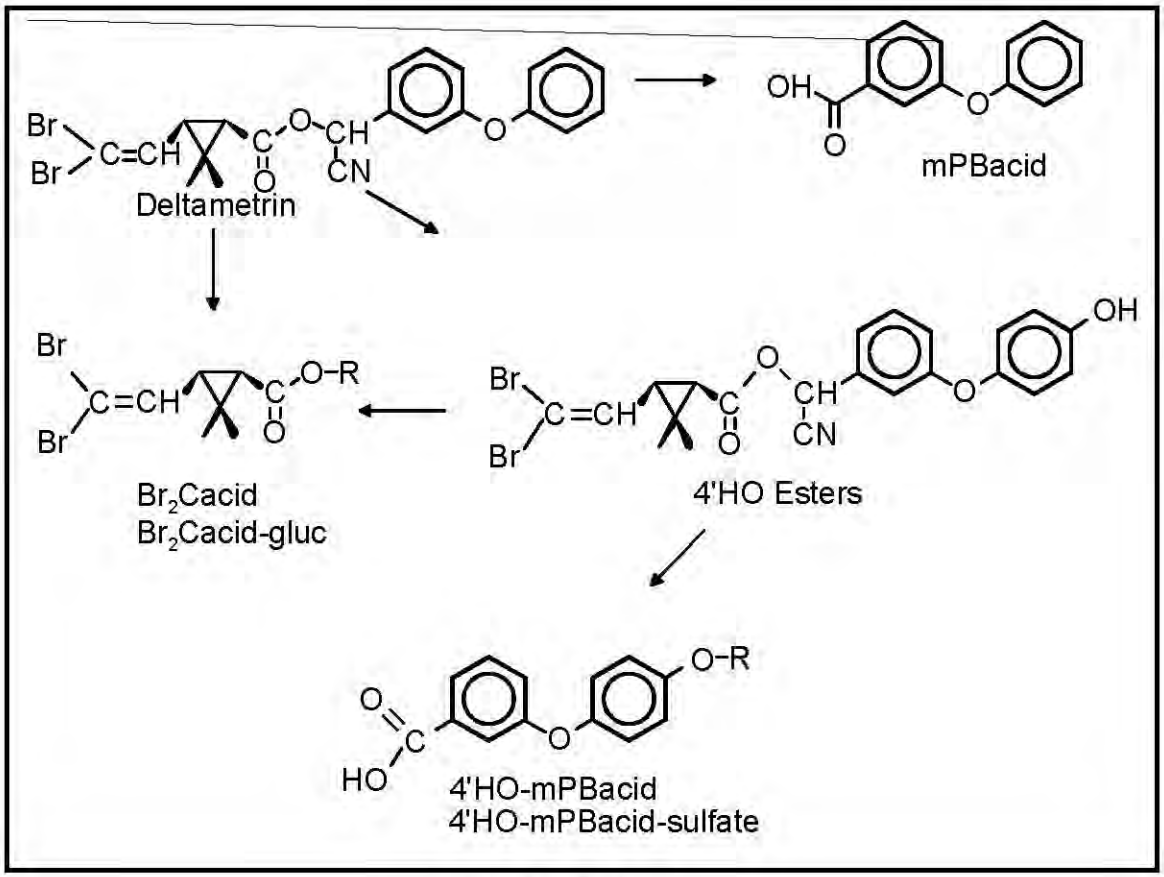
6.2.1 Metabolism

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1990) Metabolism of ^{14}C-Deltamethrin in Rats [redacted] Document A70824 6.2.1/01 9 July 1990 Unpublished See Monograph 91/414 from 1998 – Point B.5.1	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	Study follows OECD guideline 417	
2.2	**GLP**	Yes	
2.3	**Deviations**	Radioactivity in expired air was not measured.	See remarks
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	7B0235B (unlabelled) X6819A (^{14}C-Benzyl) X7506A (^{14}C-Dimethyl)	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Solid	
3.1.2.2	Purity	> 95% (labelled); 99.3% (unlabelled)	
3.1.2.3	Stability	Stable	
3.1.2.4	Radiolabelling	^{14}C-Benzyl (59.2 mCi/mmol) and ^{14}C-Dimethyl (60.0 mCi/mmol) positions	
3.2	**Test animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Crl: CD (SD) BR	
3.2.3	Source	Charles River Laboratories, USA	
3.2.4	Sex	Male and female	

3.2.5	Age/weight at study initiation	Males: Age: 5 – 9 weeks Weight: 209 – 322 g Females: Age: 5 – 9 weeks Weight 172 – 242 g	
3.2.6	Number of animals per group	Five of each sex	
3.2.7	Control animals	Two of each sex	
		4. APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	Two different radiolabelled forms of deltamethrin (^{14}C-dimethyl or ^{14}C-benzyl, purity >95%) were given to sixty, 5 – 9-week old rats (Crl:CD(SD)BR) as follows: 1. single oral low dose (0.55 mg/kg bw), 2 groups (5 animals/sex in each group) 2. multiple oral low doses (14 daily nonradiolabelled doses followed by a single radiolabelled dose on the 15th day) (0.55 mg/kg bw), 2 groups (5 animals/sex in each group) 3. single oral high dose (5.50 mg/kg bw), 2 groups (5 animals/sex in each group) Additionally, two female rats and two male rats were used as control animals. Urine and faeces were collected at various times during the study and analysed for total radioactivity by liquid scintillation counting (LSC). Thin-layer chromatography (TLC) and high pressure liquid chromatography (HPLC) were used for the characterization and identification of the metabolites. Treated animals were sacrificed 7 days after administration of the radiolabelled dose. Selected tissue samples (femur, brain, fat (urogenital), ovaries, testes, heart, liver, large intestine including caecum, small intestine, kidneys, lungs, muscle, spleen, stomach, uterus, blood) and residual carcass were collected for analysis of total radioactivity by liquid scintillation counting (LSC).	
4.2	**Results and discussion**	***Distribution***: Tissue and carcass residues were low (less than 2% of the total dose administered) 7 days postdose. The fat contained the highest concentration of ^{14}C residues for either ^{14}C label with radioactivity concentrations ranging from 0.05 to 0.09 ppm (µeq/g) for the low dose and from 0.50 to 0.84 ppm (µeq/g) for the high dose. The residues of ^{14}C in the blood 7 days after administration of ^{14}C-deltamethrin were less than 0.01 ppm (µeq/g). ***Excretion***: The majority of the radioactivity was eliminated with the urine (31% to 56%, including cage wash, wipe and rinse) and in faeces (36% to 59%), 7 days postdose. The rate of elimination was relatively fast. The material balances for groups ranged from 84% to 96%. The majority of the radioactivity was eliminated within 24 h after dosing (19 – 47% with the urine (without cage wash, wipe and rinse), 32 – 55% in faeces). Females generally excreted more radioactivity with the urine and less in the faeces than males for the dimethyl label. However, for the benzyl label males generally excreted more radioactivity with the urine and less in the faeces than females.	

		Metabolism: Deltamethrin was metabolized by cleavage of the ester bond and hydroxylation on the 4' position of the alcohol moiety (not necessarily in that order). A portion of the products resulting from cleavage of the ester bond were conjugated before being excreted with the urine (see Figure A6.2.1-1). For animals receiving ^{14}C-benzyl deltamethrin, 30% to 49% of the dose was excreted with the urine as 4'SO_4-mPBacid and 2% to 4% of the dose as the conjugated mPBacid. For these same animals, 17% to 46% of the dose was excreted in the faeces as deltamethrin. For animals receiving the ^{14}C-dimethyl deltamethrin, 22% to 38% of the dose was excreted with the urine as Br_2CA-glucuronide and 4% to 10% as the unconjugated Br_2CA. For these same animals, 21% to 35% of the dose was excreted in the faeces as deltamethrin. The animals receiving the high dose excreted a higher percentage in the faeces as deltamethrin and a lower percentage in the urine of metabolites with the cleaved ester bond (Br_2CA-glucuronide). No unchanged deltamethrin or metabolites containing the ester bond was observed in the urine although unchanged deltamethrin was a major ^{14}C residue in the faeces. No other metabolites comprising greater than 10% of the ^{14}C dose were present in urine or the faecal samples assayed.	
4.3	**Conclusion**		
4.3.1	Reliability	1	
4.3.2	Deficiencies	No	

Figure A6.2.1-1 The major metabolites of deltamethrin in rats



EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted.
Results and discussion	The applicant's version is adopted.
Conclusion	The applicant's version is adopted Absorption (see also remarks): Fairly rapid but limited to approximately 56% (based on excretion in urine, cage wash, wipe and rinse 7 days postdose) Excretion: Rapid and almost completely (84-96%) within 7 days. The majority of the radioactivity was eliminated with the urine (31 to 56%) and in faeces (36 to 59%) 7 days postdose. The majority of the radioactivity was eliminated within 24 hrs after dosing (19-47% with the urine (without cage wash, wipe and rinse), 32-55% in faeces). Females generally excreted more radioactivity with the urine and less in the faeces than males for the dimethyl label. For the benzyl label males generally excreted more radioactivity with the urine and less in the faeces than females. Distribution: Tissue residues were low 7 days postdose (<2% of the total dose administered). Highest residues were found in fat. Metabolism: Metabolised by cleavage of the ester bond and hydroxylation on the 4'position of the alcohol moiety (not necessarily in that order). A portion of the products resulting from cleavage of the ester bond were conjugated before being excreted with the urine. Different metabolites were presented in the urine. Unchanged parent compound was the major compound in faeces.
Reliability	1
Acceptability	Acceptable. The deviation from OECD guideline 417 is considered not to compromise the scientific validity of the study.
Remarks	In this study no examination of expired air was made. However, previous works reported in the open literature[1,2] or in the draft assessment report of deltamethrin (evaluation of deltamethrin during the procedure of inclusion into Annex I under Directive 91/414/EEC) have demonstrated that there was no measurable $^{14}CO_2$ generated by rats after oral administration. A gastrointestinal absorption of 75% was estimated for deltamethrin based on urine excretion data ([redacted] 1990) and bile excretion data ([redacted] 1993). [1]Cole LM, Ruzo LO, Wood EJ and Casida JE. Pyrethroid metabolism: Comparative fate in rats of tralomethrin, tralocythrin, deltamethrin and (1*R*,*aS*)-*cis*-cypermethrin. J. Agric. Food Chem. 1982, 30: 631-636. [2]Ruzo LO, Unai T and Casida JE. Decamethrin metabolism in rats. J. Agric. Food Chem., 1978, 26: 918-925.

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1993) (^{14}C-Benzyl)-Deltamethrin: Distribution – Kinetics and Excretion After Single Intravenous Administration to Female Rats [redacted] Document A51513 6.2.1/02 5 August 1993 Unpublished See Monograph 91/414 from 1998 – Point B.5.1	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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; OECD 417	
2.2	**GLP**	Yes	
2.3	**Deviations**	Only one dose level was used.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	0B018853 (unlabelled) X8595A (^{14}C-benzyl labelled)	
3.1.2	Specification	As given in Section 2.	
3.1.2.1	Description	4% in toluene (unlabelled)	
3.1.2.2	Purity	99.5% (unlabelled); > 95% (58.9 mCi/mmol) (^{14}C-benzyl labelled)	
3.1.2.3	Stability	Stable	
3.1.2.4	Radiolabelling	Benzyl position	
3.2	**Test animals**		
3.2.1	Species	Rat	
3.2.2	Strain	HAN-Ibm Wistar rats	
3.2.3	Source	BRL Biological Research Laboratories Ltd, Switzerland	
3.2.4	Sex	Female	
3.2.5	Age/weight at study initiation	Age: 7 – 10 weeks old Weight: 180 – 209 g	
3.2.6	Number of animals per group	Three	
3.2.7	Control animals	Three	

		4. APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	The distribution and excretion of [^{14}C-benzyl]-deltamethrin (radiochemical purity >95%) were examined in 12 female Wistar rats (HAN-Ibm) receiving a single intravenous dose (in the tail vein) at 2.4 mg/kg bw. Urine and faeces samples were collected at 1, 4, 24 and 120 h after dosing and selected organs/tissues (heart, liver, kidneys, ovaries, brain, muscle (leg), abdominal fat, skin (backregion), spinal cord, sciatic nerve and blood) were analysed for radioactivity by liquid scintillation counting.	
4.2	**Results and discussion**	***Distribution***: At 1 h after administration, the blood level amounted to 3.01 µg eq/g. At this time point, highest amounts of radioactivity were found in the liver (6.05 µg eq/g), kidney (3.11 µg eq/g), fat (2.15 µg eq/g) and ovaries (3.99 µg eq/g). Lowest values were detected in the brain, the spinal cord and the sciatic nerve (0.22 – 0.33 µg eq/g). From 1 h to 120 h, radioactivity was rapidly eliminated from the blood with a half-life of 5.5 h. Half-lives in fat, sciatic nerve and skin backregion were >24 h, 28 h and 15 h, respectively. After 120 h, all values were below 0.08 µg eq/g except for fat (1.40 µg eq/g) and ovaries (0.13 µg eq/g). ***Excretion***: Deltamethrin was rapidly eliminated with the urine with an average of 55%. An amount of 48 – 50% was excreted with the urine within the first 24 h and about 10% within the first 4 h. After 120 h, faecal excretion amounted, on average, to 27%. The major amount of 24% was excreted in the faeces within the first 48 h. Taking into account the cage wash (on average 5%), total excreted radioactivity amounted on average to 87%.	
4.3	**Conclusion**		
4.3.1	Reliability	1	
4.3.2	Deficiencies	No	

