Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonized classification and labelling at EU level of

2,3,5,6-tetrafluoro-4-methylbenzyl (1*RS*,3*RS*)-3-[(*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate; Tefluthrin (ISO)

EC number: -

CAS number: 79538-32-2

CLH-O-0000001412-86-61/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

5 June 2015

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Tefluthrin (ISO);

2,3,5,6-tetrafluoro-4-methylbenzyl (1RS,3RS)-3-[(Z)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate

EC Number: -

CAS Number: 79538-32-2

Index Number: -

Contact details for dossier submitter:

BAuA
Federal Institute for Occupational Safety and Health
Federal Office for Chemicals
Friedrich-Henkel-Weg 1-25
D-44149 Dortmund, Germany

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Part A.

Part B.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Tefluthrin*** ***(ISO; 2,3,5,6-tetrafluoro-4-methylbenzyl (1RS,3RS)-3-[(Z)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate***
EC number:	-
CAS number:	***79538-32-2***
Annex VI Index number:	-
Degree of purity:	***>92.0% w/w***
Impurities:	***see confidential part***

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation
Current entry in Annex VI, CLP Regulation	-
Current proposal for consideration by RAC	Acute Tox 2; H310 Acute Tox 1; H330 Acute Tox 2; H300 STOT-RE 1; H372 (nervous system) Aquatic Acute 1; H400 Aquatic Chronic 1; H410 M-acute = 10000 M-chronic = 10000
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox 2; H310 Acute Tox 1; H330 Acute Tox 2; H300 STOT-RE 1; H372 (nervous system) Aquatic Acute 1; H400 Aquatic Chronic 1; H410 M-acute = 10000 M-chronic = 10000

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	none		none	Data conclusive but not sufficient for classification
2.2.	Flammable gases	none		none	Data conclusive but not sufficient for classification
2.3.	Flammable aerosols	none		none	Data conclusive but not sufficient for classification
2.4.	Oxidising gases	none		none	Data conclusive but not sufficient for classification
2.5.	Gases under pressure	none		none	Data conclusive but not sufficient for classification
2.6.	Flammable liquids	none		none	Data conclusive but not sufficient for classification
2.7.	Flammable solids	none		none	Data conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	none		none	Data conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	none		none	Data conclusive but not sufficient for classification
2.10.	Pyrophoric solids	none		none	Data conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	none		none	Data conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	none		none	Data conclusive but not sufficient for classification
2.13.	Oxidising liquids	none		none	Data conclusive but not sufficient for classification
2.14.	Oxidising solids	none		none	Data conclusive but not sufficient for classification
2.15.	Organic peroxides	none		none	Data conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	none		none	Data conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	Acute Tox. 2; H300		none	
	Acute toxicity - dermal	Acute Tox. 2; H310		none	
	Acute toxicity - inhalation	Acute Tox. 1; H330		none	

3.2.	Skin corrosion / irritation	none		none	Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	none		none	Conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	none		none	Data lacking
3.4.	Skin sensitisation	none		none	Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	none		none	Conclusive but not sufficient for classification
3.6.	Carcinogenicity	none		none	Conclusive but not sufficient for classification
3.7.	Reproductive toxicity	none		none	Conclusive but not sufficient for classification
3.8.	Specific target organ toxicity – single exposure	none		none	Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	STOT RE 1; H372 (nevous system)		none	
3.10.	Aspiration hazard	none		none	Data lacking
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1; H400 Aquatic Chronic 1; H410	M-acute = 10000 M-chronic = 10000	none	
5.1.	Hazardous to the ozone layer	none		none	Data lacking

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Table 4: Proposed labelling based according to the CLP Regulation

	Labelling	Wording
Pictograms	GHS06 GHS08 GHS09	
Signal Word	Danger	
Hazard statements	H300 H310 H330 H372 H410	Fatal if swallowed Fatal in contact with skin Fatal if inhaled Causes damage to organs (nervous system) through prolonged or repeated exposure Very toxic to aquatic life with long lasting effects
Suppl. Hazard statements	-	-
Precautionary statements	(P102) P271 P273 P280 P284 P301 + P310 + P330 P302 + P350 + P310 P362 P391 P405 P501	(Keep out of reach of children) Use only outdoors or in a well-ventilated area Avoid release to the environment Wear protective gloves/ protective clothing Wear respiratory protection IF SWALLOWED: Immediately call a POISON CENTER or doctor/physician. Rinse mouth IF ON SKIN: Gently wash with plenty of soap and water. Immediately call a POISON CENTER or doctor/physician Take off contaminated clothing and wash before reuse Collect spillage Store locked up Dispose of contents/container to …

Proposed notes assigned to an entry:

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

No previous classification.

2.2 Short summary of the scientific justification for the CLH proposal

Considering the reported findings in the relevant toxicological studies, a classification of the technical material as acute toxic if swallowed, in contact with skin and if inhaled (Acute Tox. 2; H300, Acute Tox. 2; H310, Acute Tox. 1; H330) and based on neurotoxic effects as specific organ toxic (STOT RE 1; H372) is proposed. For the other toxicological hazards, either the data were conclusive but not sufficient for classification or the relevant data were lacking. For aquatic ecotoxicological endpoints there is a need for classification as very toxic to aquatic life with long lasting effects for acute (Aquatic Acute 1; H400) and chronic (Aquatic Chronic 1; H410) endpoints and to fix acute and chronic M-factors.

2.3 Current harmonised classification and labelling

No current harmonised classification and labelling in Annex VI of CLP.

2.4 Current self-classification and labelling*)

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Number of Notifiers
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)			
Acute Tox. 2	H300	H300		GHS06			45
Acute Tox. 2	H310	H310		GHS09			
Acute Tox. 1	H330	H330		Dgr			
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					
Acute Tox. 2	H300	H300		GHS06			23
Acute Tox. 2	H310	H310		GHS09			
Acute Tox. 3	H331	H331		Dgr			
Aquatic Acute 1	H400	H400					
Acute Tox. 2	H300	H300		GHS06	M(Chronic)=100		6
Acute Tox. 2	H310	H310		GHS09			
Eye Dam. 1	H318	H318		GHS05			
Acute Tox. 1	H330	H330		GHS08			
STOT RE 2	H373	H373		Dgr			
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					
Acute Tox. 2	H300	H300		GHS06			3
Acute Tox. 3	H311	H311		Dgr			
Acute Tox. 2	H330	H330					

*) *http://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/cl-inventory/view-notification-summary/93193 (July 2014)*

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Tefluthrin is an active substance in the meaning of Regulation (EC) No. 1107/2009 (replaces Directive 91/414/EEC) meaning all hazard classes are subject to harmonised classification at Community level and no other justification is needed.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

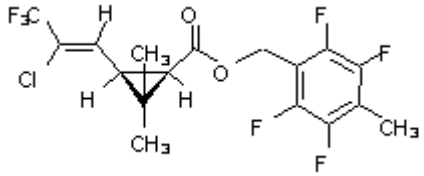
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

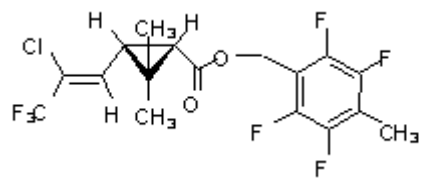
Table 5: Substance identity

EC number:	-
EC name:	-
CAS number (EC inventory):	-
CAS number:	79538-32-2
CAS name:	Cyclopropanecarboxylic acid, 3-[(1Z)-2-chloro-3,3,3-trifluoro-1-propen-1-yl]-2,2-dimethyl-, (2,3,5,6-tetrafluoro-4-methylphenyl)methyl ester, (1R,3R)-rel-
IUPAC name:	2,3,5,6-tetrafluoro-4-methylbenzyl (1RS,3RS)-3-[(Z)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate
CLP Annex VI Index number:	-
Molecular formula:	$C_{17}H_{14}ClF_7O_2$
Molecular weight range:	418.73 g/mol

Structural formula:



Z-(1 *R*, 3 *R*)



Z-(1 *S*, 3 *S*)

1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Tefluthrin		≥ 920 g/kg	

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Impurities	See confidential annex		

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks

1.2.1 Composition of test material

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	solid	Walter, 2001	visual
Melting/freezing point	44.6°C	Walter, 2001	measured
Boiling point	156°C (at 1 mm Hg)	Walter, 2001	measured
Relative density	1.48	Walter, 2001	measured, with technical substance
Vapour pressure	8.4×10^{-3} Pa at 20 °C 2.1×10^{-2} Pa at 30 °C 5.1×10^{-2} Pa at 40 °C	Walter, 2001	measured
Surface tension	69.0 mN/m at 25°C (saturated solution)	Walter, 2001	measured
Water solubility	1.6×10^{-2} mg/L (purified water) 1.5×10^{-2} mg/L (at pH 5) 1.6×10^{-2} mg/L (at pH 9) all at 20 °C	Walter, 2001	measured
Partition coefficient n-octanol/water	$\log K_{o/w} = 6.4$ at 20 °C	Walter, 2001	measured
Flash point	165 ± 5°C	Jackson, 1999	measured
Flammability	melted, but did not propagate combustion	Jackson, 1999	measured
Explosive properties	not explosive	Jackson, 1999	estimated
Self-ignition temperature	440 ± 5°C	Jackson, 1999	measured
Oxidising properties	not oxidizing	Jackson, 1999	measured
Granulometry	no data		
Stability in organic solvents and identity of relevant degradation products	no data		
Dissociation constant	Tefluthrin does not possess any functional groups that will protonate or deprotonate in the environmental pH range.	Walter, 2001	measured
Viscosity	no data		

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant in this dossier

2.2 Identified uses

Tefluthrin is an insecticide intended to be used in sugar beet and fodder beet.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
EEC A.15 (Auto-Ignition Temperature (Liquids and Gases))	440 ± 5°C		Jackson, 1999
EEC A.10 (Flammability (Solids))	negative		Jackson, 1999
EEC A.12 (Flammability (Contact with water))	negative		Jackson, 1999
EEC A14 (explosiveness)	negative	estimated, conclusive	Jackson, 1999
EEC A 17 (oxidizing properties)	negative	estimated, conclusive	Jackson, 1999

3.1 Conclusions on classification and labelling

Tefluthrin has no properties with respect to flammability, explosive and oxidising properties that lead to a classification.

4 HUMAN HEALTH HAZARD ASSESSMENT

The summaries included in this proposal are partly copied from the Draft Assessment Report (DAR August 2008) and the Additional Report (AR December 2009). Compared to the DAR changes in the AR were minor and restricted to section 'short term toxicity' and 'further studies' (additional studies on impurities).