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant
Materials and methods	The applicant's version is adopted.
Results and discussion	The applicant's version is adopted.
Conclusion	The applicant's version is adopted. Excretion: Rapid and almost completely (87%) within 120 hrs. After 120 hrs an amount of 55% was excreted with the urine and 27% in the feaces. The major amount of 50% was excreted with the urine within the first 24 hrs and about 24% was excreted in the faeces within the first 48 hrs. Distribution: Widely distributed. Highest amounts of radioactivity were found in the liver, kidneys, fat and ovaries. Half-lives in blood, fat, sciatic nerve and skin backregion were 5.5 hrs, >24 hrs, 28 hrs and 15 hrs, respectively.
Reliability	1
Acceptability	Acceptable. The deviation from OECD guideline 417 is considered not to compromise the scientific validity of the study.
Remarks	

6.2.2 Percutaneous absorption

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (2003) (^{14}C) Decis EW15 – *In Vitro* Dermal Penetration Study Using Rat Skin [redacted] Document C037106 6.2.2/01 19 November 2003 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	OECD 417/428	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin EW 15 (oil in water emulsion)	
3.1.1	Lot/Batch number	10562A (labelled) 97B0276B3 (unlabelled)	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Milky white emulsion	
3.1.2.2	Purity	99.6% (unlabelled); > 98.0% (labelled)	
3.1.2.3	Stability	Stable as stored in proper conditions	
3.1.2.4	Radiolabelling	Benzyl position (specific activity 4.24 MBq/mg)	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	CD Sprague Dawley	
3.2.3	Source	Charles River (UK) Ltd, UK	
3.2.4	Sex	Male	

3.3	**Administration/ Exposure**		
3.3.1	Preparation of test substance	Skin samples were cut from dermatomed slice and placed onto the receptor chamber of the flow-through diffusion cell. The donor chamber was then fixed in place providing an exposure area of 0.64 cm^2 skin and the assembled diffusion cell inserted in-line in the flow-through set-up. The high and low dose formulations were supplied to HLS Ltd by the Study Sponsor. The formulations were stored frozen until required for each dose application. On the day of application, the formulation was whirlmixed and magnetically stirred, the radiochemical purity subsequently assessed by HPLC and the concentration determined.	
3.3.2	Concentration of test substance	0.12 and 15 g/l	
3.3.3	Specific activity of test substance	4.24 MBq/mg	
3.3.4	Volume applied	10 µl/cm^2	
3.3.5	Size of test site	0.64 cm^2	
3.3.6	Exposure period	8 hours	
3.3.7	Sampling time	High dose: hourly – low dose: two-hourly	
3.3.8	Samples	Receptor fluid, skin swabs, *stratum corneum*, rest of skin.	
		4. RESULTS AND DISCUSSION	X1
4.1	**Recovery of labelled compound**	101.9% (high dose) 95.16% (low dose)	
4.2	**Percutaneous absorption**	6.44% (high dose) 10.05% (low dose)	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The rate and extent of absorption was investigated following topical application of the insecticide deltamethrin to excised rat skin in an EW (oil in water emulsion) formulation (Decis EW15), at two dose concentrations. The selected nominal concentrations were a high level of 15 g/l, equivalent to the commercially supplied concentrate, and a low level of 0.12 g/l, corresponding to one in-use application rate of the product. Flow-through diffusion cells were prepared at each dose level. Dermatomed membranes (approximately 300 µm thickness) were maintained in the cells at approximately 32°C. The integrity of the membranes was first tested using titrated water. After removal of the residual titrated water, the formulations were applied to the unoccluded skin samples at a rate of 10 µ1/cm^2.	

		The skin samples were exposed to the test material for 8 hours, after which time the remaining dose was washed off the skin with a mild detergent solution. Receptor fluid samples were collected, at hourly intervals for the high level dose and every two hours for the low level dose, for the duration of the study (24 hours). The solubility of deltamethrin in the receptor fluid was demonstrated to be sufficient for the study and not to be rate limiting to the absorption process. At the end of the study, the skin samples were tape stripped to remove residual surface dose and the *stratum corneum*. Tape strips of the *stratum corneum* were analysed in batches of three in order to provide information on the distribution of radioactivity within this compartment.	
5.2	**Results and discussion**	The group mean distributions of radioactivity are summarised in Table A6.2.2-1. These data showed that the total amounts of applied radioactivity absorbed by 24 hours were 6.449% and 10.05% at the high and low dose levels respectively.	X1
5.3	**Conclusion**		X2
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table A6.2.2-1 Table for Percutaneous Absorption (*in vitro* test)

Dose level	High	Low
Receptor fluid (including receptor at termination)	0.655	3.771
Skin	5.794	6.278
Total % absorbed (receptor fluid + skin)	6.449	10.05
Total % in *stratum corneum*	24.58	47.93
Total % Non-absorbed	70.87	37.18
Total % Recovered	101.9	95.16

Results are expressed as mean % applied radioactivity

	EVALUATION BY COMPETENT AUTHORITIES
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted.
Results and discussion	The applicant's version is adopted with following comment: X1: The amount retained in the upper quarter layer of *stratum corneum* after washing was not considered to be absorbed. The total absorbed dose over 24 hrs was 21.44% and 38.21% at the high and low dose levels, respectively.
Conclusion	The applicant's version is adopted with following comment: X2: The total absorbed dose over 24 hrs was 21.44% and 38.21% at the high and low dose levels, respectively (amount retained in the upper quarter of *stratum corneum* not included).
Reliability	1
Acceptability	Acceptable.
Remarks	The dermal absorption of deltamethrin was discussed during Technical Meeting 1, 2010 (February 15-19th 2010). It was agreed upon to disregard the amount retained in the upper layer (top first quarter tape strips) of *stratum corneum* in the *in vitro* studies.

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (2003) (^{14}C) Decis EC 25 – Comparative *In Vitro* Dermal Penetration Study Using Human and Rat Skin [redacted] Document C037107 6.2.2/02 3 November 2003 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	OECD 417/428	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin EC25 (emulsifiable concentrate)	
3.1.1	Lot/Batch number	10562A (labelled) 97B0276B3 (unlabelled)	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Formulation: colourless liquid	
3.1.2.2	Purity	> 98.0% (radiolabelled) – 99.6% (unlabelled)	
3.1.2.3	Stability	Stable as stored in proper conditions	
3.1.2.4	Radiolabelling	Benzyl ^{14}C position (4.24 MBq/mg)	
3.2	**Test Animals**		
3.2.1	Species	Rat, human skin	
3.2.2	Strain	CD Sprague Dawley rat	
3.2.3	Source	Rat: Charles River (UK) Ltd, UK Human skin : International Institute for the Advancement of Medicine, USA	
3.2.4	Sex	Male (rat) – Female (Human)	

3.3	**Administration/ Exposure**		
3.3.1	Preparation of test substance	Skin samples were cut from dermatomed slice and placed onto the receptor chamber of the flow-through diffusion cell. The donor chamber was then fixed in place providing an exposure area of 0.64 cm^2 skin and the assembled diffusion cell inserted in-line in the flow-through set-up. The dose formulations were supplied to Huntingdon Life Science Ltd by the Study Sponsor. The formulations were stored at -20°C until required for each dose application. The radiochemical purity of each formulation was assessed by HPLC prior to each dose application.	
3.3.2	Concentration of test substance	High: 25.0 g/l Low: 0.118 g/l	
3.3.3	Specific activity of test substance	4.24 MBq/mg	
3.3.4	Volume applied	10 µl/cm^2	
3.3.5	Size of test site	0.64 cm^2	
3.3.6	Exposure period	8 hours	
3.3.7	Sampling time	High dose: hourly; low dose: two-hourly	
3.3.8	Samples	Receptor fluid, skin swabs, *stratum corneum*, rest of skin.	
		4. RESULTS AND DISCUSSION	
4.1	**Recovery of labelled compound**	High dose: human skin: 101.3% rat skin: 99.83% Low dose: human skin: 96.45% rat skin: 96.12%	
4.2	**Percutaneous absorption**	High dose human skin: 0.546% rat skin: 10.56% Low dose human skin: 0.525% rat skin: 13.76%	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The rate and extent of absorption was investigated following topical application of the insecticide deltamethrin to excised human and rat skin in an EC (emulsifiable concentrate) formulation (Decis EC 25), at two dose concentrations. The selected nominal concentrations were a high level of 25 g/l, and a low level of 0.118 g/l, corresponding to in-use application rates of the product. Flow-through diffusion cells were prepared for each skin type at each dose level. Dermatomed membranes (approximately 300 µm thickness) were maintained in the cells at approximately 32°C. The integrity of the membranes was first tested using titrated water. After removal of the residual titrated water, the [^{14}C]-Decis EC 25 was applied to the unoccluded skin samples at a rate of 10 µl/cm^2.	

		The skin samples were exposed to the test material for 8 hours, after which time the remaining dose was washed off the skin with a mild detergent solution. Receptor fluid samples were collected, at hourly intervals for the high dose level and two-hourly intervals for the low dose level for the duration of the study (24 hours). The solubility of deltamethrin in the receptor fluid was demonstrated to be sufficient for the study and not to be rate limiting to the absorption process. At the end of the study, the skin samples were tape stripped to remove residual surface dose and the *stratum corneum*.	
5.2	**Results and discussion**	The group mean distributions of radioactivity are summarised in Table A6.2.2-2.	
		These data show that the total amounts of applied radioactivity absorbed by 24 hours at the high dose level were 0.546% and 10.56% and at the low dose level the amounts absorbed were 0.525% and 13.76% in human and rat skin, respectively. Therefore, the total amount of radioactive material absorbed was 19.32 times greater for rat skin than for human skin at the high dose level and 26.20 times greater for rat skin than human skin following application of the low dose.	X1
		In this study it was shown that the radioactive material detected in the *stratum corneum* at 24 hours was most likely to be lost *in vivo* by desquamation and upward renewal of the skin cells with time and was therefore, considered to be non-absorbed material.	X2
		In each case the results show that the rat skin has a higher absorption than human skin and is over-predictive of the dermal penetration of deltamethrin in man.	
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table A6.2.2-2 Table for Percutaneous Absorption (*in vitro* test)

Dose level	**High**		**Low**	
Species	**Human**	**Rat**	**Human**	**Rat**
Receptor fluid (including receptor at termination)	0.126	1.003	0.351	7.254
Skin	0.420	9.55	0.174	6.503
Total % Absorbed (receptor fluid + skin)	0.546	10.56	0.525	13.76
Total % in *stratum corneum*	6.20	16.75	18.70	55.32
Total % Non-absorbed (including *stratum corneum*)	100.8	89.28	95.92	82.36
Total % Recovered	101.3	99.83	96.45	96.12

Results are expressed as mean % applied radioactivity.

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted.
Results and discussion	The applicant's version is adopted with following comment: X1: The total amount of radioactive material absorbed (absorbable amount of radioactivity in *stratum corneum* included) was 4 times greater for rat skin than for human skin at the high dose level and 3.6 times greater for rat skin than human skin following application of the low dose. X2: The amount retained in the upper quarter layer of *stratum corneum* after washing was not considered to be absorbed.
Conclusion	The applicant's version is adopted with following comment: The total amounts of applied radioactivity absorbed by 24 hours at the high dose level were 6.75% and 27.30% and at the low dose level the amounts absorbed were 19.22% and 69.08% in human and rat skin, respectively (amount retained in the upper quarter layer of *stratum corneum* not included). The total amount of radioactive material absorbed was 4 times greater for rat skin than for human skin at the high dose level and 3.6 times greater for rat skin than human skin following application of the low dose.
Reliability	1
Acceptability	Acceptable.
Remarks	The dermal absorption of deltamethrin was discussed during Technical Meeting 1, 2010 (February 15-19th 2010). It was agreed upon to disregard the amount retained in the upper layer of *stratum corneum* (amount of radioactivity found in the top first quarter tape strips) in the *in vitro* studies. The values obtained from this *in vitro* rat and human study together with data from the *in vivo* rat study ([redacted] 2004) have been used to estimate the extent to which dermal absorption of deltamethrin through human skin is likely to occur. Dermal absorption *in vitro* and *in vivo* and through rat and human skin are compared using the following expression: ***In vivo*:Human** ~ *In vivo*: Rat x *In vitro*: Human / *In vitro*: Rat In the *in vivo* rat study ([redacted], 2004) approximately 4.82% of the applied high dose level formulation (concentrate) and 6.79% of the applied low dose formulation (spray dilution) was absorbed over 144 hrs. In the *in vitro* rat study approximately 27.30% of the applied high dose level formulation and 69.08% of the applied low dose formulation was absorbed over 24 hrs. In the *in vitro* human study approximately 6.75% of the applied high dose level formulation and 19.22% of the applied low dose formulation was absorbed over 24 hrs. Using data obtained in the dermal absorption studies refered to above it is estimated that the likely dermal absorption of deltamethrin in man equates to approximately **1.19% for the concentrate** (4.82 x 6.75/27.30) and **1.89% for the a.i. when diluted in the spray solution** (6.79 x 19.22/69.08).

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (2004) (^{14}C) Deltamethrin – *In Vivo* Dermal Absorption Study in the Male Rat [redacted] Document C037108 6.2.2/03 15 January 2004 Unpublished	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	OECD 417/427	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin 25 EC (emulsifiable concentrate)	
3.1.1	Lot/Batch number	10562A (labelled) – 97B0276B3 (unlabelled)	
3.1.2	Specification	As given in Section 2.	
3.1.2.1	Description	Formulation: colourless liquid	
3.1.2.2	Purity	> 98.0% (labelled); 99.6% (unlabelled)	
3.1.2.3	Stability	Stable as stored in proper conditions	
3.1.2.4	Radiolabelling	Benzyl ^{14}C (4.24 MBq/mg)	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague Dawley (Crl:CD® BR)	
3.2.3	Source	Charles River (UK) Ltd, UK	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	Age: 6 – 8 weeks Weight: 174 – 227 g	X1
3.2.6	Number of animals per group	Five	
3.2.7	Control animals	None	

3.3	**Administration/ Exposure**		
3.3.1	Preparation of test substance	An area of dorsal skin (at least 3 x 4 cm) was clipped approximately 16 to 24 hours prior to dosing. At dosing, a silicone rubber saddle was secured in place on the clipped area of skin using cyanoacrylate adhesive. The dose formulation was applied to the clipped area using a calibrated pipette. After application of 120 µl of the dose solution, the test sites were covered to prevent loss of test substance and allow air circulation. The dose formulations were supplied to HLS Ltd by the Study Sponsor. The formulations were stored at -20°C until required for each dose application. The radiochemical purity of each formulation was assessed by HPLC, prior to each dose application.	
3.3.2	Concentration of test substance	High: 25 g/l Low: 0.118 g/l	
3.3.3	Specific activity of test substance	4.24 MBq/mg	
3.3.4	Volume applied	10 µl/cm²	
3.3.5	Size of test site	3 x 4 cm	
3.3.6	Exposure period	8 hours	
3.3.7	Sampling time	0-8 and 8-24 and then 24 hourly until sacrifice for urine, faeces and cage washings. At sacrifice: treated skin, skin surrounding dose site, untreated skin, residual carcass, urine, faeces.	
3.3.8	Samples	Urine, faeces, cage washings, treated skin, surrounding dose site, untreated skin and residual carcass.	
		4. RESULTS AND DISCUSSION	
4.1	**Recovery of labelled compound**	Low dose: 76.91 – 98.05% High dose: 90.66 – 100.60%	
4.2	**Percutaneous absorption**	Low dose: 5.02% High dose: 4.02%	X2
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	The rate and extent of absorption of radioactivity was investigated following topical application of deltamethrin, in an EC (emulsifiable concentrate) formulation, Decis EC25, at two dose concentrations to male rats. The selected nominal concentrations were a high level of 25 g/l, equivalent to the commercially supplied concentrate, and a low level of 0.118 g/l, corresponding to an in-use application rate of the product. A preliminary study was conducted on three groups of four male rats to obtain an indication of the proportion of the test substance absorbed through the skin and excreted, retained in the skin, or remaining on the skin surface at each dose level. The results from the preliminary study were used to determine the sacrifice times in the main study, the need to investigate the material remaining in the skin, and its localisation, and any requirement to examine the tissue distribution of the radioactivity.	

		On the basis of the results of the preliminary study it was decided to employ the same sacrifice times in both of the main experiments (24, 72 and 144 hours after dose application) and to introduce a sacrifice time at 8 hours to investigate absorption prior to the dose swabbing procedure. The tape stripping procedure was included in the main studies to determine the distribution of the radioactivity through the skin. The main study consisted of four groups of five male rats, at each dose level, which were exposed to the test material for 8 hours. At the end of the exposure period the remaining dose was washed off the skin with a mild detergent solution. One group of animals at each dose level were sacrificed at 8, 24, 72 and 144 hours after administration. Urine, faeces and cage wash were collected at 8 hours, 24 hours and daily until termination. At termination the dose site was tape stripped to remove the *stratum corneum*. The remaining treated skin, a small area of skin surrounding the dose site, untreated skin and residual carcass were retained for analysis.	
5.2	**Results and discussion**	The group mean distributions of radioactivity are summarised in Table A6.2.2-3 below. By 144 hours the total amount of radioactivity absorbed was 4.02% of the applied high dose level formulation and 5.02% of the applied low dose level formulation. The radioactivity remaining in the *stratum corneum* after washing was potentially absorbable, but it was demonstrated that the majority was lost by desquamation and upward renewal of the epidermis, thus the activity remaining in the *stratum corneum* was not considered to be absorbed in this case.	X2
5.3	**Conclusion**		
5.3.1	Reliability	1	
5.3.2	Deficiencies	No	

Table A6.2.2-3 Group mean distributions of radioactivity

Group number	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Sacrifice time (hours)	**8**	**24**	**72**	**144**	**8**	**24**	**72**	**144**
Nominal dose (g/l)	**25**	**25**	**25**	**25**	**0.118**	**0.118**	**0.118**	**0.118**
% Recovered by washing procedures (skin swab + gauze wash)	68.14	68.12	80.18	77.67	55.12	54.78	61.25	69.82
% Dose remaining on skin surface	1.53	9.68	9.76	14.01	4.34	21.62	15.42	13.65
% In *stratum corneum*	22.50	12.91	5.11	2.76	30.09	14.27	9.32	4.19
Total % non-absorbed (including scissor wash)	92.27	90.76	95.08	94.47	89.63	90.68	85.99	87.66
% In excreta	0.24	1.06	2.00	3.08	0.20	1.36	4.04	4.55
% In tissues	0.58	2.27	0.76	0.76	0.14	0.09	0.09	0.11
Total % direct absorption	0.82	3.33	2.77	3.84	0.34	1.45	4.13	4.67
% In treated skin (after tape stripping)	1.62	1.07	0.30	0.18	1.91	1.37	0.74	0.35
Total % absorbed (direct absorption + treated skin)	2.44	4.40	3.07	4.02	2.25	2.83	4.88	5.02
Total % recovered	94.71	95.16	98.15	98.49	91.89	93.50	90.87	92.68

Results are expressed as mean % applied radioactivity.

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted with following comment: X1: The bodyweight in the rats ranged at dosing between 174 to 227 g (the OECD guideline no. 427 recommends rats of 200-250 g bodyweight). However, since the variation in weight of the animals did not exceed ±20% of the mean bodyweight, this deviation was not considered to affect the integrity of the study.
Results and discussion	The applicant's version is adopted with following comment: X2: At 144 hours the total amount of radioactivity absorbed was 4.82% of the applied high dose level formulation and 6.79% of the applied low dose level formulation (the amount retained in the upper layer of *stratum corneum* not included).
Conclusion	By 144 hours the total amount of radioactivity absorbed was 4.82% of the applied high dose level formulation and 6.79% of the applied low dose level formulation (the amount retained in the upper layer of *stratum corneum* not included).
Reliability	1
Acceptability	Acceptable.
Remarks	The dermal absorption of deltamethrin was discussed during Technical Meeting 1, 2010 (February 15-19th 2010). It was agreed upon to disregard the amount retained in the upper layer of *stratum corneum* in the *in vivo* study and to use 144 hrs values. The values obtained from this *in vivo* rat study together with data from the *in vitro* rat and human study ([redacted] 2003) have been used to estimate the extent to which dermal absorption of deltamethrin through human skin is likely to occur. Dermal absorption *in vitro* and *in vivo* and through rat and human skin are compared using the following expression: ***In vivo*:Human** ~ *In vivo*: Rat x *In vitro*: Human / *In vitro*: Rat In the *in vivo* rat study approximately 4.82% of the applied high dose level formulation (concentrate) and 6.79% of the applied low dose formulation (spray dilution) was absorbed over 144 hrs. In the *in vitro* rat study approximately 27.30% of the applied high dose level formulation and 69.08% of the applied low dose formulation was absorbed over 24 hrs. In the *in vitro* human study approximately 6.75% of the applied high dose level formulation and 19.22% of the applied low dose formulation was absorbed over 24 hrs. Using data obtained in the dermal absorption studies refered to above it is estimated that the likely dermal absorption of deltamethrin in man equates to approximately **1.19% for the concentrate** (4.82 x 6.75/27.30) and **1.89% for the a.i. when diluted in the spray solution** (6.79 x 19.22/69.08).

6.3 Short-term repeated dose toxicity (28 days)

6.3.1 Repeated dose toxicity (oral)

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [✓]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	These studies are not required as a sub-chronic toxicity study is available in a rodent (see Point 6.4.1)	
Undertaking of intended data submission [ ]		

EVALUATION BY COMPETENT AUTHORITIES	
EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	
Materials and methods	
Conclusion	
Reliability	
Acceptability	
Remarks	The applicant's justification is adopted.

6.3.2 Repeated dose toxicity (dermal)

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1993) 21-Dermal Toxicity Study in Rats with Deltamethrin Technical [redacted] Document A50968 6.3.2/01 9 April 1993 Unpublished See Monograph 91/414 from 1998 – Point B.5.3	X3
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	Study follows OECD guideline 410	
2.2	**GLP**	Yes	
2.3	**Deviations**	No additional satellite group for recovery/reversibility phase.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	2N0398B2	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Off-white powder	
3.1.2.2	Purity	99.6%	
3.1.2.3	Stability	Stable as stored in proper conditions	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Sprague-Dawley Crl:CD^{S} BR VAF/Plus®	X4
3.2.3	Source	Charles River Laboratories Inc, USA	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	Age: 8 weeks Weight: Males: 235 – 288 g Females: 154 – 214 g	
3.2.6	Number of animals per group	Five of each sex	
3.2.7	Control animals	Five of each sex	

3.3	**Administration/ Exposure**	Dermal	
3.3.1	Duration of treatment	21 days	
3.3.2	Frequency of exposure	7 days per week for 3 weeks	
3.3.3	Postexposure period	None	
3.3.4	**Dermal**		
3.3.4.1	Area covered	10% of body surface	
3.3.4.2	Occlusion	Porous	X1
3.3.4.3	Vehicle	Polyethylene glycol 400	
3.3.4.4	Concentration in vehicle	0, 16.67, 50, 166.67 mg/ml (corresponding to 0, 100, 300 and 1000 mg/kg/day)	
3.3.4.5	Total volume applied	6 ml/kg	
3.3.4.6	Duration of exposure	6 hours	
3.3.4.7	Removal of test substance	Clean gauze moistened with distilled water	
3.3.4.8	Controls	Vehicle	
3.4	**Examinations**		
3.4.1	Observations		
3.4.1.1	Clinical signs	Yes; daily	
3.4.1.2	Mortality	Yes; twice daily	
3.4.2	Body weight	Yes; weekly	
3.4.3	Food consumption	Yes; weekly	
3.4.4	Water consumption	No	
3.4.5	Ophthalmoscopic examination	No	
3.4.6	Haematology	Yes Number of animals: All animals Time points: end of study Parameters: Haematocrit, haemoglobin concentration, erythrocyte count, total and differential leukocyte count, platelet count, clotting time, reticulocyte count, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and mean corpuscular volume (MCV)	X5

3.4.7	Clinical chemistry	Yes Number of animals: All animals Time points: end of study Parameters: Sodium, potassium, calcium, chloride, phosphorus, glucose, urea, blood urea, nitrogen, total bilirubin, creatinine, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase. Albumine/globuline ratio, fasting glucose	
3.4.8	Urinalysis	No	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes Organs: liver, kidneys, testes, brain.	
3.5.2	Gross and histopathology	Yes All dose groups Kidneys, liver, skin, all gross lesions. Histopathology: liver and kidneys from control and high dose group; skin and gross lesions from all dose groups.	
3.5.3	Other examinations	-	
3.5.4	Statistics	ANOVA	X2
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	There were no overt clinical signs of toxicity in the study animals. A number of incidental observations were noted throughout the groups and included malaligned incisors, hairloss, scabbing at areas other than the application site, and nontreatment-related dermal irritation in the binder tape area.	
4.1.2	Mortality	No mortality occurred	
4.2	**Body weight gain**	No statistically significant differences in mean body weights or weight gain were observed among the groups. However, body weight gain appeared to be decreased slightly in the 300 mg/kg/day males during days 1 – 8, and in the 1000 mg/kg/day males on days 1 – 8 and 8 – 15. There were no apparent differences in mean body weight or weight gain between the control and 100 mg/kg/day rats.	
4.3	**Food consumption and compound intake**	No statistically significant differences in food consumption (grams/animal/day) were noted among the groups. However, food consumption appeared marginally to slightly decreased during days 1 – 8 in the 300 and 1000 mg/kg/day males. No other apparent differences in food consumption were noted.	
4.4	**Ophthalmoscopic examination**	No Ophthalmoscopic examination was performed.	
4.5	**Blood analysis**		
4.5.1	Haematology	There were no statistically significant or biologically meaningful differences in haematology data among the groups.	