Some details of the summaries were not included when considered not important for a decision on the classification and labelling of the present active substance. On the other hand, some additional information was given if considered necessary. For more details please refer to both the DAR and AR.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Toxicokinetics and metabolism studies in rats demonstrate that tefluthrin is not extensively absorbed and is rapidly eliminated from the body. The higher proportion of the administered dose was in faeces (53-67 %) than in urine (20-34 %), and was more pronounced in male rats (62-67 % in faeces and 20-26 % in urine). Only negligible amounts of radioactivity from ^{14}C-alcohol-tefluthrin were exhaled as $^{14}CO_2$. The total residue in the carcass accounted for approximately 3 % or less of the administered dose. Among the tissues, liver contained approximately 0.1 to 0.7 % of the administered dose; kidney and abdominal fat contained significantly lower levels of radioactivity. Concentrations of radioactivity declined in other tissues rapidly to low levels by 96 hours after dosing. The half-lives of elimination of radioactivity for liver and fat were 5 and 13 days, respectively. Repeated oral dosing did not affect the tissue distribution of radioactivity. The pattern of distribution was similar in both sexes.

In the dog, a similar pattern of excretion was observed to that in rats with a higher proportion of the administered dose excreted in faeces than in urine and slightly more pronounced in males. Within 96 hours of dosing, only low levels of radioactivity remained in tissues with no pronounced sex difference.

The absorbed dose was metabolised extensively by oxidation of the aliphatic groups in the acid and alcohol moieties and by ester cleavage. An array of metabolites was produced based on various permutations of these reactions. Following repeated oral dosing, fat residues comprised of a mixture of unchanged tefluthrin and a mixture of palmitic acid and oleic acid esters of hydroxylated tefluthrin metabolites.

Studies to investigate the dermal absorption of tefluthrin across rat and human epidermis have been conducted with a blank CS (microencapsulated) formulation, representative of formulation YF11853, which contains a nominal 200 g tefluthrin/L.

The *in vitro* studies were conducted according to the draft TG OECD 428 (December 2000). In these studies, the dermal penetration of tefluthrin from the CS concentrate was very low through both rat and human skin.

The data show that the *in vitro* rat skin is considerably more permeable than *in vitro* human skin. If the residues in skin are considered the factor between rat skin and human skin *in vitro* is approximately 6.5. Based on the results of the *in vivo* study in rats and the factor 6.5 a dermal absorption through *in vivo* human skin after 24 hours of 0.12 % of the applied dose is estimated.

4.1.2 Human information

No studies submitted by the applicants

4.1.3 Summary and discussion on toxicokinetics

Studies in animals revealed an oral absorption of ca 30% within 96h for the active substance. The total residue in the carcass accounted for approximately 3 % or less of the administered dose and was widely distributed. Highest residues were measured in liver, kidneys and fat. Concentrations of radioactivity declined in other tissues rapidly to low levels by 96 hours after dosing. The half-lives of elimination of radioactivity for liver and fat were 5 and 13 days, respectively. Repeated oral dosing did not affect the tissue distribution of radioactivity. The pattern of distribution was similar in both sexes.

Dermal absorption was calculated to be 0.12 % (based on *in vivo* rat, and *in vitro* comparison rat vs. human skin).

4.2 Acute toxicity

Table 11: Summary table of relevant acute toxicity studies

Type of Study	Species	Result	Reference
Acute oral LD_{50}	Rat	21.8 mg/kg (m)/ 34.6 mg/kg (f)	Southwood (1985, TOX2004-2666)
Acute oral LD_{50}	Mouse	45.6 mg/kg (m)/ 56.5 mg/kg (f)	Southwood (1985, TOX2004-2666)
Acute dermal LD_{50}	Rat	316 mg/kg (m)/ 177 mg/kg (f)	Southwood (1985, TOX2004-2666)
Acute inhalation LC_{50} (4 hr)	Rat	41.9 mg/m^3 (m) 37.1 mg/m^3 (f)	McLean et al (1986, TOX2004-2669)

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Tefluthrin exhibits high acute oral toxicity both in rats and mice. The LD_{50} value were estimated to be 21.8 mg/kg bw for rats and 45.6 mg/kg bw in mice. The most common signs of toxicity in rats included tremors, splayed gait, loss of stability, urinary incontinence, salivation and upward curvature of the spine and in mice shaking, sides pinched in, urinary incontinence and upward curvature of the spine.

Report: Southwood J (1985, TOX2004-2666), PP993: Acute Oral Toxicity, Acute Intraperitoneal Toxicity and Acute Dermal Toxicity Studies. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/986, study dates September to November 1983 (in-life phase). (Syngenta File No. ICI993/0636)

Guidelines: 92/69/EEC B.1 ≅ OECD 401 (1992)

Deviations: None
GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.
Acceptability: The study is considered to be acceptable.

Materials and methods:
Tefluthrin (PP993) technical; batch number P14; analysed purity 90.4 % w/w tefluthrin.

Groups of five male and five female Alderley Park, SPF, albino rats received a single oral dose of 10.1, 25.5, 47 or 100 mg/kg of tefluthrin as a solution in corn oil. All the animals were fasted for 16 to 20 hours prior to dosing.The animals were assessed daily for the following 14 days for any signs of systemic toxicity and their body weights were recorded at intervals throughout the study. Animals *in extremis* and those surviving to the end of the study were killed and subjected to a macroscopic examination *post mortem.*

Findings:

General observations: At doses of 100 and 47 mg/kg all of the animals, and at a dose of 25.5 mg/kg two males, died within the first four days of the study (please see table below).

Table 12: Acute Oral Toxicity of Tefluthrin in the Rat (Cumulative Mortality)

Dose Level	Time after Dosing	Number of Deaths	
(mg/kg)	(Days)	Male	Female
10.1	15 (total)	0/5	0/5
25.5	1	0/5	0/5
	2	2/5	0/5
	15 (total)	2/5	0/5
47	1	0/5	0/5
	2	4/5	5/5
	4	5/5	5/5
	15 (total)	5/5	5/5
100	1	0/5	5/5
	2	5/5	5/5

No signs of toxicity were seen in any of the animals (male or female), at 10.1 mg/kg bw. Signs of toxicity were present in all animals dosed with 25.5, 47 and 100 mg/kg on day 1 and persisted in some surviving animals until day 6. The most common signs of toxicity included tremors, splayed gait, loss of stability, urinary incontinence, salivation and upward curvature of the spine.

Initially all the animals showed a decrease in body weight, due to fasting prior to dosing, but by day 6 all of the surviving rats had increased in body weight when compared with initial weights. Thereafter all surviving rats increased in body weight.

Gross pathology: No macroscopic abnormalities were seen.

Conclusion:

The acute oral median lethal dose for male rats was calculated to be 21.8 mg/kg tefluthrin (approximate 95 % confidence limits 10.1, 47 mg/kg) and for female rats was 34.6 mg/kg tefluthrin (approximate confidence limits 25.5, 47 mg/kg).

According to Regulation (EC) No 1272/2008 the low oral LD_{50} value of 21.8 mg/kg bw in rats tefluthrin requires classification as ‘Fatal if swallowed’ (H300, Acute Tox. 2).

Report: Southwood J (1985, TOX2004-2666), PP993: Acute Oral Toxicity, Acute Intraperitoneal Toxicity and Acute Dermal Toxicity Studies. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/986, study dates September to November 1983 (in-life phase). (Syngenta File No. ICI993/0636)

Guidelines: 92/69/EEC B.1 ≅ OECD 401 (1992)

Deviations: None

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin (PP993) technical; batch number P14; analysed purity 90.4 % w/w tefluthrin.

Groups of five male and five female Alderley Park, SPF, albino mice received a single oral dose of 9.8, 48, 97 and 125 mg/kg of tefluthrin. A further group of five male mice received 23.4 mg/kg tefluthrin.

The animals were assessed daily for the following 14 days for any signs of systemic toxicity and their body weights were recorded at intervals throughout the study. Animals *in extremis* and those surviving to the end of the study were killed and subjected to a macroscopic examination *post mortem*.

Findings:

General observations: As shown in the table below all mice dosed at 125, 4 males and 3 females at 97 mg/kg and 4 males and 2 females at 48 mg/kg died. There were no mortalities at 9.8 or 23.4 mg/kg.

Table 13: Acute Oral Toxicity of Tefluthrin in the Mouse (Cumulative Mortality)

Dose Level	Time after Dosing	Number of Deaths	
(mg/kg)	(Days)	Male	Female
9.8	15 (total)	0/5	0/5
23.4	15 (total)	0/5	-
48	1	4/5	2/5
	15 (total)	4/5	2/5
97	1	4/5	3/5
	15 (total)	4/5	3/4[$]
125	1	5/5	5/5
	15 (total)	5/5	5/5

[$] one mouse escaped on day 7

Signs of toxicity were not seen in any of the animals given 9.8 mg/kg, but became apparent in all other animals on the day of dosing and persisted in some survivors until Day 4. The most common signs were shaking, sides pinched in, urinary incontinence and upward curvature of the spine.

Initially all of the animals decreased in body weight (due to the pre-dose fast), but by Day 6 most had increased or equalled their initial body weight. Thereafter, with the exception of the surviving female given 97 mg/kg, all the mice increased in body weight.

Gross pathology: No macroscopic abnormalities were seen.

Conclusion:

The acute oral median lethal dose was determined to be 45.6 mg/kg to male mice (95 % confidence limits 23.6, 69.0 mg/kg) and 56.5 mg/kg to female mice (95 % confidence limits 0.2, 90.0 mg/kg). The LD_{50} in mice is estimated to be 45.6 mg/kg bw.

4.2.1.2 Acute toxicity: inhalation

Tefluthrin exhibits high acute inhalative toxicity in rats with the estimated LD_{50} value of 0.037 mg/L (4h, nose only, aerosol). Signs of toxicity were dose related symptoms of neurotoxicity.

Report:	McLean Head L and Bennett I (1986, TOX2004-2669), Tefluthrin: 4 Hour Acute Inhalation Toxicity Study in the Rat. Central Toxicology Laboratory; UK., Syngenta Unpublished Report No. CTL/P/1558, study dates 11 February 1986 to 25 February 1986 (in-life phase). (Syngenta File No. ICI993/0081)
Guidelines:	92/69/EEC B.2 ≅ OECD 403 (1981)
Deviations:	Air-flow rates are given but no measure of variability is given. The geometric standard deviation and equilibration period are not reported.
GLP:	This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.
Acceptability:	The study is considered to be acceptable.

Materials and methods:

Tefluthrin technical; batch No. P18; analysed purity 96.0 % w/w tefluthrin.