4.5.2	Clinical chemistry	Statistically significant differences in clinical chemistry data were limited to a decreased glucose level in the 300 mg/kg/day females. This difference was not considered biologically meaningful since a similar change was not observed in the 1000 mg/kg/day females. No other statistically significant or apparent differences in clinical chemistry data were noted.	
4.5.3	Urinalysis	No urinalysis was performed.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	There were no statistically significant or biologically meaningful differences in absolute or relative organ weight data among the groups.	
4.6.2	Gross and histopathology	Test article-related microscopic changes were observed in the treated skin of animals from the 100, 300 and 1000 mg/kg/day groups. The changes included dermal abscesses, chronic dermatitis, exudate on the epidermal surface, mononuclear cell foci in the dermis, epidermal necrosis, parakeratosis, ulcers and epidermal vesiculation. There was no dose-response relationship in the incidence or severity of the dermal changes among the groups. One-half or more of the rats from each of the three test article-treated groups exhibited normal treated skin. No test article-related changes were observed in the liver or kidneys of the 1000 mg/kg/day animals.	
4.7	**Other**	Gross necropsy findings were generally unremarkable. Individual findings were of low incidence and appeared to be sporadically distributed among the groups.	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Groups of five male and five female rats (Sprague Dawley Crl: CD^{S} BR VAF Plus®) were dermally administered deltamethrin (purity 99.6%) for three weeks at respective doses of 100, 300 and 1000 mg/kg bw/day. The test article was mixed with polyethylene glycol 400 (PEG 400). The control animals (5 animals/sex) received the vehicle only. A complete gross necropsy examination was performed on all animals. The liver and kidneys from control and high-dose animals, and the treated skin, untreated skin and gross lesions from all animals were examined microscopically.	X4
5.2	**Results and discussion**	No mortality or clinical signs of toxicity were observed during the study. Mean body weight gain and food consumption appeared to be slightly decreased for males of the 300 and 1000 mg/kg bw/day groups (not statistically significant). There were no treatment-related effects on clinical pathology, necropsy or organ weight data. Signs of dermal irritation were observed in animals in all treated groups. Substance-related microscopic dermal changes in these groups included dermal abscesses, chronic dermatitis, exudate on the epidermal surface, mononuclear cell foci in the dermis, epidermal necrosis, parakeratosis, ulcers and epidermal vesiculation.	X6
5.3	**Conclusion**		

5.3.1	LO(A)EL	> 1000 mg/kg	X7
5.3.2	NO(A)EL	1000 mg/kg	X8
5.3.3	Other	-	
5.3.4	Reliability	1	
5.3.5	Deficiencies	No	

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted with following corrections: X3: 21-Day Dermal Toxicity Study in Rats with Deltamethrin Technical (not 21-Dermal Toxicity Study in Rats with Deltamethrin Technical). X4: Sprague-Dawley Crl:CD® BR VAF/Plus® (not Sprague-Dawley Crl: CD^S BR VAF/Plus®). The applicant's version is adopted with following comments: X1: Each rat's dose was held in contact with the skin using a porous 2x3 inch 8-ply gauze dressing which was secured in place with Coban wrap. X5: Clotting time was not examined (this fact is considered not to compromise the scientific validity of the study). X2: Continous data were analyzed by One Way Analysis of Variance (ANOVA). When significance was observed with ANOVA, control to treatment group comparisons were performed using Dunnett's Test or a modified version of Dunnett's Test. All tests were two-tailed with a minimum significance level of 5%.
Results and discussion	The applicant's version is adopted with following comment: X6: The dermal irritation was noted at study day 4 or later.
Conclusion	The applicant's version is adopted with following amendments: X7: The LOAEL systemic effects was >1000 mg/kg bw/day. The LOAEL local effects was 100 mg/kg bw/day. X8: The NOAEL systemic effects was 1000 mg/kg bw/day. The NOAEL local effects could not be determined in this study since marked signs of dermal irritation were noted in treated skins in animals in all treated groups. The only substance related effect noted in this study was dermal irritation. Signs of dermal irritation were noted in treated skin in animals in all treated groups. Therefore no NOEL was determined in this study. The NOAEL systemic toxic effects was 1000 mg/kg bw/day since there was no evidence of any systemic toxic effect in this study. No NOAEL local effects was determined in this study since marked signs of dermal irritation were noted in treated skin in animals in all treated groups.
Reliability	1
Acceptability	Acceptable. The deviation from OECD guideline no. 410 is considered not to compromise the scientific validity of the study.
Remarks	In this study dermal irritation was noted in some rats after repeated exposure with deltamethrin. However, the irritation noted in this study was not considered significant for a classification of the substance as irritant to skin (when compared to EC criteria for tests on animals at single exposure).

6.3.3 Repeated dose toxicity (inhalation)

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1978) RU 22974 (Decis) Inhalation Toxicity Study in Rats 14 x 6 Hour Exposures Over a Period of 3 Weeks [redacted] Document A41948 6.3.3/01 19 October 1978 Unpublished See Monograph 91/414 from 1998 – Point B.5.3	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	Study follows OECD guideline 412	
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement, but was conducted in line with good scientific practice.	
2.3	**Deviations**	Temperature and humidity were not in keeping with guidelines. There was no satellite group for reversibility/recovery phase.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	6E0861	
3.1.2	Specification	As given in Section 2	X1
3.1.2.1	Description	White powder	
3.1.2.2	Purity	Not specified	X2
3.1.2.3	Stability	Stable as stored at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	CD	
3.2.3	Source	Charles River, UK	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	Seven weeks Males: 210 – 215 g Females: 158 – 161 g	
3.2.6	Number of animals per group	Eight of each sex	

3.2.7	Control animals	Yes – Eight of each sex	
3.3	**Administration/ Exposure**	Inhalation (whole body exposure)	
3.3.1	Duration of treatment	14 days	
3.3.2	Frequency of exposure	5 days per week for 2 weeks and 4 days per week on third week	
3.3.3	Postexposure period	Till day 22 (sacrifice)	
3.3.4	**Inhalation**		
3.3.4.1	Concentrations	Nominal concentration 0, 1, 10, 50 mg/m^3 Analytical concentration 0, 3.0, 9.6, 56.3 mg/m^3	
3.3.4.2	Particle size	86 – 87% < 5.5 µm	
3.3.4.3	Type or preparation of particles	Wright dust generator	
3.3.4.4	Type of exposure	Inhalation (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/day, 5 days per week for 2 weeks and 4 days per week on third week	
3.3.4.8	Controls	Air only	
3.4	**Examinations**		
3.4.1	Observations		
3.4.1.1	Clinical signs	Yes; every 30 minutes during exposure	
3.4.1.2	Mortality	Yes; every 30 minutes during exposure	
3.4.2	Body weight	Yes; daily, upon arrival to the end of the study	
3.4.3	Food consumption	Yes; daily	
3.4.4	Water consumption	Yes; daily	
3.4.5	Ophthalmoscopic examination	No	
3.4.6	Haematology	Yes Number of animals: All animals Time points: end of study Parameters: Packed cell volume, haemoglobin, red cell count, mean corpuscular haemoglobin concentration (MCHC), mean cell volume (MCV), total white cell count (WBC), differential count, platelet count, thrombotest	
3.4.7	Clinical chemistry	Yes Number of animals: All animals Time points: end of study Parameters: urea, plasma glucose, total proteins, albumin, alkaline phosphatase, glutamic pyruvic transaminase, sodium, potassium, calcium, inorganic phosphorus, cholesterol, creatinine.	

3.4.8	Urinalysis	Yes Number of animals: 5 rats from control and each dose group Time points: end of study Parameters: appearance, volume, , specific gravity, pH, protein, glucose, blood, bile pigments, urobilinogen, ketones, total reducing substances, microscopy of spun particles	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes All dose groups Organs: liver, kidneys, adrenals, testes, epididymides, uterus, ovaries, spleen, brain, heart, pituitary, thyroids, prostate	
3.5.2	Gross and histopathology	Yes All dose groups Organs: brain, spinal cord, pituitary, thyroid, parathyroid, thymus, oesophagus, salivary glands, stomach, small and large intestines, liver, pancreas, kidneys, adrenals, spleen, heart, trachea, lungs, aorta, gonads, uterus, prostate, urinary bladder, lymph nodes, peripheral nerve, bone marrow, skin, eyes, larynx, ovaries, seminal vesicles, ileum, caecum, skeletal muscle	X3 X4
3.5.3	Other examinations	None	
3.5.4	Statistics	Analysis of variance and Student's 't' test were performed on bodyweight, food and water consumption, urinalysis, haematology, blood chemistry and organ weight data in order to assess the statistical significance of any intergroup differences. In addition, Williams' test was performed on selected parameters showing separation from control values.	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	Rats exposed to the dust of deltamethrin showed symptoms as licking of the inside of the mouth, blinking, washing and scratching of the face and skin, and ptyalism.	X5
4.1.2	Mortality	There were no mortalities.	X6
4.2	**Body weight gain**	Statistically significant reduced body weight gain was noted in male rats in all three groups exposed to the dust of deltamethrin. Compared to control values, lower amounts of food were consumed by rats in all three groups exposed to the dust of deltamethrin.	X7 X8
4.3	**Food consumption and compound intake**	Lower food consumption was noted for rats in all three treatment groups.	X8
4.4	**Ophthalmoscopic examination**	No ophthalmoscopic examination was performed.	
4.5	**Blood analysis**		
4.5.1	Haematology	No biologically significant changes were noted.	X9

4.5.2	Clinical chemistry	Statistically significant increases above control values were calculated for serum sodium values in both male and female rats in the intermediate and high dose groups. An increased high group mean urea concentration was obtained for male rats in the high dose group.	
4.5.3	Urinalysis	No biologically significant changes were noted.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	Increases ($p<0.05$) in organ weights (relative values) occurred in adrenal (males) at 56 mg/m^3. Decreases ($p<0.05$) in organ weights (relative values) occurred in heart (females) at 56 mg/m^3. Reduction in absolute organ weights of males were recorded for the heart, liver and spleen.	
4.6.2	Gross and histopathology	No treatment-related gross or microscopic changes were observed except for scarring of the ears in rats exposed at the intermediate and high dosage levels. This effect was considered indirectly related to the irritant nature of deltamethrin.	X10
4.7	**Other**	-	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Groups of eight male and eight female albino rats (Charles River CD®) were exposed whole body to dust aerosol atmospheres of deltamethrin (purity not specified) at respective concentrations of 3, 10 and 56 mg/m^3, 6-h a day, 5 days a week for 2 weeks and 4 days on the 3rd week (a total of 14 exposures). The controls (8 animals/sex) received air only. The average percentage of particulate deltamethrin considered respirable (≤ 5.5 µm mean aerodynamic diameter) was about 87%.	
5.2	**Results and discussion**	All rats survived to treatment. Rats exposed to the dust of deltamethrin showed symptoms as licking of the inside of the mouth, blinking, washing and scratching of the face and skin, and ptyalism.	X6
		Hypersensitivity and aggressive behaviour were also noted. Additionally, ataxia and walking with arched backs were confined to rats exposed at the high dose level. All rats became normal between exposures with the exception of one rat in the high dose group walking with an arched back prior to exposure 7 and 13.	X5
		Statistically significant reduced body weight gain were noted in male rats in all three groups exposed to the dust of deltamethrin. Compared to control values, lower amounts of food were consumed by rats in all three groups exposed to the dust of deltamethrin.	X7 X8

		Statistically significant increases above control values were calculated for serum sodium values in both male and female rats in the intermediate and high dose groups. An increased high group mean urea concentration was obtained for male rats in the high dose group. Increases ($p<0.05$) in organ weights (relative values) occurred in adrenal (males) at 56 mg/m³. Decreases ($p<0.05$) in organ weights (relative values) occurred in heart (females) at 56 mg/m³.	
		No treatment-related gross or microscopic changes were observed except for scarring of the ears in rats exposed at the intermediate and high dosage levels. This effect was considered indirectly related to the irritant nature of deltamethrin.	X10
		No NOEL for male and female rats was determined in this study. Clinical signs (irritative and neurological effects) were seen in all rats exposed to the dust of deltamethrin.	X11
5.3	**Conclusion**		
5.3.1	LO(A)EL	-	X12
5.3.2	NO(A)EL	< 3 mg/m³	X13
5.3.3	Other	-	
5.3.4	Reliability	1	
5.3.5	Deficiencies	No	

Table A6.3.3-1 Results of Clinical Chemistry

Parameter changed	Group 1 (control)		Group 2 (low dose)		Group 3 (intermediate dose)		Group 4 (high dose)	
	m	f	m	f	m	f	m	f
Urea (mg%) (Days 18 and 19)	26 SD 1.4	32 SD 5.2	25 SD 2.6	32 SD 5.2	30 SD 4.3	40* SD 5.1	36†§ SD 5.6	38 SD 4.1
Sodium (m Eq/l) (Days 18 and 19)	142 SD 2.1	141 SD 0.8	143 SD 2.6	142 SD 2.3	146‡§ SD 1.6	147‡§ SD 4.3	147†¤ SD 1.2	150†¤ SD 1.9

Level of statistical significance: * = 5% ('t' test) § 5%
(compared to control values) ‡ = 1% ¤1% (Williams' test)
† = 0.1%

SD = Standard deviation

Table A6.3.3-2 Results of Repeated Dose Toxicity Study

Parameter	Control		Low dose		Medium dose		High dose		Dose response +/-	
	m	f	m	f	m	f	m	f	m	f
Number of animals examined	8	8	8	8	8	8	8	8		
Body weight										
Gain Days 0 – 4	43	25	45	25	45	22	45	22	/	/
Days 5 – 22	97	45	81 *	46	75 **	41	76 **	48	-	/
Organs										
Heart weight	1.3 SD 0.17	0.8 SD 0.08	1.1† SD 0.07	0.8 SD 0.07	1.1‡ SD 0.07	0.8 SD 0.10	1.0§ SD 0.07	0.7 SD 0.09	/	-
Adrenals weight	51 SD 10.9	65 SD 9.6	56 SD 7.6	57 SD 11.6	52 SD 9.5	63 SD 10.4	57 SD 11.2	62 SD 14.1	+	/

* $p < 0.05$ in comparison with control value
** $p < 0.01$ in comparison with control value
Level of statistical significance: † = 5% ('t' test)
(compared to control values) ‡ = 1%
§ = 0.1%
SD = Standard deviation

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted with following comments: X1: The temperature and humidity were not in keeping with guidelines in this study. The temperature in the exposure chamber varied between 21 and 29°C and the humidity varied between 13-99% (recommended values according to the OECD guideline no. 412 are 22±3°C and 30-70% humidity). The maximum increase in temperature during any single exposure was 5°C. The maximum increase in humidity during any single exposure was 46%. This occurred during the first exposure of rats in the highest dose group. The deviations from OECD guideline no. 412 are considered not to compromise the scientific validity of the study. X2: The purity of the test substance was not specified in this study. However, according to Annex Confidential Data and Information it is stated by the applicant that the purity of batch no. 6E0861 is sufficient (i.e. 98%). X3: Microscopic examination was performed on tissues from all rats in the highest dose group and the control group. Tissues from rats in the low- and intermediate dose groups were not included in this examination. X4: Aorta, prostate, salivary gland, seminal vesicle, skin were preserved but not processed further.
Results and discussion	The applicant's version is adopted with following comments: X5: In addition clinical signs such as hypersensitivity, aggressive behaviour and hyperactivity were noted in rats of the intermediate and high dosage levels, and ataxia and walking with arched backs were confined to rats exposed at the high dose level. X6: Substance related deaths were noted in three males and two females of the high dose group (0.54 g/m^3). X7: Statistically significant reductions in mean bodyweight gain were noted at 3 mg/m^3 and above in males. The reductions when compared to controls were 16%, 23% and 22% for the 3, 9.6 and 56.3 mg/m^3 groups, respectively. X8: No statistically significant decreases in food consumption were noted. X9: Statistically significant lower group mean values of packed cell volume and red blood cell count were recorded for female rats in the highest dose group. These findings were considered not biologically significant. X10: The irritant nature of deltamethrin manifested itself in scratching at the eyes, flanks and ears. In addition ptyalism was noted in all exposed groups. Scarring of the ears was noted in rats exposed at the intermediate and high dosage levels and was considered a consequence to excessive scratching. The scratching noted at all exposed groups was considered indirectly related to the irritant nature of deltamethrin but may also be due to the neurotoxic nature of the substance (a response to the effect of the substance on nerve endings resulting in pain sensation and consequently to excessive scratching).

	X11: Clinical signs of irritation were noted in rats at the dosage level of 3 mg/m^3 and above. Clear clinical signs of neurotoxicity were evident at 9.6 and 56 mg/m^3 At the lowest dosage level (3 mg/m^3) scratching was noted. This effect was considered to be related to the irritant nature of deltamethrin but may also be due to the neurotoxic nature of the substance. Statistically significant reduced bodyweight gain was noted in males in all treated groups.
Conclusion	The applicant's version is adopted with following amendments: X12: The LOAEL was 3 mg/m^3. X13: The NOAEL was not dermined in this study. No NOEL was determined in this study. Clinical signs (irritative and neurotoxic) were noted in animals in all treated groups. Statistically significant reduced bodyweight gain (>10%) was noted in males in all treated groups. In addition minor changes in biochemical parameters were noted in animals at the dosage level of 9.6 mg/m^3 and above, and organ weight changes were noted in animals at the highest dosage level of 56 mg/m^3. No NOAEL was determined in this study. The clinical signs and reduced bodyweight gain noted at the lowest dosage level (3 mg/m^3) and above was considered adverse effects. Scratching noted at all dosage levels was considered to be related to the irritant nature of deltamethrin but may also be due to the neurotoxic nature of the substance (a response to the effect of the substance on nerve endings).
Reliability	2
Acceptability	Acceptable. The deviations from OECD guideline no. 412 are considered not to compromise the scientific validity of the study.
Remarks	

6.4 Subchronic toxicity

6.4.1 Subchronic oral toxicity test

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1977) RU 22974 – Assessment of Toxicity to Rats by Oral Administration for 13 Weeks (followed by a 4-week withdrawal period) [redacted] Document A70872 6.4.1/01 21 March 1977 Unpublished See Monograph 91/414 from 1998 – Point B.5.3	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	Study follows OECD guideline 408	See remarks
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement, but was conducted in line with good scientific practice.	
2.3	**Deviations**	Highest dose level was too low.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	17	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	Not given	See remarks
3.1.2.3	Stability	Stable as stored at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	CD	
3.2.3	Source	Charles River Laboratories, UK	
3.2.4	Sex	Males and females	

3.2.5	Age/weight at study initiation	Weanlings Males: 152 – 153 g Females: 132 g	
3.2.6	Number of animals per group	20 of each sex	
3.2.7	Control animals	Yes. 20 of each sex.	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Duration of treatment	90 days	
3.3.2	Frequency of exposure	Daily	
3.3.3	Postexposure period	4 weeks	
3.3.4	**Oral**		
3.3.4.1	Type	Gavage	
3.3.4.2	Concentration	Gavage: 0.1, 1.0, 2.5, 10 mg/kg bw	X1
3.3.4.3	Vehicle	Polyethylene glycol	X2
3.3.4.4	Concentration in vehicle	Not reported	
3.3.4.5	Total volume applied	5 ml/kg for the first four weeks, 2.5 ml/kg thereafter.	
3.3.4.6	Controls	Vehicle only	
3.4	**Examinations**		
3.4.1	Observations		
3.4.1.1	Clinical signs	Yes; daily	
3.4.1.2	Mortality	Yes; daily	
3.4.2	Body weight	Yes; initially and then weekly	
3.4.3	Food consumption	Yes; recorded and mean weekly intake calculated	
3.4.4	Water consumption	Yes. Visual examination of the water bottles was maintained. Consumption for each cage in Groups 1 (Control) and 5 (10.0 mg/kg/day) was measured daily for a 5-day period during week 7, and consumption for each cage in Groups 1 (Control), 4 (2.5 mg/kg/day) and 5 (10.0 mg/kg/day) was measured daily for a 5-day period during week 12. In addition, consumption for each cage in all groups was measured daily for a 5-day period during week 8.	
3.4.5	Ophthalmoscopic examination	Yes; before treatment and at weeks 6 and 13 from controls and high dose (10.0 mg/kg)	

3.4.6	Haematology	Yes Number of animals: 10 males and 10 females from control and high dose Time points: weeks 0, 6 and 12 Parameters: Haematocrit, haemoglobin concentration, erythrocyte count, total and differential leukocyte count, platelet count, (week 12), thrombotest (week 12), mean corpuscular haemoglobin concentration (MCHC) and mean cell volume (MCV)	
3.4.7	Clinical chemistry	Yes Number of animals: 5 males and 5 females from controls and high dose Time points: weeks 6 and 12 Parameters: plasma urea, plasma glucose, total serum proteins, serum protein electrophoresis and AG ratio, serum alkaline phosphatase (SAP), serum glutamic, pyruvic transaminase, sodium, potassium	
3.4.8	Urinalysis	Yes Number of animals: 5 males and 5 females from controls and high dose Time points: weeks 6 and 12 Parameters: specific gravity, pH, protein, glucose, reducing substances, ketones, bile pigments, urobilinogen, haemoglobin, microscopy of spun particles	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes Organs: liver, kidneys, adrenals, testes, uterus, ovaries, spleen, brain, heart, thyroid, pituitary	
3.5.2	Gross and histopathology	Yes High dose group and controls Organs: brain, spinal cord, pituitary, thyroid, thymus, salivary glands, small and large intestines, liver, pancreas, kidneys, adrenals, spleen, heart, trachea, lungs, aorta, gonads, uterus, female mammary gland, prostate, urinary bladder, lymph nodes, peripheral nerve, skin, eyes, bone marrow, caecum, colon, duodenum, ileum, jejunum, oesophagus, ovaries, seminal vesicles, skeletal muscle, stomach, tongue	X3
3.5.3	Other examinations	Neurological examination (reflex tests) before treatment, and during week 6 and 13 from controls and high dose groups (10 mg/kg bw)	
3.5.4	Statistics	Student's "t" test	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	No overt signs of reaction to treatment were recorded although during the neurological examination at week 6 it was noted that some rats treated at 10.0 mg/kg/day were slightly hypersensitive when compared with the control rats. There was no evidence of hypersensitivity among these rats after 13 weeks of treatment.	