Groups of five male and five female rats were exposed nose-only for a single four-hour period to aerosol target concentrations of 5, 20, 50 or 65 mg/m^3. A similar group of control animals was exposed to air only.

Clinical observations, body weights and food consumption were measured throughout the study. At the end of the scheduled period, the animals were killed and subjected to an examination *post mortem.* Selected organs were weighed and specified tissues were taken for subsequent histopathology.

Findings:

General observations: The achieved mean analysed concentrations of 7.7, 14.9, 39.9 and 60.5 mg/m^3 tefluthrin accounted for greater than 80 % of the total particulate. The three highest dose levels had a respirable (≤ 2.5 μm aerodynamic equivalent diameter (AED) content greater than 90 % and a mass median aerodynamic diameter (D_{50}) of approximately 1.3 μm. The analysed and particulate aerodynamic particle size distributions for all dose levels showed a good correlation at respirable levels.

Exposure to 65 mg/m^3 tefluthrin resulted in severe toxic reactions and all animals died or were killed during exposure or shortly afterwards (please see table below). Exposure of this group was

terminated after 198 minutes. Two females in the 50 mg/m^3 tefluthrin group were killed *in extremis* after exposure.

Table 14: Acute Inhalation Toxicity of Tefluthrin in the Rat: Mortality Data

Dose Level (mg/m^3)	Day Number	Number of Deaths	
		Male	Female
0	15 (total)	0/5	0/5
5	15 (total)	0/5	0/5
20	15 (total)	0/5	0/5
50	1	0	2
	15 (total)	0/5	2/5
65	1	5	5
	15 (total)	5/5	5/5

Animals in the 20, 50 and 65 mg/m^3 tefluthrin groups showed dose related symptoms of neurotoxicity. Neurotoxic symptoms were reversible in animals, which survived.

In the 50 mg/m^3 tefluthrin group, some CNS effects were still apparent on day 2, including tremors, tip-toe gait, splayed gait and reduced stability. Piloerection was seen in some animals up to day 11 (please see table below).

Table 15: Intergroup Comparison of the Incidence of Selected Clinical Observations

	Target Concentration of Tefluthrin (mg/m^3)									
	Males					Females				
Observation	0	5	20	50	65	0	5	20	50	65
Piloerection	5 (1)	7 (1-4)	8 (1-5)	19 (1-6)	1 (1)	5 (1)	6 (1-4)	10 (1-5)	27 (1-11)	2 (1)
Salivation	0	3 (1)	5 (1)	4 (1)	0	0	1 (1)	4 (1)	4 (1)	0
Reduced stability	0	0	3 (1-2)	7 (1-2)	2 (1)	0	0	6 (1-2)	8 (1-2)	1 (1)
Tremors	0	0	0	7 (1-2)	0	0	0	0	7 (1-2)	0
Tonic convulsions	0	0	0	0	5 (1)	0	0	0	0	3 (1)
Respiratory noise	2 (14-15)	6 (2-15)	11 (1-5)	26 (1-15)	4 (1)	0	6 (4-15)	8 (1-5)	28 (1-15)	3 (1)

Total number of observations followed by (day number(s) during which the observation was made)

The mean body weight of all surviving animals in all groups including control was reduced following exposure. This effect was not dose related but was greatest in the 50 mg/m^3 tefluthrin females. The 50 mg/m^3 tefluthrin females did not exceed their starting weight until day 4, but after day 5 the weight gain of all test females was similar to that of controls.

There were no statistically significant differences in food consumption in treated groups compared with control groups.

Gross pathology, organ weights, histopathology**:** The apparently dose related effect on the kidney (see table below) in animals which survived to day 15 was small and in the absence of associated histopathological findings was considered not to be toxicologically significant. The increase in lung weight and lung abnormalities (which consisted of red, dark and/or mottled surfaces), seen in one male and three females in the top dose, together with the persistence of respiratory noise in the 20 and 50 mg/m^3 tefluthrin animals indicate that the respiratory system, including the lung, was a probable target organ for toxicity.

Table 16: Intergroup Comparison of Selected Organs: Final Body weight Ratios (g/100g) – Paired Organs Weighed Together

	Target Concentration of Tefluthrin (mg/m^3)									
	Males					Females				
Organ	0	5	20	50	65#	0	5	20	50	65#
Kidney	0.715	0.751	0.768*	0.774**	0.961	0.694	0.721	0.697	0.738	0.888
Liver	4.706	4.929	5.010	4.630	4.892	4.056	3.976	3.981	4.451	3.800
Lung	0.465	0.469	0.484	0.483	0.636	0.539	0.569	0.525	0.539	0.738
Testis	0.965	0.951	1.001	1.061*	1.141	-	-	-	-	-

\# Animals killed on day 1. Organ weight ratios not compared statistically with controls
** Statistically significant difference from control group mean, 1 % level (Student's t-test, 2-sided)
* Statistically significant difference from control group mean, 5 % level (Student's t-test, 2-sided)

Conclusion: The four-hour median lethal concentration of tefluthrin was calculated to be 49.1 mg/m³ for males and 37.1 mg/m³ for females (combined 42.7 mg/m³).

According to Regulation (EC) No 1272/2008 the low inhalative LC_{50} value of 0.037 mg/L in rats tefluthrin requires classification as 'Fatal if inhaled' (H330, Acute Tox. 1).

4.2.1.3 Acute toxicity: dermal

Tefluthrin revealed high acute dermal toxicity in rats which resulted in the estimated dermal LD_{50} value of 177 mg/kg bw. Signs of toxicity became apparent in most animals on day 1 and still persisted by day 15 in some rats until the end of the study. The most common signs were stains around nose, chromodacryorrhoea, splayed gait, upward and/or downward curvature of the spine and signs of urinary incontinence. Signs of skin irritation, including desquamation, scabbing and new skin formation, became apparent on day 3 and persisted in two animals until day 15.

Report: Southwood J (1985, TOX2004-2666), PP993: Acute Oral Toxicity, Acute Intraperitoneal Toxicity and Acute Dermal Toxicity Studies. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/986, study dates September to November 1983 (in-life phase). (Syngenta File No. ICI993/0636)

Guidelines: 92/69/EEC B.3 ≅ OECD 402 (1987)

Deviations: Due to extreme discomfort at dose levels of 2000 mg/kg (all males and females) and at 1000 mg/kg (one female) the substance was left only for approximately 2 hours.

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin (PP993) technical; batch No. P14; analysed purity 90.4 % w/w tefluthrin.

Groups of five male and five female Alderley Park, SPF, albino rats received a single dermal application of 100, 500, 1000 or 2000 mg/kg of undiluted tefluthrin, in addition a further group of five female rats received an application of 50 mg/kg. The test substance was kept in contact with the clipped dorso-lumbar region of the rats for 24 hours by means of an occlusive dressing for most of the rats. Due to extreme discomfort observed in some of the rats, the application period was shortened to approximately 2 hours for all the animals in the 2000 mg/kg group and one female in the 1000 mg/kg group.

The animals were assessed daily for the following 14 days for any signs of systemic toxicity and their body weights were recorded at intervals throughout the study. Animals *in extremis* and those surviving to the end of the study were killed and subjected to a macroscopic examination *post mortem*.

Findings:
General observations:

As shown in the table below all the rats dosed at 2000 and 1000 mg/kg, two males and four females at 500 mg/kg and two females at 100 mg/kg died or were killed *in extremis* by day 6 of the study.

Table 17: Acute Dermal Toxicity of Tefluthrin in the Rat (Cumulative Mortality)

Dose Level	Time after Dosing	Number of Deaths	
(mg/kg)	(Days)	Male	Female
50	15 (total)	-	0/5
100	2	0/5	1/5
	3	0/5	2/5
	15 (total)	0/5	2/5
500	2	1/5	0/5
	3	1/5	2/5
	5	2/5	3/5
	6	2/5	4/5
	15 (total)	2/5	4/5
1000	2	1/5	1/5
	3	1/5	4/5
	4	4/5	4/5
	5	5/5	5/5

Dose Level	Time after Dosing	Number of Deaths	
	15 (total)	5/5	5/5
2000	1	0/5	1/5
	2	0/5	4/5
	3	3/5	4/5
	4	3/5	5/5
	5	4/5	
	6	5/5	
	15 (total)	5/5	5/5

Signs of toxicity became apparent in most animals on day 1 and still persisted by day 15 in some rats until the end of the study. The most common signs were stains around nose, chromodacryorrhoea, splayed gait, upward and/or downward curvature of the spine and signs of urinary incontinence. There were clinical signs of neuromuscular incoordination in some animals. These effects were reversible but were evident at the lowest dose (100 mg/kg in males and 50 mg/kg bw in females, respectively). Signs of skin irritation, including desquamation, scabbing and new skin formation, became apparent on day 3 and persisted in two animals until day 15.

Table 18: Clinical observations in male rats

ACUTE DERMAL TOXICITY TO THE RAT: CLINICAL OBSERVATIONS AND THE NUMBER OF MALE ANIMALS AFFECTED

ANALYSIS FOR DAYS: 1 TO 15 SEX: MALES

CLINICAL OBSERVATION	GROUP 01 1 ML/KG	GROUP 02 2 ML/KG	GROUP 03 0.5 ML/KG	GROUP 04 0.1 ML/KG
BIZARRE BEHAVIOUR	0- 0	1- 1	4- 2	11- 4
CLONIC CONVULSIONS	1- 1	1- 1	1- 1	0- 0
TREMORS	2- 2	0- 0	1- 1	0- 0
FOUND DEAD	4- 4	4- 4	1- 1	0- 0
KILLED IN EXTREMIS-TOXIC	1- 1	1- 1	1- 1	0- 0
KILLED TERMINATION	0- 0	0- 0	3- 3	5- 5
DIARRHOEA	0- 0	1- 1	0- 0	0- 0
SIGNS OF DIARRHOEA	2- 1	1- 1	12- 1	1- 1
ABNORMAL GAIT (SEE TEXT)	0- 0	0- 0	0- 0	2- 1
ATAXIA	0- 0	1- 1	0- 0	0- 0
SPLAYED GAIT	2- 1	3- 2	8- 3	20- 4
TIP TOE GAIT	0- 0	3- 1	6- 2	2- 1
CHROMODACRYORRHEA	13- 5	14- 5	9- 5	36- 5
SALIVATION	1- 1	2- 2	1- 1	0- 0
STAINS AROUND NOSE	15- 5	11- 5	42- 5	71- 5
SIGNS OF URINARY INCONTIN	7- 3	8- 3	15- 4	0- 0
URINARY INCONTINENCE	2- 1	0- 0	0- 0	0- 0
DOWNWD CURVATURE OF SPINE	3- 3	14- 5	9- 5	7- 4
UPWARD CURV'URE OF SPINE	10- 5	10- 4	35- 5	63- 5
NO. OF ANIMALS	5	5	5	5