4.1.2	Mortality	During the first three weeks of the study, 4 control males, 1 male treated with 0.1 mg/kg/day, 4 males treated with 2.5 mg/kg/day, 1 male treated with 10.0 mg/kg/day and 4 females treated with 10.0 mg/kg/day died. Rats that died during the first 2 weeks of the study were replaced by rats of similar bodyweight selected from spare animals which had been receiving the appropriate dosage since the start of the study. One control male and 1 male recovery 2.5 mg/kg/day which died during week 3 were not replaced. The pathology common to the majority of these decedents was lung congestion. These deaths were not considered to be a direct result of treatment with deltamethrin, but possibly to be due to the vehicle polyethylene glycol 200 inadvertently entering the respiratory tract. The dosage volume of 5.0 ml/kg was reduced to 2.5 ml/kg at the end of week 4 and no more deaths occurred after this time.	
4.2	**Body weight gain**	Bodyweight gains among males receiving deltamethrin at 10.0, 2.5 or 1.0 mg/kg/day were lower than those of the controls throughout the treatment period, although the difference from the controls was only statistically significant for rats receiving 10.0 or 2.5 mg/kg/day. During the withdrawal period, the rate of bodyweight gain was marginally higher for males previously treated with deltamethrin when compared with the control value although the overall gains were similar for all groups previously treated with deltamethrin. Bodyweight gains among treated females were similar to those of the controls, during the treatment period. During the withdrawal period gains among females previously treated were similar or higher than those of the controls.	X4
4.3	**Food consumption and compound intake**	There was no evidence of a marked effect on food intake during the treatment period; all groups consumed within ± 5% of the control intake. During the withdrawal period, all males previously receiving deltamethrin consumed more food than the controls, and food consumption among females previously receiving 10.0, 2.5 or 1.0 mg/kg/day was higher than that of the controls.	
4.4	**Ophthalmoscopic examination**	Ophthalmoscopy performed during weeks 6 and 13 did not reveal any evidence of treatment-related ocular damage in rats receiving 10.0 mg/kg/day.	
4.5	**Blood analysis**		
4.5.1	Haematology	Investigation of haematological parameters for rats receiving 10.0 mg/kg/day after 6 and 12 weeks of treatment, revealed no evidence of treatment-related disturbance.	
4.5.2	Clinical chemistry	There was no evidence of a treatment-related effect on blood chemistry parameters measured for rats receiving 10.0 mg/kg/day after 6 and 12 weeks of treatment. The differences from control values which attained a level of statistical significance were considered to have arisen fortuitously and to be of no toxicological significance as all values were well within the accepted range for the strain of rat employed.	
4.5.3	Urinalysis	Urinalysis investigations performed during week 6 and 12 revealed similar values for controls and rats receiving 10.0 mg/kg/day.	

4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	There was no evidence of a treatment-related effect on the weight of any organ examined after treatment for 13 weeks. Similarly, following the withdrawal period, weights of organs examined from rats previously receiving deltamethrin were similar to those of the controls. Small differences which attained a level of statistical significance were considered to be due to intergroup disparity in bodyweight or to have arisen fortuitously and to be of no toxicological significance.	
4.6.2	Gross and histopathology	There was no evidence of any treatment-related macroscopic change seen in rats killed after 13 weeks of treatment or in rats killed at the end of the 4-week withdrawal period. No histopathological change or variation from normal was seen in the sections examined that were considered to be related to the administration of deltamethrin and consequently tissues from rats in the lower dosage groups, or from rats killed at the end of the 4-week withdrawal period were not examined histologically.	
4.7	**Other**		
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Deltamethrin (purity not specified) was administered by oral gavage as a solution in polyethylene glycol 200 (PEG 200) to groups (20 animals/sex/group) of CD rats (Sprague-Dawley) for 13 weeks at respective doses of 0.1, 1.0, 2.5 and 10 mg/kg bw/day. The control animals (20 animals/sex) received the vehicle only. Before treatment began, and during weeks 6 and 13, ten males and ten females from the control group and five rats from the highest dose level group were subjected to a neurological examination (segmental reflexes, postural reactions, locomotor system and general observations were studied). At termination of the study five males and five females from each group were observed for reversibility, persistence or delayed occurrence of toxic effects for a recovery period of 4 weeks.	
5.2	**Results and discussion**	There were no treatment-related deaths during the study. Slight hypersensitivity was noted in some female and male rats receiving 10 mg/kg bw/day at week 6. The behaviour of these rats was normal by week 13. Statistically significant lower body weight gain was noted in males receiving deltamethrin at doses of 2.5 and 10 mg/kg bw/day. During the recovery period, the rate of body weight gain among these rats was marginally higher than that of controls. There were no effects on parameters concerning haematology, clinical chemistry, urinalysis or ophthalmoscopy. There were no substance-related effects on any organ weights. Neurological examination did not give any indication of treatment-related interference with any reflexes. No substance-related gross- or microscopic changes were observed.	

5.3	**Conclusion**		
5.3.1	LO(A)EL	2.5 mg/kg bw/day (M) – 10 mg/kg bw/day (F)	X5
5.3.2	NOEL	1 mg/kg bw/day (M) – 2.5 mg/kg bw/day (F)	
5.3.3	Other	-	
5.3.4	Reliability	2	
5.3.5	Deficiencies	No	

Table A6.4.1-1 Group Mean Bodyweights (g) During Treatment Period

Weeks	Group 1 Control		Group 2 0.1 mg/kg/day		Group 3 1.0 mg/kg/day		Group 4 2.5 mg/kg/day		Group 5 10.0 mg/kg/day	
Number of animals examined	m	f	m	f	m	f	m	f	m	f
	20	20	20	20	20	20	20	20	20	20
0	152	132	152	132	153	132	152	132	152	132
1	213	168	214	167	214	170	215	172	206	172
2	265	192	264	186	263	193	264	195	260	195
3	313	208	312	206	313	213	310	215	302	216
4	354	231	352	226	351	232	347	235	341	232
5	392	247	388	239	385	248	380	257	373	250
6	417	262	420	257	414	263	405	269	395	265
7	441	269	440	265	434	269	429	274	421	269
8	465	276	457	270	452	276	447	284	439	277
9	483	285	482	274	469	284	466	295	459	288
10	503	291	498	281	483	289	482	300	475	292
11	520	296	514	291	497	296	492	303	488	297
12	533	304	531	300	512	305	504	310	499	303
13	540	303	538	299	517	302	509	310	504	302
Weight gain weeks 0 – 13	388	171	386	167	364	170	357*	178	352*	170

* $p < 0.05$ in comparison with control value

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted with following corrections: X1: Concentration: 0.1, 1.0, 2.5, 10 mg/kg bw/day (not 0.1, 1.0, 2.5, 10 mg/kg bw). X2: Vehicle: Polyethylene glycol 200 The applicant's version is adopted with following comment: X3: Aorta, colon, jejunum, mammary gland, salivary gland, seminal vesicle, second eye, skin, tongue and trachea were preserved but not processed further.
Results and discussion	X4: Statistically significant reductions in mean bodyweight gain were noted at 2.5 mg/kg bw/day and above in males. The reductions when compared to controls were 8% and 9% for the 2.5 and 10 mg/kg bw/day groups, respectively.
Conclusion	The applicant's version is adopted with following amendment: X5: LOAEL: 10 mg/kg bw/day (males and females). In this study clinical signs indicating neurotoxicity (hypersensitivity at week 6) were noted in male and female rats at the dosage level of 10 mg/kg bw/day, and statistically significant reduced bodyweight gain (<10%) was noted in males at the dosage levels of 2.5 and 10 mg/kg bw/day. The NOEL was determined at 1 and 2.5 mg/kg bw/day in males and females, respectively. The NOAEL was set at 2.5 mg/kg bw/day based on clinical signs indicating neurotoxicity noted in males and females at the dosage level of 10 mg/kg bw/day. The reduced bodyweight gain noted in males at the dosage level of 2.5 mg/kg bw/day and above was not considered adverse since the reductions were below 10%.
Reliability	2
Acceptability	Acceptable. The deviation from OECD guideline no. 408 is considered not to compromise the scientific validity of the study.
Remarks	The study was conducted before the requirements of the more recent OECD 408 guideline of 1998 and follows the previous version of OECD 408 guideline. The neurotoxicological examination used in the study was limited compared to the requirements of the more recent guideline. The highest dosage level used in the study was too low (indicated by the abscence of reduced bodyweight gain in females). However, higher dose levels were used in another rat study later performed (Ryle *et al.*, 1991a). The purity of the test substance was not specified in the study. However, the effects noted in the study were similar to the effects noted in another rat study later performed with sufficient purity (Ryle *et al.*, 1991a).

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1991a) Deltamethrin Toxicity Studies in Rats by Dietary Administration for 13 Weeks with a 4-Week Recovery Period [redacted] Document A70875 6.4.1/02 3 July 1991 Unpublished See Monograph 91/414 from 1998 – Point B.5.3	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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; OECD 408	See remarks
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	9N1239B2	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	Beige coloured powder	
3.1.2.2	Purity	98.9%	
3.1.2.3	Stability	Stable	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Crl:CD (SD) BR	
3.2.3	Source	Charles River Breeding Laboratories, USA	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	~ 1 month Males: ~ 20 g Females: ~ 15 g	X1
3.2.6	Number of animals per group	20 of each sex (with 10 of each sex held for a 4-week recovery); a satellite group of 5 animals of each sex was concurrently run	
3.2.7	Control animals	Yes. 20 of each sex with 10 of each sex held for a 4-week recovery for the initial 13-week study and the supplementary study	

3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	90 days with a 4-week recovery
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	4 weeks
3.3.4	**Oral**	
3.3.4.1	Type	In food
3.3.4.2	Concentration	Food – 0, 30, 300, 1000 (supplementary study), 3000 and 6000 ppm (corresponding to 0, 2, 24, 72, 241 and 425 mg/kg bw/day for males; and 0, 3, 30, 84, 272 and 444 mg/kg bw/day for females Food consumption per day *ad libitum*
3.3.4.3	Vehicle	None
3.3.4.4	Concentration in vehicle	Not applicable
3.3.4.5	Total volume applied	Not applicable
3.3.4.6	Controls	Plain diet
3.4	**Examinations**	
3.4.1	Observations	
3.4.1.1	Clinical signs	Yes; daily
3.4.1.2	Mortality	Yes; twice daily
3.4.2	Body weight	Yes; at assignment to test group, study initiation and then weekly
3.4.3	Food consumption	Yes; weekly
3.4.4	Water consumption	Yes; daily monitoring by visual appraisal; measurements week 1 for main study; weeks 1 and 12 for the supplementary study
3.4.5	Ophthalmoscopic examination	Yes; all at initiation; control and high dose groups at week 13
3.4.6	Haematology	Yes Number of animals: All surviving animals Time points: week 1 and end of study Parameters: Packed cell volume, haemoglobin, red cell count, mean corpuscular haemoglobin concentration, mean corpuscular volume, total white cell count, platelet count, differential WBC counts, cell morphology, thrombotest
3.4.7	Clinical chemistry	Yes Number of animals: All surviving animals Time points: week 1 and end of study Parameters: Total protein, albumin, globulin, urea nitrogen, creatinine, sodium, potassium, calcium, inorganic phosphorus, chloride, total cholesterol, alkaline phosphatase, total bilirubin, glucose, glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase

3.4.8	Urinalysis	Yes Number of animals: All surviving animals Time points: end of study or other Parameters: Volume, pH, specific gravity, protein, glucose, ketones, bile pigments, urobilinogen, haem pigments, epithelial cells, polymorphonuclear leucocytes, mononuclear leucocytes, erythrocytes, organisms, renal tubule casts, sperm, other abnormal constituents	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes Organs: liver, kidneys, adrenals, testes, uterus, ovaries, spleen, brain, heart, thyroid, pituitary	
3.5.2	Gross and histopathology	Yes All dose groups Organs: brain, spinal cord, pituitary, thyroid, parathyroid, thymus, oesophagus, salivary glands, stomach, small and large intestines, liver, pancreas, kidneys, adrenals, spleen, heart, trachea, lungs, aorta, gonads, uterus, female mammary gland, prostate, urinary bladder, lymph nodes, peripheral nerve, bone marrow, skin, eyes, tongue, vagina, harderian gland head, seminal vesicles, skeletal muscle, ovaries, larynx, pharynx, femur	X2 X3
3.5.3	Other examinations	Neurological examination (reflex tests)	
3.5.4	Statistics	All statistical analyses were carried out separately for males and females. Data relating to food and water consumption were analysed on a cage basis. For all other parameters, the analyses were carried out using the individual animal as the basic experimental unit. Food consumption data were analysed using cumulative cage totals, and water consumption data were analysed as the total recorded intake over selected time periods. Bodyweight data were analysed using weight gains. A series of statistical analyses (Bartlett's test, ANOVA, Student's 't' test, Williams' test, Kruskal-Wallis and Shirley's test) were used.	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	Animals treated at 1000 ppm showed uncoordinated movement, unsteady gait, hunched posture, increased sensitivity to sound, piloerection, dark extremities and emaciated appearance. Body tremors, "wet dog shakes", spasmodic convulsions, semi-closed eyes, poor grooming, subdued behaviour, wet urogenital fur and emaciation were additionally noted in animals treated at 3000 and 6000 ppm. The incidence and severity of the clinical signs among animals receiving 1000 ppm declined from week 3 of treatment and, on the whole were no longer apparent after 8 weeks of treatment. No clinical signs considered to be related to previous treatment were noted during the recovery period in both studies.	