Table 19: Clinical observations in female rats

ACUTE DERMAL TOXICITY TO THE RAT: CLINICAL OBSERVATIONS AND THE NUMBER OF FEMALE ANIMALS AFFECTED

ANALYSIS FOR DAYS: 1 TO 15 SEX: FEMALES

CLINICAL OBSERVATION	GROUP 01 1 ML/KG	GROUP 02 2 ML/KG	GROUP 03 0.5 ML/KG	GROUP 04 0.1 ML/KG	GROUP 05 0.05 ML/KG
BIZARRE BEHAVIOUR	0- 0	0- 0	0- 0	0- 0	2- 2
CLONIC CONVULSIONS	1- 1	0- 0	0- 0	0- 0	0- 0
COMATOSED	0- 0	0- 0	0- 0	1- 1	0- 0
WRITHING	0- 0	0- 0	0- 0	1- 1	0- 0
FOUND DEAD	3- 3	5- 5	4- 4	1- 1	0- 0
KILLED IN EXTREMIS-TOXIC	2- 2	0- 0	0- 0	1- 1	0- 0
KILLED TERMINATION	0- 0	0- 0	1- 1	3- 3	5- 5
ABNORMAL GAIT (SEE TEXT)	2- 1	2- 1	3- 2	0- 0	0- 0
SPLAYED GAIT	2- 2	4- 3	12- 3	29- 5	45- 5
TIP TOE GAIT	0- 0	0- 0	9- 2	2- 1	0- 0
CHROMODACRYORRHEA	9- 5	11- 5	25- 5	20- 4	11- 2
SALIVATION	1- 1	4- 4	2- 2	0- 0	0- 0
SIDES PINCHED IN	0- 0	0- 0	0- 0	5- 1	0- 0
STAINS AROUND NOSE	12- 5	3- 2	26- 5	46- 5	57- 5
SIGNS OF URINARY INCONTIN	8- 4	3- 2	21- 5	1- 1	28- 5
SEE FREE TEXT	1- 1	0- 0	0- 0	0- 0	0- 0
URINARY INCONTINENCE	2- 2	0- 0	4- 2	1- 1	5- 4
DOWNWD CURVATURE OF SPINE	6- 4	11- 5	7- 5	11- 5	0- 0
UPWARD CURV'URE OF SPINE	4- 3	1- 1	17- 3	31- 3	47- 5
GASPING	0- 0	0- 0	0- 0	1- 1	0- 0
NO. OF ANIMALS	5	5	5	5	5

Initially all of the animals decreased in body weight but by day 15 all but one had increased in weight when compared with initial body weights.

Gross pathology: No macroscopic abnormalities were seen.

Conclusion:

The acute dermal median lethal dose for male rats was calculated to be 316 mg/kg (95 % confidence limits 100, 1000 mg/kg) and for female rats was 177 mg/kg (approximate 95 % confidence limits 76, 397 mg/kg).

According to Regulation (EC) No 1272/2008 the low dermal LD_{50} value of 177 mg/kg in rats tefluthrin requires classification as 'Fatal in contact with skin' (H310, Acute Tox. 2).

4.2.1.4 Acute toxicity: other routes

No studies submitted by the applicant.

4.2.2 Human information

No studies submitted by the applicant.

4.2.3 Summary and discussion of acute toxicity

Tefluthrin has been evaluated in acute oral, dermal and inhalation toxicity studies and exhibits high acute toxicity via these routes of administration and therefore, classification is required accordingly. Signs of toxicity were mostly symptoms of neurotoxicity.

4.2.4 Comparison with criteria

The calculated oral LD_{50} value for tefluthrin is 21.8 mg/kg bw and meets the criteria according to CLP as 'Fatal if swallowed' (Acute Tox. 2; H300).

The calculated dermal LD_{50} value for tefluthrin is 177 mg/kg bw and meets the criteria according to CLP as 'Fatal in contact with skin' (Acute Tox. 2; H310).

The calculated inhalative LC_{50} value for tefluthrin is 0.037 mg/L and meets the criteria according to CLP as 'Fatal if inhaled' (Acute Tox. 1, H330)

The table below presents the toxicological results in comparison with CLP criteria.

Table 20: Toxicological results in comparison with DSD and CLP criteria

Toxicological result	CLP criteria
Oral LD_{50}, rat: 21.8 mg/kg bw	Cat. 2 (H300): $5 < LD_{50} \leq 50$ mg/kg bw (oral)
Dermal LD_{50}, rat: 177 mg/kg bw	Cat. 2 (H310): $50 < LD_{50} \leq 200$ mg/kg bw (dermal)
1. Inhalative LC_{50}, rat: 0.037 mg/L	Cat. 1 (H330): $LC_{50} \leq 0.05$ mg/l (dust/mist)

4.2.5 Conclusions on classification and labelling

Currently, tefluthrin is not classified. However, based on the results of acute oral, dermal and inhalative toxicological studies in rats the following classification according to CLP Regulation is required:

'Fatal if swallowed' (Acute Tox. 2; H300); 'Fatal in contact with skin' (Acute Tox. 2; H310) and

'Fatal if inhaled' (Acute Tox. 1; H330).

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

Four acute toxicity studies were presented in the CLH report, which is included as part of the Background document (BD). Studies were conducted by oral, inhalatory and dermal routes.

In an acute oral toxicity study (Southwood, 1985) groups of 5 male and 5 female Alderley park, SPF, albino rats received a single dose of 10.1, 25.5, 47 or 100 mg/kg bw tefluthrin (in accordance with 92/69/EEC B.1 ≅ OECD TG 401). LD_{50} values were calculated to be:

- 21.8 mg/kg bw in males
- 34.6 mg/kg bw in females

No signs of toxicity were seen in any of the animals (male or female), at 10.1 mg/kg bw. Signs of toxicity were present in all animals dosed with 25.5, 47 and 100 mg/kg bw on day 1 and persisted in some surviving animals until day 6. The most common signs of toxicity included tremors, splayed gait, loss of stability, urinary incontinence, salivation and upward curvature of the spine.

In a second acute oral toxicity study (Southwood, 1985) groups of 5 male and 5 female Alderley park, SPF, albino mice received a single dose of 9.8, 48, 97 or 125 mg/kg bw tefluthrin (in accordance with 92/69/EEC B.1 ≅ OECD TG 401). A further group of five male mice received 23.4 mg/kg tefluthrin. LD_{50} values were calculated to be:

- 45.6 mg/kg bw in males
- 56.5 mg/kg bw in females

Signs of toxicity were not seen in any of the animals given 9.8 mg/kg bw, but became apparent in all other animals on the day of dosing and persisted in some survivors until Day 4. The most common signs were shaking, sides pinched in, urinary incontinence and upward curvature of the spine.

The DS proposed that according to the CLP criteria tefluthrin should be classified in **acute oral toxicity hazard category 2** (5< ATE ≤50) with the hazard statement **H300**: Fatal if swallowed.

In an acute inhalation toxicity study (McLean *et al*, 1986) groups of 5 male and 5 female Alpk:AP rats (in accordance with 92/69/EEC B.2 ≅ OECD TG 403), were exposed for 4 hours via the nose only, to tefluthrin aerosol at target concentrations of 5, 20, 50 or 65 mg/m^3. The achieved mean analysed concentrations of 7.7, 14.9, 39.9 and 60.5 mg/m^3 tefluthrin accounted for greater than 80 % of the total particulate. The three highest dose levels had a respirable particle size (more than 90 % of particles had an aerodynamic equivalent diameter (AED) ≤ 2.5 µm and a mass median aerodynamic diameter of approximately 1.3 µm). LC_{50} values were calculated to be:

- 49.1 mg/m^3 (0.0491 mg/L) in males
- 37.1 mg/m^3 (0.0371 mg/L) in females

Animals in the 20, 50 and 65 mg/m^3 tefluthrin groups showed dose related symptoms of neurotoxicity. Neurotoxic symptoms were reversible in animals which survived. The mean body weight of all surviving animals in all groups including control was reduced compared to pre-treatment. This effect was not dose related but was greatest in the 50 mg/m^3 females. The 50 mg/m^3 females did not exceed their starting weight until day 4, but after day 5 the weight gain of all test females was similar to that of controls.

The dose related effect on the kidney in animals which survived to day 15 was small and in the absence of associated histopathological findings was considered not to be toxicologically significant. The increase in lung weight and lung abnormalities (which consisted of red, dark and/or mottled surfaces), seen in one male and three females in the top dose, together with the persistence of respiratory noise in the 20 and 50 mg/m^3 animals indicate that the respiratory system, including the lung, was a probable target organ for toxicity.

The DS proposed that according to the CLP criteria tefluthrin should be classified in **acute inhalation toxicity hazard category 1** (0 < ATE ≤ 0.05 mg/L, for dusts and mists), hazard statement **H330**: Fatal if inhaled.

In an acute dermal toxicity study (Southwood, 1985) groups of 5 male and 5 female Alderley park, SPF, albino rats received a single dermal application of 100, 500, 1000 or 2000 mg/kg bw of undiluted tefluthrin (in accordance with 92/69/EEC B.3 ≅ OECD TG 402). In addition, a group of 5 female rats received an application of 50 mg/kg bw. The test substance was kept in contact with the clipped dorso-lumbar region of the rats for 24 hours by means of an occlusive dressing for most of the rats. Due to extreme discomfort observed in some of the rats, the application period was shortened to approximately 2 hours for all the animals in the 2000 mg/kg bw group and one female in the 1000 bw mg/kg group.
LD_{50} values were calculated to be:

- 316 mg/kg bw in males
- 177 mg/kg bw in females

Signs of toxicity became apparent in most animals on day 1 and persisted to day 15 in some rats until the end of the study. The most common signs were stains around nose, chromodacryorrhoea, splayed gait, upward and/or downward curvature of the spine and signs of urinary incontinence. There were clinical signs of neuromuscular incoordination in some animals. These effects were reversible but were evident at the lowest dose (100 mg/kg in

males and 50 mg/kg bw in females, respectively).

The DS proposed that according to the CLP criteria tefluthrin should be classified in **acute dermal toxicity hazard category 2** (50 < ATE ≤ 200), hazard statement **H310**: Fatal in contact with with skin.

Comments received during public consultation

Two MSCAs supported the proposed classification.

Assessment and comparison with the classification criteria

Following a comparison of the available acute oral and dermal LD_{50} values and inhalation LC_{50} values with the classification criteria, RAC supports the conclusion of the DS that according to CLP Regulation tefluthrin should be classified in Category 1 for acute inhalation toxicity and Category 2 for acute oral and dermal toxicity:

- **Acute Tox. 1 - H330**: Fatal if inhaled (LC_{50} values of 0.0491 mg/L in male rats and 0.0371 mg/L in female rats are within the range 0 < ATE ≤ 0.05 mg/L for dusts and mists).
- **Acute Tox. 2 - H300**: Fatal if swallowed (acute oral LD_{50} of 21.8 mg/kg bw in male rats and 34.6 mg/kg bw in female rats and acute oral LD_{50} of 45.6 mg/kg bw in male mouse are within the range 5 < ATE ≤ 50 mg/kg bw)
- **Acute Tox. 2 - H310**: Fatal in contact with with skin (acute dermal LD_{50} of 177 mg/kg bw in male rats and 177 mg/kg bw in female rats are within the range 50 < ATE ≤ 200 mg/kg bw)

4.3 Specific target organ toxicity – single exposure (STOT SE)

There is no evidence of specific target organ toxicity after single oral exposure of tefluthrin. Specific organ toxicity was observed only at dose levels where lethality was already observed (please refer to acute oral study in rats).

After single inhalative exposure to tefluthrin transient clinical signs of neurotoxicity and respiratory noise were already observed at sub-lethal dose level of 0.02 mg/L [LC_{50}=0.037 mg/L]. Furthermore, after single dermal exposure to tefluthrin clinical signs of neuromuscular incoordination were observed in some animals at 100 mg/kg bw (males) and 50 mg/kg bw (females), dose levels below the calculated LD_{50} value of 177 mg/kg bw (e.g. upward curvature if spine, spayed gait, tip toe gait). However, according to the Guidance on the application of the CLP criteria (Version 3.0, November 2012): '*Care must be taken not to classify for STOT-SE for effects which are not yet lethal at a certain dose, but would lead to lethality within the numeric classification criteria. In other words, if lethality would occur at relevant doses then a classification for acute toxicity would take precendence and STOT-SE would not be assigned'.* Hence, for the present active substance no classification with STOT-SE is proposed.

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

No toxicity to a specific organ in the absence of lethality was observed after single oral exposure in rats.

After a single inhalation exposure in rats, dose related increase in transient respiratory noise below lethal dose level [0.02 mg/L 4h] was observed. Together with changes in lung weight and

histopathology a lethal dose levels, the lung was an probable target organ for toxicity. Further clinical signs (salivation, piloerection, reduced stability) were either observed in control animals or restricted to day 1 and 2 after exposure.

After single dermal exposure to tefluthrin clinical signs of neuromuscular incoordination (e.g. upward curvature if spine, spayed gait, tip toe gait) were observed in some animals at 100 mg/kg bw (males) and 50 mg/kg bw (females), dose levels below the calculated LD_{50} value of 177 mg/kg bw.

Based on available human information (for details please refer to 4.12.1.4) transient neurotoxic effects for pyrethroid insecticides were mostly described as symptoms of paraesthesia.

Taken together all available information classification with STOT-SE for the active substance tefluthrin is not needed, because the neurotoxic effects observed at non-lethal dose levels would lead to lethality within the numeric classification criteria. Therefore, according to Guidance on the application of the CLP criteria classification for acute toxicity take precedence and STOT-SE is not be assigned.

4.3.2 Comparison with criteria

Table 21: Toxicological results in comparison with CLP criteria

CLP CRITERIA	
Category 1 (H370) Oral (rat): C ≤ 300 mg/kg bw Dermal (rat or rabbit): C ≤ 1000 mg/kg bw Inhalative (rat, dust/mist/fume): ≤ 1 mg/L/4 h	Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure - reliable and good quality evidence from human cases or epidemiological studies; or - observations from appropriate studies in experimental animals in which significant and/or severe toxic effects of relevance to human health were produced at generally low exposure concentrations.
Category 2 (H371) Oral (rat): 2000 ≥ C > 300 mg/kg bw Dermal (rat or rabbit): 2000 ≥ C > 1000 mg/kg bw Inhalative (rat, dust/mist/fume): 5 ≥ C > 1 mg/L/4 h	Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following single exposure - observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations.
Category 3 (H335/H336) Guidance values do not apply (mainly based on human data)	Transient target organ effects This category only includes narcotic effects and respiratory tract irritation. These are target organ effects for which a substance does not meet the criteria to be classified in Categories 1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function.

4.3.3 Conclusions on classification and labelling

Classification and labelling is not needed.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier submitter's proposal

The DS reported that there was no evidence of specific target organ toxicity after single oral exposure of tefluthrin. Specific organ toxicity was observed only at dose levels where lethality was already observed in the acute oral studies on rats.

After a single inhalation exposure in rats, a dose-related increase in transient respiratory noise at below the lethal dose level was observed (LC_{50} 0.037 mg/L, 4h). Together with changes in lung weight and histopathology at lethal dose levels, the lung was a probable target organ for toxicity. Further clinical signs (salivation, piloerection, reduced stability) were either observed in control animals or were restricted to days 1 and 2 after exposure.

After single dermal exposure to tefluthrin clinical signs of neuromuscular incoordination (e.g. upward curvature of spine, splayed gait, tip toe gait) were observed in some animals at 100 mg/kg bw (males) and 50 mg/kg bw (females). These dose levels were below the calculated LD_{50} value of 177 mg/kg bw.

Based on the available human information, transient neurotoxic effects for pyrethroid insecticides were mostly described as symptoms of paraesthesia.

Taking all the available information together, the DS concluded that classification with STOT-SE for the active substance tefluthrin was not needed. Therefore, in accordance with the Guidance on the application of the CLP criteria (CLP Guidance), classification for acute toxicity takes precedence and STOT-SE is not assigned.

Comments received during public consultation

One MSCA supported the DS conclusion that tefluthrin should not be classified for STOT-SE.

Assessment and comparison with the classification criteria

Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following single exposure should be classified as STOT SE 1 or 2 according to the CLP Regulation. Classification should be supported by evidence associating single exposure to the substance with a consistent and identifiable toxic effect that clearly impacts health. Classification as STOT SE 3 is limited to substances that have narcotic effects or cause respiratory tract irritation.

According to the CLP Guidance (version 4.0, section 3.8.2.5) *"STOT-SE and acute toxicity are independent of each other and both may be assigned to a substance if the respective criteria are met. However, care should be taken not to assign each class for the same effect, in other words a double classification for the same effect has to be avoided. STOT-SE will be considered where there is clear evidence for a specific organ toxicity especially in absence of lethality".* Furthermore, section 3.8.1 mentions that "*STOT SE Categories 1 and 2 for non lethal significant and/or severe toxic effects are the basis for classification with the category reflecting the dose level required to cause the effect. Category 3 covers transient effects occurring after single exposure, specifically respiratory tract irritation and narcotic effects*".

RAC agrees with the DS that tefluthrin does not fulfil the criteria for STOT SE by oral, dermal or inhalation routes of exposure. Tefluthin does not fulfil the criteria for STOT SE 3 since it didn't cause respiratory tract irritation or narcotic effects.

However, in relation to a STOT SE classification, RAC considered the unusual and severe effects reported in an eye irritation study (Southwood, 1987). In that study, 0.1mL (≈ 33.5 - 50 mg/kg bw) tefluthrin was instilled into the conjunctival sac of one eye of each of six New Zealand White male rabbits (in accordance with 92/69/EEC B.5, equivalent to OECD TG 405). Prior to instillation of tefluthrin, all rabbits were pretreated intraveneously with an analgesic to prevent pain and discomfort. The findings reported are described under "Summary of the Dossier submitter's proposal" in the section "RAC evaluation of eye corrosion/irritation".

RAC considered the effects described via eye contact to be severe, since they could not be prevented by analgesic administration and they led to the premature sacrifice of 4/6 rabbits.

However, RAC is of the opinion that these symptoms occurred due to pain and paraesthesia. The latter effect is a transient effect specific to pyrethroids and has been reported in human subjects exposed to the active substance by skin contact. Under Directive 67/548/EC (DSD), paraesthesia was not regarded as an irritant effect justifying classification as Xi; R38. The S-phrase S24 was, however, required for substances seen to cause this effect. Under CLP, paraesthesia is not specifically addressed by classification and labelling elements and is not considered to fulfil the CLP criteria for STOT SE 1 or 2.

RAC agrees that the end users are sufficiently protected against paraesthesia via eye contact by the precautionary statements that follow from the Acute Tox. classification in Category 1 and 2 – especially Acute Tox. 2 (dermal) with the precautionary statements P262 (Do not get in eyes, on skin, or on clothing) and P280 (Wear protective gloves/protective clothing/eye protection/face protection).

In conclusion, RAC is of the opinion that tefluthrin does not fulfil the criteria for **STOT SE** and agrees with the DS proposal not to classify tefluthrin for this hazard class.

4.4 Irritation

4.4.1 Skin irritation

Table 22: Summary table of the relevant skin irritation study

Type of Study	Species	Result	Reference
Acute skin irritation	Rabbit	Slightly irritating, no classification	Southwood (1985, TOX2004-2667)

4.4.1.1 Non-human information

Report: Southwood J (1985, TOX2004-2667), PP993: Skin Irritation and Eye Irritation Studies. Central Toxicology Laboratory; UK., Syngenta Unpublished Report No. CTL/P/987, study dates September to October 1983 (in-life phase). (Syngenta File No. ICI993/0631)

Guidelines: 92/69/EEC B.4 ≅ OECD 404 (1992)

Deviations: None

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin (PP993) technical; batch number P14; analysed purity 90.4 % w/w tefluthrin.

A group of six male New Zealand White albino rabbits received a single four-hour application of approximately 0.5 mL of the test substance to the shorn flank. The test substance was held in place with an occlusive dressing. The application site was cleansed with methylated spirits and water at the end of the 4-hour dosing period.

The animals were assessed for up to 13 days for any signs of skin irritation. The Draize scale was used to assess the degree of erythema and oedema at the application sites approximately 1 hour, 1, 2 and 3 days after removal of the dressings and then at intervals up to 14 days until all sites appeared normal. Mean erythema and oedema scores were calculated. Body weights were recorded at the start of the study.

Findings:

General observations: Approximately one hour following decontamination, three of the six rabbits showed very slight erythema which persisted in two animals for up to twenty hours following decontamination. Two of the six animals could not be scored for erythema because of moderate to severe erythema adjacent to the application site. Erythema was observed adjacent to the application site for 169 hours following decontamination and was obviously caused by rubbing or scratching.