4.1.2	Mortality	All rats receiving 3000 or 6000 ppm, and 3 rats (2 females and 1 male) receiving 1000 ppm were either found dead or killed in extremis due to severe reaction to treatment during the first 3 weeks of compound administration.	
4.2	**Body weight gain**	Statistically significant reduced body weights were noted for males and females receiving 3000 and 6000 ppm. Statistically significant reduced bodyweight gain was noted for females receiving 30 and 300 ppm, and for males and females receiving 1000 ppm. During the recovery period, bodyweight gain was marginally greater for animals previously treated with 1000 ppm deltamethrin in comparison with concurrent controls.	X4
4.3	**Food consumption and compound intake**	Food consumption and water intake was statistically significantly reduced for animals receiving 1000, 3000 and 6000 ppm. During the recovery period food consumption for females previously treated with 1000 ppm deltamethrin was marginally greater than that of concurrent controls, and food intake for males previously treated at this same dosage level became similar to that of controls.	
4.4	**Ophthalmoscopic examination**	No treatment-related effects.	
4.5	**Blood analysis**		
4.5.1	Haematology	No treatment-related effects.	
4.5.2	Clinical chemistry	No treatment-related effects.	
4.5.3	Urinalysis	No treatment-related effects.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	No treatment-related effects.	
4.6.2	Gross and histopathology	No treatment-related effects.	
4.7	**Other**	-	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Deltamethrin (purity 98.9%) was administered by admixture with the diet to rats of the Crl:CD (SD) BR strain (20 animals/sex/group) at concentrations of 30, 300, 3000 and 6000 ppm for 13 weeks. The concentrations corresponded to a dose rate of 2, 24,241 and 425 mg/kg bw/day for males, and 3, 30, 272 and 444 mg/kg bw/day for females. The control animals (20 animals/sex) received the feed only. A supplementary study (20 animals/sex/group) was commenced at a dietary inclusion level of 0 and 1000 ppm following premature sacrifice of rats receiving 3000 and 6000 ppm due to severe reaction to treatment in the initial study. The concentrations corresponded to 0 and 72 mg/kg bw/day for males, and 0 and 84 mg/kg bw/day for females. Selected animals (10 rats/sex/group) from the initial and supplementary study groups were retained for a further 4-week recovery period and given untreated diet.	

5.2	**Results and discussion**	All rats receiving 3000 or 6000 ppm, and 3 rats (2 females and 1 male) receiving 1000 ppm were either found dead or killed in extremis due to severe reaction to treatment during the first 3 weeks of treatment. Animals treated at 1000 ppm showed uncoordinated movement, unsteady gait, hunched posture, increased sensitivity to sound, piloerection, dark extremities and emaciated appearance. Body tremors, "wet dog shakes", spasmodic convulsions, semi-closed eyes, poor grooming, subdued behaviour, wet urogenital fur and emaciation were additionally noted in animals treated at 3000 and 6000 ppm. The incidence and severity of the clinical signs among animals receiving 1000 ppm declined from week 3 of treatment and, on the whole were no longer apparent after 8 weeks of treatment. No clinical signs considered to be related to previous treatment were noted during the recovery period in both studies. Statistically significant reduced body weights were noted for males and females receiving 3000 and 6000 ppm. Statistically significant reduced bodyweight gain was noted for females receiving 30 and 300 ppm, and for males and females receiving 1000 ppm. During the recovery period, bodyweight gain was marginally greater for animals previously treated with 1000 ppm deltamethrin in comparison with concurrent controls. Food consumption and water intake was statistically significantly reduced for animals receiving 1000, 3000 and 6000 ppm. During the recovery period food consumption for females previously treated with 1000 ppm deltamethrin was marginally greater than that of concurrent controls, and food intake for males previously treated at this same dosage level became similar to that of controls. There were no treatment-related effects concerning ophthalmoscopy, haematology, biochemistry or urinalysis parameters. There were no substance-related effects on any organ weights. No substance-related gross- or microscopic changes were observed. No NOEL was determined for females in this study due to reduced body weight gain in females receiving deltamethrin at 30 ppm. Additionally, deaths, clinical signs (poor clinical condition and neurological disturbances), reduced food consumption and decreased water intake were noted in females receiving deltamethrin at 1000 ppm. The NOEL for male rats was 300 ppm based on death, clinical signs (poor clinical condition and neurological disturbances), reduced body weight gain, decreased food consumption and decreased water intake noted in males receiving deltamethrin at 1000 ppm.	
5.3	**Conclusion**		
5.3.1	LO(A)EL	30 ppm in females	
5.3.2	NOEL	300 ppm in males	X5
5.3.3	Other	-	
5.3.4	Reliability	1	
5.3.5	Deficiencies	No	

Table A6.4.1-2 Incidence of Principal Clinical Signs

Group	Control		30 ppm		300 ppm		1000 ppm		3000 ppm		6000 ppm	
	m	f	m	f	m	f	m	f	m	f	m	f
No. of rats/group	40	40	20	20	20	20	20	20	20	20	20	20
Uncoordinated movement	-	-	-	-	-	-	19	18	20	19	20	20
Unsteady gait	-	-	-	-	-	-	13	7	19	15	20	20
Hunched posture	-	-	-	-	-	-	12	13	16	14	19	18
"Wet dog" shakes	-	-	-	-	-	-	-	-	2	-	1	-
Increased sensitivity to sound	-	-	-	-	-	-	14	10	16	13	20	15
Gasping	-	-	-	-	-	-	-	-	2	-	5	2
Body tremors	-	-	-	-	-	-	-	-	5	-	5	3
"Shuffling" on abdomen	-	-	-	-	-	-	-	-	1	-	9	6
Pilo-erection	-	-	-	-	-	1	13	8	8	11	12	19
Spasmodic convulsion	-	-	-	-	-	-	-	-	-	-	6	3
Wet urogenital fur	-	-	-	-	-	-	1	2	-	9	-	12
Poor grooming	-	-	-	-	-	-	1	1	1	4	2	14
Dark extremities	-	-	-	-	-	-	8	-	-	-	-	-
Pale extremities	-	-	-	-	-	-	-	-	1	-	-	-
Subdued behaviour	-	-	-	-	-	-	2	-	-	-	-	-
Increased grooming	-	-	-	-	-	-	3	2	-	-	1	-
Emaciation	-	-	-	-	-	-	4	3	1	2	-	-
Semi-closed eyes	-	-	-	-	-	-	-	1	-	-	11	3

Table A6.4.1-3 Group Mean Bodyweight Gain (g/rat)

Group	Control (Initial study)		Control (Supplem. Study)		30 ppm		300 ppm		1000 ppm (Supplem. Study)		3000 ppm		6000 ppm	
Weeks	m	f	m	f	m	f	m	f	m	f	m	f	m	f
0 – 1	54.9	32.8	60.4	34.9	53.5	27.9†	52.6	27.8†	-2.8§	2.9§	-12.6‡	-2.3‡	-24.6‡	-16.3‡
SD	8.2	7.1	11.1	13.5	8.9	6.0	8.8	4.6	14.5	8.0	12.0	7.5	7.5	5.8
0 – 2	104.6	58.3	111.9	59.5	106.4	49.9	106.1	53.1	21.9§	16.8§	5.5‡	8.1‡	-	-
SD	18.6	12.0	16.7	12.9	15.8	8.7	14.0	8.4	27.3	14.8	18.4	12.8		
% of control	-	-	-		102	86	101	91	20	28	5	14		
0 – 13	389.2	173.9	358.4	164.5	366.2	156.0†	401.8	152.3‡	288.0§	143.2§	-	-	-	-
SD	62.1	19.1	58.8	18.9	52.9	26.1	54.5	18.0	62.8	25.3				
% of control	-	-	-		94	90	103	88	80	87				
13 – 17	30.4	5.9	18.3	3.7	16.9	5.9	26.3	9.1	24.7	8.5	-	-	-	-
SD	12.8	12.4	9.2	9.7	7.1	2.9	9.0	5.9	14.8	5.7				

SD = Standard deviation
Kruskal Wallis analysis of mean ranks applied to female data Weeks 13 – 17
Level of significance in comparison with controls:
† = p<0.05 (Williams's test)
‡ = p<0.01 (Williams' test)
§ = p<0.01 (Student's 't' test)

Table A6.4.1-4 Mean Cumulative Food Intake (g/rat)

Group	Control (Initial study)		Control (Supplem. Study)		30 ppm		300 ppm		1000 ppm (Supplem. Study)		3000 ppm		6000 ppm	
Weeks	m	f	m	f	m	f	m	f	m	f	m	f	m	f
1	200	153	216	150	190	145	192	148	79§	81§	83‡	79‡	78‡	67‡
SD	9.9	11.0	17.7	6.4	18.8	8.6	9.9	6.6	2.8	5.4	12.6	6.3	9.1	4.0
% of control	-	-	-	-	95	95	96	97	37	54	42	52	39	44
1 – 13	2742	2027	2650	1988	2627	1882	2775	2132	2116§	1739¤	-	-	-	-
SD	149.0	193.4	56.2	135.7	99.2	141.2	92.3	149.5	88.2	81.0				
% of control	-	-	-	-	96	93	101	105	80	87				
14 – 17	803	556	765	613	738	640	870	564	726	681	-	-	-	-
SD	7.1	25.5	15.8	29.8	55.7	58.7	41.3	13.0	36.8	140.0				

SD = Standard deviation
Level of significance in comparison with controls: ‡ = p<0.01 (Williams' test)
¤ = p<0.05 (Student's 't' test)
§ = p<0.01

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted with following comments: X1: At the start of treatment the animals were approximately 6 weeks old and the weight (g) ranged from 138-193 for males and 115-153 for females. X2: Histopathological examination was performed only on the supplementary study (control animals and 1000 ppm group animals). X3: Hardian gland, head, larynx, pharynx and tongue were preserved but not processed further.
Results and discussion	The applicant's version is adopted with following comments: X4: Statistically significant reductions in mean bodyweight gain were noted in males at 1000 ppm (20%), and in females at 30 ppm (10%), 300 ppm (12%), 1000 ppm (13%) and above. Reduced bodyweight gain was also noted in males and females at 3000 ppm (weeks 0-2: 95% in males, 86% in females). At 6000 ppm group mean bw gain at week 0-1 was -25 g/rat for males and -16 g/rat for females. Table A6.4.1-4: Level of significance in comparison with controls: §=p<0.01 (student's 't' test). The applicant's version is adopted with following correction: Table A6.4.1-2: At the dosage level of 300 ppm one male showed clinical signs of pilo-erection (not one female).
Conclusion	The applicant's version is adopted with following amendment: X5: No NOEL was determined for females. In this study mortalities, clinical signs (poor clinical condition and neurotoxic effects), reduced bodyweight gain, reduced food consumption and decreased water intake were noted in males and females at 1000 ppm and above. Reduced bodyweight gain was also noted in females at 30 and 300 ppm. The NOEL in male rats was set at 300 ppm. The NOAEL in males was set at 300 ppm based on mortality, clinical signs (poor condition and neurotoxic effects) and reduced bodyweight gain (>10%) noted at 1000 ppm and above. No NOEL was determined for females. The NOAEL for females was set at 30 ppm based on reduced bodyweight gain (>10%) noted at 300 ppm and above, and mortalities and clinical signs (poor condition and neurotoxic effects) noted at 1000 ppm and above.
Reliability	1
Acceptability	Acceptable.
Remarks	The study was conducted before the requirements of the more recent OECD 408 guideline of 1998 and follows the previous version of OECD 408 guideline. The neurotoxicological examination recommended in the more recent OECD guideline 408 was not performed in this study.