Approximately one hour following decontamination, four rabbits showed very slight oedema, which persisted in two animals for up to twenty hours following decontamination (see table below). Two of the six animals could not be scored for oedema because of severe oedema adjacent to the application site. Oedema was observed adjacent to the application site for 169 hours following decontamination and was obviously caused by rubbing or scratching.

Table 23: Individual and Mean Skin Irritation Scores (Draize Scale) in the Rabbit

Time after decontamination	Erythema Animal Numbers						Oedema Animal Numbers					
	4	**5**	**6**	**7**	**8**	**9**	**4**	**5**	**6**	**7**	**8**	**9**
After 30-60 min.	1	1	1	0	0	0	1	1	1	1	0	0
After 20 hours	0	1	1	0	#	#	0	1	0	1	#	#
After 48 hours	0	0	0	0	#	#	0	0	0	0	#	#
After 72 hours	0	0	0	0	#	#	0	0	0	0	#	#
After 96 hours	0	0	0	0	#	#	0	0	0	0	#	#
After 169 hours	0	0	0	0	#	#	0	0	0	0	#	#
After 264 hours	0	0	0	0	0	0	0	0	0	0	0	0
Mean score	0.16						0.16					

Unable to score due to irritation adjacent to the application site
Mean scores are based on the 20-72 hour values

Additional signs of irritation were observed from 1-169 hours following decontamination and they included thickening, desquamation and hardening.

Conclusion:

Tefluthrin caused slight irritation to rabbit skin. However, the recorded values do not trigger the required CLP criteria for classification as irritating to skin.

4.4.1.2 Human information

No studies submitted by the applicant.

4.4.1.3 Summary and discussion of skin irritation

Tefluthrin caused slight irritation to rabbit skin. However, the recorded values do not trigger the required CLP criteria for classification as irritating to skin.

4.4.1.4 Comparison with criteria

Highest score observed in skin irritation testing was < 1 for erythema and oedema. As the results did not meet the CLP criteria [Irritating to skin (category 2, H315): at least in 2/3 tested animals a positive response of mean value of ≥ 2.3 - ≤ 4.0 for erythema/eschar or for oedema] classification and labelling is not needed.

4.4.1.5 Conclusions on classification and labelling

In summary and based on the submitted data, tefluthrin did not meet the criteria to be classified for skin irritation/corrosion according to criteria in CLP Regulation.

RAC evaluation of skin corrosion/irritation
Summary of the Dossier submitter's proposal In a skin irritation study (Southwood, 1985) six male New Zealand White albino rabbits received a single four-hour application of approximately 0.5 mL tefluthrin to the shorn flank (in accordance with 92/69/EEC B.4 ≅ OECD 404). Tefluthrin caused slight irritation to rabbit skin. The DS concluded that the recorded Draize values did not meet the CLP criteria for classification as irritating to skin. **Comments received during public consultation** No comments received during public consultation **Assessment and comparison with the classification criteria** In the skin irritation study (Southwood, 1985), 2/6 rabbits could not be scored due to moderate to severe erythema and severe oedema adjacent to the application site. The mean Draize score observed was maximally 0.33 over 20 – 72 hours for both erythema and oedema in the remaining 4 rabbits. This means that the criteria for classification as irritating to skin are not met (*ie*. in at least 2/3 tested animals a mean score of ≥ 2.3 - ≤ 4.0 for erythema/eschar or for oedema). RAC supports the conclusion of the DS that according to CLP Regulation tefluthrin does **not** meet the criteria for classification for skin irritation.

4.4.2 Eye irritation

Table 24: Summary table of the relevant eye irritation study

Type of Study	Species	Result	Reference
Acute eye irritation	Rabbit	Slightly to mildly irritating, no classification	Southwood (1985, TOX2004-2667)
Acute eye irritation	Rabbit	Slightly to mildly irritating, no classification	Southwood (1987, TOX2004-2668)

4.4.2.1 Non-human information

Report: Southwood J (1985, TOX2004-2667), PP993: Skin Irritation and Eye Irritation Studies. Central Toxicology Laboratory; UK., Syngenta Unpublished Report No. CTL/P/987, study dates September to October 1983 (in-life phase). (Syngenta File No. ICI993/0631)

Guidelines: 92/69/EEC B.5 ≅ OECD 405 (1987)

Deviations: Only two rabbits were included in the study rather than the required minimum of three

GLP: This study was performed prior to the GLP certification of Laboratories but was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be supplementary.

Materials and methods:

Tefluthrin (PP993) technical; batch number P14; analysed purity 90.4 % w/w tefluthrin.

Tefluthrin (0.1 mL or 0.01 mL) was instilled into the conjunctival sac of one eye of each of two rabbits and an assessment of initial pain was made. Twenty to thirty seconds after dosing, the eye of the rabbit dosed with 0.1 mL was irrigated for approximately one minute with 100-150 mL of water. The irrigated eye was assessed 1-2 hours and 5-6 hours post-dosing, prior to the animal being killed. The non-irrigated test eye (treated with 0.01 mL) was assessed 1-2 hours and 3-4 hours post-dosing, prior to the animal being killed.

Findings:

General observations: Both of the rabbits showed a slight initial pain reaction (class 2 on a 0-5 scale) following instillation of tefluthrin into the eye.

In the non-irrigated eye, no corneal opacity or iritis was observed. Slight conjunctival redness and moderate or slight discharge was observed at both readings taken at 1-2 and 3-4 hours following instillation. Approximately 3 hours after instillation, the animal was observed to be experiencing severe pain and discomfort and so the animal was killed.

In the irrigated eye, no corneal opacity or iritis was observed. Slight or moderate conjunctival redness, slight or mild chemosis and extreme discharge was observed up to 5-6 hours following instillation. Approximately 5-6 hours after instillation, the animal was observed to be experiencing severe discomfort and so the animal was killed (see table below).

Table 25: Eye Irritation Scores (Draize Scale) in the Rabbit

Animal/Time	Cornea	Iris	Conjunctiva
Non-irrigated: 1-2 hours	0.0	0.0	6.0
Non-irrigated: 3-4 hours	0.0	0.0	4.0
Irrigated: 1- 2 hours	0.0	0.0	12.0
Irrigated: 5-6 hours	0.0	0.0	6.0

Conclusion:

Tefluthrin caused severe pain or discomfort and was a slight irritant in both the irrigated and non-irrigated rabbit eye. However, the study was considered to be supplementary and can not be used for classification.

Report: Southwood J (1987, TOX2004-2668), Tefluthrin: Eye Irritation to the Rabbit. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1846, study dates January to February 1987 (in-life phase). (Syngenta File No. ICI993/0083)

Guidelines: 92/69/EEC B.5 ≅ OECD 405 (1987)

Deviations: Six rabbits were treated during the study, but only two were examined for at least 3 days, due to mortalities. The eye irritation classification was therefore based on limited data.

GLP: This study was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin technical; batch number P14; analysed purity 90.4 % w/w tefluthrin.

Prior to the instillation of the test substance, all rabbits were pre-treated (intravenously) with an analgesic. Tefluthrin (0.1 mL) was instilled into the conjunctival sac of one eye of each of six rabbits and an assessment of initial pain was made.

The eyes were examined, with the aid of fluorescein from day 1 after dosing, for a maximum of 17 days (in one animal), to assess the grade of ocular reaction.

Findings:

General observations: Immediately following dosing, three rabbits had slight, two had moderate and one had practically no initial pain (despite pre-dosing with analgesic). As a consequence, four rabbits received a second dose and one animal received two further doses of the analgesic. One animal was assessed for up to 4 days and one assessed for 17 days. Four animals were killed on the day of dosing, one approximately one hour after instillation.

All five animals which were observed 2 hours following dosing showed conjunctival effects which consisted of slight or moderate redness, slight or mild chemosis and slight or severe discharge. There were no corneal or iridial effects (see table below). Of the two surviving animals, all signs of irritation had disappeared by three or nine days after instillation.

Table 26: Eye Irritation Scores (Draize Scale) in the Rabbit

Time	Cornea/Iris					Conjunctiva														
						Discharge					Redness					Chemosis				
Animal No.	**9**	**10**	**11**	**12**	**13**	**9**	**10**	**11**	**12**	**13**	**9**	**10**	**11**	**12**	**13**	**9**	**10**	**11**	**12**	**13**
After ≈1 hr	0	0	0	0	0	3	1	3	3	3	1	2	1	2	2	2	2	2	2	1
After 1 day	0	-	0	-	-	0	-	0	-	-	2	-	1	-	-	2	-	0	-	-
After 2 days	0	-	0	-	-	0	-	0	-	-	2	-	1	-	-	2	-	0	-	-
After 3 days	0	-	0	-	-	0	-	0	-	-	1	-	0	-	-	1	-	0	-	-
Mean score 24-72 hrs	0.0					0.0					1.2					0.8				

- animal dead

Animal number 14 had a moderate initial pain reaction and was killed within 1 hour following dosing

Additional observations included convoluted eyelids, thickened eyelids, erythema of the upper and/or lower eyelid and Harderian discharge. In addition, all animals showed responses which were consistent with animals experiencing sensory effects (paraesthesia) such as excessive blinking, shaking of the head and pawing of the eye. Four of the six animals showing paraesthesia effects were distressed and were humanely killed. The final irritation assessment was therefore based on the limited data on the three animals killed on day 1 and the two surviving animals.

Conclusion:

Tefluthrin was a mild irritant to the rabbit eye and has the potential to cause the additional effect paraesthesia. However, the recorded values do not trigger the required CLP criteria for classification as irritating to eyes.

4.4.2.2 Human information

No studies submitted by the applicant.

4.4.2.3 Summary and discussion of eye irritation

Tefluthrin caused mild irritation to the rabbit eye and has the potential to cause the additional effect paraesthesia. However, the recorded values do not trigger the required CLP criteria for classification as irritating to eye.

4.4.2.4 Comparison with criteria

As the study findings did not reach the critical thresholds to be classified as eye irritant according CLP criteria [Irritating to eyes (category 2, H319): at least in 2/3 tested animals a positive response of corneal opacity: ≥ 1 and/or iritis: ≥ 1 and/or conjunctival redness: ≥ 2 and/or conjunctival oedema (chemosis): ≥ 2] classification and labelling is not needed.

4.4.2.5 Conclusions on classification and labelling

In summary and based on the submitted data tefluthrin did not meet the criteria to be classified for eye irritation/corrosion according to the criteria in CLP Regulation.

RAC evaluation of eye corrosion/irritation

Summary of the Dossier submitter's proposal

In an eye irritation study (Southwood, 1987) tefluthrin (0.1mL) was instilled into the conjunctival sac of one eye of each of six New Zealand White male rabbits (in accordance with 92/69/EEC B.5 ≅ OECD TG 405). Prior to instillation of tefluthrin, all rabbits were pretreated intraveneously with an analgesic to prevent pain and discomfort. The following findings were reported:

- Immediately following dosing, three rabbits had slight, two had moderate and one had practically no initial pain (despite pre-dosing with analgesic). As a consequence, four rabbits received a second dose and one animal received two further doses of the analgesic.
- All rabbits showed effects of paraesthesia (excessive blinking, shaking of the head and pawing of the eye).
- Four of the six rabbits were distressed and were humanely killed on the day of dosing. One approximately one hour after instillation.
- Conjunctival effects (slight or moderate redness, slight or mild chemosis and slight or severe discharge) in all five rabbits 2 hours following dosing.
- Of the two surviving animals, all signs of irritation had disappeared by three or nine days after instillation.

The DS concluded that tefluthrin did not meet the criteria to be classified for eye irritation/corrosion according to the CLP Regulation.

Comments received during public consultation

One MSCA commented on the quality of the eye irritation study.The MSCA questioned the validity of the test presented in the dossier. According to the MSCA, the evaluation criteria on the eye damage/irritation are based on the severity of the eye damage, and the reversibility within the observation period of 21 days in the Southwood study did not seem to be relevant for the assessment of eye irritation. Besides, no information was provided relating to the assessment of the animals up to 4 and 17 days.

Assessment and comparison with the classification criteria

The mean scores for a substance to be classified as eye irritant according CLP criteria (Irritating to eyes (category 2, H319)) are:

at least in 2/3 tested animals a positive response of

- corneal opacity: ≥ 1 and/or
- iritis: ≥ 1 and/or
- conjunctival redness: ≥ 2 and/or
- conjunctival oedema (chemosis): ≥ 2

following grading at 24, 48 and 72 hours after installation of the test material, and which fully reverses within an observation period of 21 days.

As can be seen from Table 26 in the CLH report, the two surviving rabbits (no 9 and 11) had a mean score < 2 for both conjunctival redness and chemosis. Accordingly, the remaining rabbits (no 10, 12, 13 and 14) should have had a mean score > 2 for conjunctival redness or conjunctival chemosis after day 1, 2 and 3 (if they had not been killed on the day of dosing) if classification in category 2; H319 would have been warranted. This is actually possible from the data in Table 26 of the CLH report, but it seems unlikely since the scores of the two surviving rabbits drop from day 1 to day 3. Since the assessment is based on only two rabbits (1/3 of the tested animals) the available data are not adequate to determine the eye irritation potential of tefluthrin.

Based on the limited data available (four of the six rabbits had to be humanely killed on the day of dosing since administration was painful and distressing), RAC does not support classification for severe eye damage/eye irritation.

4.4.3 Respiratory tract irritation

No studies (conducted in non-humans or humans) concerning respiratory tract irritation were available. In the acute inhalation study, transient respiratory noise was observed below lethal dose levels, and histopathological findings were noted at lethal dose level.

Neither histopathological findings nor practical observations in humans are available. In summary and based on the submitted data, tefluthrin did not meet the criteria to be classified as respiratory tract irritant.

4.5 Corrosivity

No specific studies regarding corrosion were submitted. Corrosion was not seen in the studies for dermal or eye irritation. Hence, no classification for corrosion of skin or eye was needed.

4.6 Sensitisation

4.6.1 Skin sensitisation

Table 27: Summary table of the relevant skin sensitisation study

Type of Study	Species	Result	Reference
Skin sensitisation	Guinea pig	Not a sensitiser	Barber (1984, TOX2004-2670)

4.6.1.1 Non-human information

Report: Barber J (1984, TOX2004-2670), PP993: Skin Sensitisation Study. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1118, study dates September to October 1983. (Syngenta File No. ICI993/0079)

Guidelines: 96/54/EC B.6 ≅ OECD 406 (1992)
The study was performed prior to the above guideline but has been checked for compliance with the above

Deviations: lt is not reported whether or not signs of irritation were seen during the induction phase of the main study. The individual weights of the animals were not recorded only the overall weight range prior to the start of the study was given. The results of the positive control study were not included in this report.

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin technical; batch No. P14; analysed purity 90.4 % w/w tefluthrin.

The sensitisation potential of tefluthrin technical was assessed using a method based on the maximisation test of Magnusson and Kligman (1970).

A group of 20 test and 10 control young adult female Alpk: Dunkin Hartley guinea pigs were used for the main study. Two main procedures were involved; (a) the induction of an immune response; (b) a challenge of that response.

In test animals, the induction phase involved 3 intradermal injections of a 5 % w/v preparation of tefluthrin in corn oil, a 5 % w/v preparation of tefluthrin in a 1:1 preparation of corn oil: Freund's complete adjuvant (FCA) and a 1:1 preparation of corn oil:FCA to a shorn area of the scapular region. This was followed 1 week later by a topical induction using the undiluted test substance under an occlusive dressing for 48 hours. For control animals the intradermal injections were corn oil:FCA x2 and corn oil alone, and the topical applications were as for the test animals except that dressings only were applied. Application sites were checked one day after removal of the dressings.

In the challenge phase, two weeks after completion of the induction phase, a 50 % w/v preparation of tefluthrin in corn oil (0.05 - 0.1 mL) was applied to the shorn left flank and a 10 % w/v preparation in corn oil was applied to the shorn right flank of test animals under an occlusive dressing for 24 hours.

Skin sites were examined approximately 1 and 2 days after removal of the dressings.

Findings:

General observations: One animal was found dead prior to challenge applications and one animal had slight scabbing outside the application area.

Twenty-four hours following challenge with a 50 % (w/v) solution, one animal had scattered, mild redness, but this did not persist and no erythema was seen in any other test animal. One control animal had scattered, mild redness at the forty-eight hour reading only and a second control animal had scattered, mild redness at both the twenty-four and forty-eight hour readings; however, this was considered to have been caused by scratching and these values were excluded from the numerical assessment (see table below).

It was calculated that 5.2 % of the test animals responded and 11.1 % of the control animals responded.

No erythema was seen in any of the test animals following challenge with a 10 % (w/v) solution but one control animal had scattered, mild redness at both the twenty-four and forty-eight hour readings.

It was calculated that none of the test animals responded but that 10 % of the control animals responded.

Table 28: Maximisation Test: Summary of Skin Responses

Scored after		24 hours	48 hours
Negative control	50 % w/v preparation	1/10?	1/10?
	10 % w/v preparation	0/10	0/10
Test groups	50 % w/v preparation	1/19	0/19
	10 % w/v preparation	0/19	0/19

? erythema thought to be due to scratching and therefore not included in the numerical assessment

Conclusion:

When previously-induced guinea-pigs were challenged with either 50 % or 10 % solutions of tefluthrin in corn oil, no sensitisation responses were elicited.

4.6.1.2 Human information

No studies submitted by the applicant.

4.6.1.3 Summary and discussion of skin sensitisation

Tefluthrin is not a dermal sensitizer.

4.6.1.4 Comparison with criteria

In the stud it was not reported whether or not signs of irritation were seen during the induction phase of the main study and therefore it is not possible to compare on basis of concentration for intradermal induction. However, this is considered acceptable, since the previously induced guinea-pigs were challenged with either 50 % or 10 % solutions of tefluthrin and no sensitisation responses were elicited.

4.6.1.5 Conclusions on classification and labelling

Classification and labelling is not needed.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal
In a GPMT skin sensitisation study (Barber, 1984) a group of 20 test and 10 control young adult female Alpk Dunkin Hartley guinea pigs were used (in accordance with 96/54/EC B.6 ≅ OECD TG 406). The intradermal induction was conducted using 5 % tefluthrin solutions. Following challenge, the following findings were reported:

- 5.2 % of the test animals responded (erythema) and 11.1 % of the control animals responded when challenged with a 50 % (w/v) tefluthrin solution.
- No erythema was seen in any of the test animals following challenge with a 10 % (w/v) solution

It was not reported whether or not signs of irritation were seen during the induction phase and therefore it is not possible to determine whether this was the maximum non-irritating intradermal concentration.

The DS concluded that when previously-induced guinea-pigs were challenged with either 50 % or 10 % solutions of tefluthrin in corn oil, no sensitisation responses were elicited. According to the CLP criteria, tefluthrin should therefore not be classified as a skin sensitiser.

Comments received during public consultation
No comments were received during public consultation.

Assessment and comparison with the classification criteria
In the Skin Sensitisation study where previously-induced guinea-pigs were challenged with either 50 % or 10 % solutions of tefluthrin in corn oil, erythema was seen in only 1/19 guinea-pigs in the 50 % group (and 1/10 in the control).

RAC agrees with the DS conclusion that tefluthrin should **not** be classified as a skin sensitiser, since positive skin reactions were observed in less than 30% of exposed animals.

4.6.2 Respiratory sensitisation

No data/information (from non-humans or humans) was submitted that would allow an evaluation of sensitising properties for the respiratory tract.

4.7 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Tefluthrin was not tested in a 28-day oral toxicity study.
In a 13-week dietary study in rats, a significant reduction in body weight gain was seen of both sexes fed 350 ppm (31.8 mg/kg bw/d), the NOAEL was considered to be 150 ppm (13.6 mg/kg bw/d)

In a 13-week oral study in dogs, via capsule administration, whole body tremors were seen in one female dog at the high dose of 1.5 mg/kg/day on day 4, approximately 3 hours after dosing. There was full recovery within one hour and these signs were not observed again in this animal. A slight, statistically significant increase in mean thyroid weight was noted in females at 1.5 mg/kg bw/d. In a one-year dog study, ataxia and tremors (indicative of neurotoxicity) were seen in 9/12 dogs at 2 mg/kg bw/d mostly during the first few weeks of treatment. One male dog at 2 mg/kg bw/d died during week 36. This dog showed signs of neurological effects earlier in the study. A small reduction in body weight gain was also noted in males at 2 mg/kg bw/d.

Dermal administration of tefluthrin to rats for 21 days resulted in behavioural responses indicative of paraesthesia, but no systemic toxicity at all dose levels. Signs of severe skin irritation were observed at 50 mg/kg bw/d that may have been exacerbated by the animals biting and chewing the application sited. No indication of skin irritation was observed at lower dose levels.