			Official use only
		1. REFERENCE	
1.1	**Reference**	[redacted] (1977) RU 22974 Oral Toxicity Study in Beagle Dogs (Repeated dosage for 13 weeks followed by a 20-week observation period) [redacted] Document A70871 6.4.1/03 9 June 1977 Unpublished See Monograph 91/414 from 1998 – Point B.5.3	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Bayer CropScience AG	
1.2.2	Companies with letter of access	n.a.	
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**	Study follows OECD guideline 409	See remarks
2.2	**GLP**	No, the study was conducted prior to the introduction of GLP as a standard requirement, but was conducted in line with good scientific practice.	
2.3	**Deviations**	Low number of animals in control- and low level dosage groups.	
		3. MATERIALS AND METHODS	
3.1	**Test material**	Deltamethrin	
3.1.1	Lot/Batch number	Lot 17	
3.1.2	Specification	As given in Section 2	
3.1.2.1	Description	White powder	
3.1.2.2	Purity	Not given	See remarks
3.1.2.3	Stability	Not specified but deltamethrin is not known to decompose at room temperature	
3.2	**Test Animals**		
3.2.1	Species	Dog	
3.2.2	Strain	Pure-bred Beagle	
3.2.3	Source	E G Crowley, UK; Olac Ltd, UK; or laboratory breeding stock	
3.2.4	Sex	Males and females	
3.2.5	Age/weight at study initiation	Age: Males: 17 – 37 weeks Females: 17 – 35 weeks Weight: Males: 7.5 – 10.3 kg Females: 5.8 – 9.5 kg	

3.2.6	Number of animals per group	Three of each sex for the low dose group Five of each sex for all other dose groups.	
3.2.7	Control animals	Yes. Three of each sex	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Duration of treatment	90 days	
3.3.2	Frequency of exposure	Daily	
3.3.3	Postexposure period	20 weeks	
3.3.4	**Oral**		
3.3.4.1	Type	In gelatine capsules	
3.3.4.2	Concentration	0, 0.1, 1.0, 2.5, 10.0 mg/kg/day	
3.3.4.3	Vehicle	Polyethylene glycol €200 (PEG 200)	
3.3.4.4	Concentration in vehicle	Not reported	
3.3.4.5	Total volume applied	0.2 ml/kg	
3.3.4.6	Controls	Gelatin capsules only with PEG 200.	
3.4	**Examinations**		
3.4.1	Observations		
3.4.1.1	Clinical signs	Yes; daily	
3.4.1.2	Mortality	Yes; daily	
3.4.2	Body weight	Yes; weekly	
3.4.3	Food consumption	Yes; daily	
3.4.4	Water consumption	Yes; at intervals	
3.4.5	Ophthalmoscopic examination	Yes; at initiation and at weeks 5 and 12 (dosing) and weeks 5 and 18 (recovery)	
3.4.6	Haematology	Yes Number of animals: All surviving animals Time points: before initiation and at weeks 6 and 12 (dosing) and weeks 5 and 16 (recovery) Parameters: Erythrocyte sedimentation rate (ESR), packed cell volume (PCV), haemoglobin, red cell count, reticulocyte count, mean corpuscular haemoglobin concentration, mean cell volume, total white cell count, platelet count, prothrombin index	
3.4.7	Clinical chemistry	Yes Number of animals: All surviving animals Time points: before initiation, weeks 6 and 12 of dosing, weeks 5 and 16 of recovery Parameters: Plasma urea, plasma glucose, total serum proteins, serum protein electrophoresis and AG ratio, serum alkaline phosphatase, serum glutamic – pyruvic transaminase, serum glutamic oxaloacetic transaminase, serum bilirubin, sodium, potassium	

3.4.8	Urinalysis	Yes Number of animals: All surviving animals Time points: before initiation, weeks 6 and 12 of dosing, weeks 5 and 16 of recovery Parameters: pH, protein, reducing substances, glucose, ketones, bile pigments, urobilinogen, haemoglobin, epithelial cells, polymorphonuclear leucocytes, mononuclear leucocytes, erythrocytes, organisms, casts, abnormal constituents	
3.5	**Sacrifice and pathology**		
3.5.1	Organ weights	Yes Organs: liver, kidneys, adrenals, testes, uterus, prostate, thymus, spleen, brain + spinal cord, heart, thyroids, pancreas, lungs, pituitary	
3.5.2	Gross and histopathology	Yes All surviving animals Organs: brain, spinal cord, pituitary, thyroid, parathyroid, thymus, oesophagus, salivary glands, stomach, small and large intestines, liver, pancreas, kidneys, adrenals, spleen, heart, trachea, lungs, aorta, gonads, uterus, female mammary gland, prostate, urinary bladder, gall baldder, lymph nodes, peripheral nerve, bone marrow, skin, eyes, tongue, skeletal muscle	X1
3.5.3	Other examinations	Neurological examination at initiation and on weeks 6 and 12 (dosing) and weeks 5, 8, 12, 15 and 18 (recovery). EEG recordings taken.	X2
3.5.4	Statistics	Student's 't' test, described by the grand mean range (95% range)	
3.6	**Further remarks**	-	
		4. RESULTS AND DISCUSSION	
4.1	**Observations**		
4.1.1	Clinical signs	Unsteadiness, body tremors, jerking movements, vomiting and excessive salivation were noted in male and female dogs receiving 10 mg/kg bw/day. Liquid faeces were noted in all groups but occurred more frequently at dose levels of 2.5 and 10 mg/kg bw/day. Signs of dilation of the pupils were also seen in male and female dogs receiving 2.5 and 10 mg/kg bw/day. After the cessation of dosing, the only clinical sign observed was isolated incidences of liquid faeces in all recovery groups.	X3
4.1.2	Mortality	There were no deaths during the study.	
4.2	**Body weight gain**	Statistically significant decreased body weight gain and improvement in appetite were noted during the first 1 – 2 weeks of dosing in most animals receiving 10 mg/kg bw/day. During the recovery period the changes in body weight and food consumption remained similar to that established during the dosing period.	X4
4.3	**Food consumption and compound intake**	See Point 4.2.	
4.4	**Ophthalmoscopic examination**	No treatment-related effects.	

4.5	**Blood analysis**		
4.5.1	Haematology	No treatment-related effects.	
4.5.2	Clinical chemistry	No treatment-related effects.	
4.5.3	Urinalysis	No treatment-related effects.	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	No treatment-related effects.	
4.6.2	Gross and histopathology	No treatment-related effects.	
4.7	**Other**	The neurological examination showed effects upon the gag reflex (depression), the patellar reflex (hyperactivity or depression) and flexor reflex (depression). Qualitatively similar findings were also noted among the control animals. The incidence was increased among treated animals compared to the controls, although no clear dose effect could be established. The incidence was higher at the beginning of the study compared to the latter part. By the end of the recovery period, some dogs from the low level dosage groups continued to show depression of the patellar- and the gag reflex, but none of these animals were from the high dosage level groups. One dog that had received 10 mg/kg bw/day still showed depression of the flexor reflex at the end of the recovery period. The neurological changes seen in the remaining dogs had been reversed following cessation of dosing. Electroencephalograms (EEG) showed abnormal patterns in some dogs receiving 2.5 or 10 mg/kg bw/day. These abnormalities were confined almost exclusively to the occipital leads and showed persistent high amplitude, fast frequencies, often with spikes. After 5 weeks recovery one animal which had received 10 mg/kg bw/day showed abnormal spiking in all leads. No other abnormalities were seen in any recovery animals.	
		5. APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Deltamethrin (purity not specified) dissolved in polyethylene glycol (PEG) 200 was administered orally (by gelatine capsule) to groups of 17 to 37 week old beagle dogs (the control and low level dose groups contained 3 male and 3 female dogs, and the remaining three groups consisted of 5 male and 5 female dogs) for 13 weeks with a recovery period for 2 male and 2 female dogs from the three highest dosage groups to a total of 20 weeks. The dose levels were 0 (vehicle control), 0.1, 1.0, 2.5 and 10 mg/kg bw/day. Neurological examinations were conducted on all dogs before dosing commenced, after 5 weeks dosing and after 12 weeks dosing. Animals which remained undosed were examined during the recovery period.	
5.2	**Results and discussion**	There were no deaths during the study. Unsteadiness, body tremors, jerking movements, vomiting and excessive salivation were noted in male and female dogs receiving 10 mg/kg bw/day. Liquid faeces were noted in all groups but occurred more frequently at dose levels of 2.5 and 10 mg/kg bw/day. Signs of dilation of the pupils were also seen in male and female dogs receiving 2.5 and 10 mg/kg bw/day. After the cessation of dosing, the only clinical sign observed was isolated incidences of liquid faeces in all recovery groups.	

	Statistically significant decreased body weight gain and improvement in appetite were noted during the first 1 – 2 weeks of dosing in most animals receiving 10 mg/kg bw/day. During the recovery period the changes in body weight and food consumption remained similar to that established during the dosing period. The neurological examination showed effects upon the gag reflex (depression), the patellar reflex (hyperactivity or depression) and flexor reflex (depression). Qualitatively similar findings were also noted among the control animals. The incidence was increased among treated animals compared to the controls, although no clear dose effect could be established. The incidence was higher at the beginning of the study compared to the latter part. By the end of the recovery period, some dogs from the low level dosage groups continued to show depression of the patellar- and the gag reflex, but none of these animals were from the high dosage level groups. One dog that had received 10 mg/kg bw/day still showed depression of the flexor reflex at the end of the recovery period. The neurological changes seen in the remaining dogs had been reversed following cessation of dosing. Electroencephalograms (EEG) showed abnormal patterns in some dogs receiving 2.5 or 10 mg/kg bw/day. These abnormalities were confined almost exclusively to the occipital leads and showed persistent high amplitude, fast frequencies, often with spikes. After 5 weeks recovery one animal which had received 10 mg/kg bw/day showed abnormal spiking in all leads. No other abnormalities were seen in any recovery animals. There were no treatment-related effects on parameters concerning haematology, biochemistry, urinalysis or ophthalmoscopy. There were no treatment-related effects on any organ weights. No treatment-related gross or microscopic changes were detected in the nervous system of any dog. The NOEL was 1 mg/kg bw/day for male and female dogs based on liquid faeces and dilation of the pupils noted in animals receiving deltamethrin at 2.5 mg/kg bw/day. Additionally, clinical signs (neurological effects), decreased body weight gain and decreased food consumption were noted at 10 mg/kg bw/day. The relevance of the effects upon segmental reflexes were considered equivocal and of minor toxicological importance due to the fact that the incidence and the variable response in the dog study as well as the absence of a control recovery group makes it difficult to clearly deem them as primary findings induced by the treatment. The overall effects upon the general condition may at least partly play a roll. Furthermore, it was impossible to repeat the findings in a later study performed on dogs where the dose levels were equal or higher compared to this study (see Ryle *et al.*, 1991b). The relevance of the effects upon the EEG alterations were also considered equivocal and of minor toxicological importance. They must not necessarily be considered as direct cerebral or cerebellar effects but may as well be secondary to an increase in peripheral muscular tonic activity. There were no clinical signs attributable to these changes and the extensive histomorphological investigation of the brain and upper spinal cord showed no abnormal findings.	

5.3	**Conclusion**		
5.3.1	LO(A)EL	2.5 mg/kg bw/day (M & F)	
5.3.2	NOEL	1.0 mg/kg bw/day (M & F)	
5.3.3	Other	-	
5.3.4	Reliability	1	
.3.5	Deficiencies	No	

EVALUATION BY COMPETENT AUTHORITIES	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	Not relevant.
Materials and methods	The applicant's version is adopted with following comments: X1: It is not specified in the study if the parathyroid was examined. X2: Neurological examination was performed on all dogs at initiation and on weeks 5 and 12 (dosing). Two male and two female dogs from the groups that had previously received 1.0, 2.5 or 10 mg/kg bw/day were retained for a 20-week period. These dogs were subjected to a full neurological examination after a recovery period of 5, 8, 12, 15 and 18 weeks. EEG's were recorded for all animals at initiation and after 12 weeks dosing. Recordings were again taken from all the recovery animals after 5 weeks and 17 weeks recovery.
Results and discussion	The applicant's version is adopted with following comments: X3: Dilation of pupils was noted in the beginning of week 2 (not looked for during week 1). The sign was first seen 4-7 hrs after dosing and persisted throughout the day. The pupils of the dogs reacted normally prior to dosing on the following day. X4: Statistically significant reduction in mean bodyweight gain was noted for animals of the 10 mg/kg bw/day dosage group. The reduction (week 0-2) when compared to controls was 74% (males and females combined).
Conclusion	The applicant's version is adopted. In this study clinical signs (neurotoxic and gastrointestinal effects) were noted in males and females at the dosage level of 2.5 mg/kg bw/day and above. Statistically significant reduced bodyweight gain (in both sexes at 10 mg/kg bw/day) and reduced food consumption (in both sexes at 10 mg/kg bw/day) was also noted. The neurological examination showed effects upon segmental reflexes (incidence was increased among treated animals compared to control animals) and the EEG (abnormal pattern in some dogs receiving 2.5 or 10 mg/kg bw/day). The relevance of these effects was considered equivocal and of minor toxicological importance. The NOEL was determined for both sexes at 1 mg/kg bw/day. The NOAEL was determined for both sexes at 1 mg/kg bw/day based on clinical signs (dilation of pupils indicating neurotoxic effects) noted at the dosage level of 2.5 mg/kg bw/day and above, and reduced bodyweight gain noted at the dosage level of 10 mg/kg bw/day.
Reliability	2
Acceptability	Acceptable. The deviations from OECD guideline 409 are considered not to compromise the scientific validity of the study.
Remarks	The study was conducted before the requirements of the more recent OECD 409 guideline of 1998 and follows the previous version of OECD 409 guideline. The more recent OECD guideline 409 recommends an additional satellite group of 8 animals (4 per sex) in control and in top dose group for observation after the treatment period of reversibility or persistence of any toxic effects. In this study 2 animals of both sexes only from the groups receiving 1.0, 2.5, and 10.0 mg/kg bw/day were used for recovery observations.