Table 29: Summary table of relevant repeated dose toxicity studies

Type of Study	Species	Dose Levels Tested	NOAEL	Reference
Oral, 13 weeks	Rat	0, 50, 150, 350 ppm (0, 4.5, 13.6, 31.8 mg/kg bw/d)	150 ppm (13.6 mg/kg bw/d)	Stonard et al (1984, TOX2004-2672/2673)
Oral, 13 weeks	Dog	0, 0.1, 0.5, 1.5 mg/kg bw/d (capsule)	0.5 mg/kg bw/d	Kalinowski et al (1985, TOX2004-2745)
Oral, 52 weeks	Dog	0, 0.1, 0.5, 2.0 mg/kg bw/d (capsule)	0.5 mg/kg bw/d	Stonard (1986, TOX2004-2671)
Dermal, 21 day	Rat	0, 0.1, 1.0, 50 mg/kg bw/d	Systemic: 50 mg/kg bw/d; local: 0.1 mg/kg bw/d (LOAEL)	Leah (1989, TOX2004-2674/2675)

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Report: Stonard M, Banham P, Chart I *et al* (1984, TOX2004-2672/2673), PP993: 90 Day Feeding Study in Rats. Central Toxicology Laboratory; UK., Syngenta Unpublished Report No. CTL/P/1026, study dates May 1983 to September 1983 (in-life phase). (Syngenta File No. ICI993/0093, ICI993/0092)

Guidelines: 87/302/EEC B.26 ≅ OECD 408 (1981)

Deviations: Several of the clinical chemistry parameters were not measured. Ophthalmoscopic examinations were not done before the start of the study. Harderian glands rather than exorbital lachrymal glands were examined. Femur was examined but the report does not specify whether this included the joint. Bone marrow was taken from the femur, sternum was not taken. The exact areas of the spinal cord and brain which were examined are not reported.

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin (PP993) technical; batch number P14; analysed purity 90.4 % w/w, subsequent analysis 93 % w/w tefluthrin.

Groups of 20 male and 20 female rats were fed diets containing 0 (control), 50, 150 or 350 ppm tefluthrin for a period of 90 days. Samples from all dietary levels (including controls) were taken at intervals throughout the study and analysed for achieved concentration. Stability for a period of up to 2 months and homogeneity at the low and high dose were measured.

Clinical observations, body weights, food consumption, haematology and clinical biochemistry (blood and urine) were measured throughout the study. At the end of the scheduled period the animals were killed and subjected to a full examination *post mortem.* Terminal blood and bone marrow samples were taken, selected organs were weighed and specified tissues were taken for subsequent histopathology examination.

Findings:

General observations**:** Diet analysis showed that the achieved concentrations were lower than expected in a number of batches. Low and middle dose levels were within 10% of nominal concentration and the high dose level was slightly outside this range. The homogeneity stability of tefluthrin in diet at the lowest and highest concentrations were satisfactory. The chemical stability of tefluthrin at 50 ppm remained acceptably steady over the first 5 weeks and then showed a slight apparent fall at 2 months. At the highest dietary level, a slight apparent fall in concentration (approximately 10 %) was seen 3 weeks after preparation of the diet but thereafter values remained steady up to 2 months. It should be taken into account that the dates of preparation of batches of the diet and the period for which each batch was fed amounted to one month.

Dose rates (based on nominal dietary levels of tefluthrin) were calculated in terms of mg tefluthrin/kg body weight/day and are shown in the table below.

Table 30: Overall Mean Dose Received (mg/kg bw/d)

Dose Level of Tefluthrin (ppm)		
50	150	350
4.5	13.6	31.8

There were no mortalities. Few clinical abnormalities were seen: Slight retinal pallor was seen in 3/20 male rats in the 350 ppm group, therefore the eyes of male rats in the 150 ppm group were also examined, but no pallor of the retina was observed in these animals.

Body weight gain in both sexes in the 350 ppm group was reduced throughout the study as shown in the table below.

Table 31: Intergroup Comparison of Body Weight Gain (g) – Selected Time Points

	Dose Level of Tefluthrin (ppm)							
	Males				Females			
	0	50	150	350	0	50	150	350
Initial weight	127.8	127.0	126.5	126.6	108.9	111.7	111.1	110.6
Week 1	52.9	55.6	51.6	36.1**	32.5	34.4	33.6	23.0**
Week 4	189.6	195.3	190.0	171.2**	91.0	92.3	92.1	78.5**
Week 8	279.9	284.3	274.3	250.8**	130.3	133.8	131.1	116.0**
Week 13	348.9	356.3	348.4	313.4**	153.7	157.3	153.5	139.0**

** Statistically significantly different from the control group mean at the 1 % level

Food consumption (see table below) in both sexes in the 350 ppm group was reduced compared with controls, particularly during the first half of the study, but there was no effect on food utilisation.

Table 32: Intergroup Comparison of Food Consumption (g/rat/day) – Selected Time Points

	Dose Level of Tefluthrin (ppm)							
	Males				Females			
	0	50	150	350	0	50	150	350
Week 1	21.9	22.4	21.2	18.0**	17.8	18.1	17.3	15.0**
Week 4	26.7	27.3	26.7	25.5	18.4	18.9	18.4	16.7**
Week 8	24.7	24.3	23.6	23.1*	17.6	17.8	17.8	16.5
Week 13	24.0	24.3	24.1	23.1	17.3	17.3	17.4	16.3
Total (1-13)	2341.3	2361.1	2302.6	2196.9*	1646.2	1664.1	1654.0	1518.9**

** Statistically significantly different from the control group mean at the 1 % level
* Statistically significantly different from the control group mean at the 5 % level

Haematological changes associated with treatment were mainly confined to small reductions in haemoglobin, haematocrit and red blood cell count in both sexes at 350 ppm tefluthrin. A reduction in white blood cell count, mainly due to lymphocytes and neutrophils, was found only at 150 ppm. None of these changes was considered to be toxicologically significant.

A small increase in plasma urea was noted at weeks 4 and 13 in both sexes at 350 ppm tefluthrin, and in plasma cholesterol at weeks 4 and 13 in males at 150 and 350 ppm tefluthrin. Other

statistically significant differences compared with controls, in blood and urine clinical chemistry parameters, were isolated and considered not to be toxicologically significant.

There was no evidence of any effect on hepatic aminopyrine-N-demethylase activity in any group.

Gross pathology, organ weights, histopathology: There was some evidence of reduced absolute lung and heart weights in both sexes and in absolute spleen weight in females fed 350 ppm tefluthrin. However, there were no differences from control when adjusted for final body weight. In males, there was a dose-related increase in liver weights after adjustment for final body weight (see table below).

Table 33: Intergroup Comparison of Liver Weight

	Dose Level of Tefluthrin (ppm)							
	Males				**Females**			
Liver	0	50	150	350	0	50	150	350
Absolute weight	17.1	18.1	18.8**	17.9	10.2	10.3	10.1	9.6
Adjusted for final body weight	16.8	17.6*	18.6**	19.0**	10.1	10.0	9.9	10.1

** Statistically significantly different from the control group mean at the 1 % level
* Statistically significantly different from the control group mean at the 5 % level

There were no macroscopic or microscopic findings *post mortem* which could be attributed to treatment with tefluthrin.

Conclusion:

A significant reduction in body weight gain was seen in rats of both sexes fed 350 ppm tefluthrin. The NOAEL was 150 ppm tefluthrin (13.6 mg/kg bw/d) when fed to rats over a 90 day period.

Report:	Kalinowski A, Banham P, Brammer A et al (1985; TOX2004-2745), PP993: 90 Day Oral Dosing Study in Dogs. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1151, study dates April 1984 to July 1984 (in-life phase). (Syngenta File No. ICI993/0097)
Guidelines:	87/302/EEC B.27 ≅ OECD 409 (1981)
Deviations:	Urinanalysis was not performed.
GLP:	This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.
Acceptability:	The study is considered to be acceptable.

Materials and methods: Tefluthrin (PP993) technical; batch number P16; analysed purity 95.1 % w/w tefluthrin.

Groups of 4 male and 4 female beagle dogs were dosed daily with 0, 0.1, 0.5 or 1.5 mg tefluthrin/kg bw/d (tefluthrin was dissolved in corn oil and administered in gelatine capsules), for 90 days.

Clinical observations (including ophthalmoscopy), body weights, food consumption, haematology and clinical biochemistry were measured throughout the study. At the end of the scheduled period the animals were killed and subjected to an examination *post mortem.* Bone marrow samples were taken, selected organs were weighed and specified tissues were taken for subsequent histopathology examination.

Findings:

General observations: Analysis confirmed that the achieved concentrations and the chemical stability of tefluthrin in corn oil were satisfactory.

There were no mortalities. Whole body tremors were seen in one female dog in the 1.5 mg tefluthrin/kg bw/d group on day 4, approximately 3 hours after dosing. There was full recovery within one hour and these signs were not observed again in this animal. There were no other treatment-related clinical or ophthalmological findings in other dogs of either sex.

There were no treatment-related effects on body weight or food consumption in either sex.

Clinical pathology**:** There was no evidence of any treatment-related effect on any haematological parameters. Plasma triglyceride levels of males given 1.5 mg/kg bw/d were slightly raised at weeks 4, 8 and 13 (see table below), other clinical chemistry parameters were similar to control.

Table 34: Intergroup Comparison Plasma Triglyceride Levels (mg/100 mL) - Males

Week	Dose Level of Tefluthrin (mg/kg bw/d)			
	0	0.1	0.5	1.5
4	33.7	34.0	37.7	42.6
8	31.5	32.7	33.4	41.6**
13	35.2	33.2	35.2	45.4**

** Statistically significantly different from the control group mean at the 1 % level

Gross pathology, organ weights, histopathology: There was a slight increase in the thyroid gland weights of the females in the 1.5 mg tefluthrin/kg bw/d group (see table below).

Table 35: Intergroup Comparison of Thyroid Weight (g) - Females

Dose Level of Tefluthrin (mg/kg bw/d)			
0	0.1	0.5	1.5
0.804	0.837	0.790	1.008*

* Statistically significantly different from the control group mean at the 5 % level

There were no macroscopic or microscopic findings *post mortem* which could be attributed to treatment with tefluthrin.

Conclusion:

The NOAEL was 0.5 mg tefluthrin/kg bw/d in dogs over 90 days, based on the neurotoxicity observed in 1 female treated at 1.5 mg/kg bw/d on day 4.

Report:	Stonard M (1986, TOX2004-2671 main report, 1987 and 1990 supplements), Tefluthrin: 1 Year Oral Dosing Study in Dogs. Central Toxicology Laboratory; UK., Syngenta Unpublished Report No. CTL/P/1575, study dates 29 January 1985 to 10 February 1986 (in-life phase). (Syngenta File No. ICI993/0102 main report, ICI993/0099 and ICI993/0100 supplements)
Guidelines:	67/548/EEC B.30 ≅ OECD 452 (1981)
Deviations:	There was no urinalysis in this study. Gamma glutamyl transpeptidase and ornithine decarboxylase were not measured. Accessory genital organs were only taken at *post mortem* examination if grossly abnormal. Sternum with bone marrow was not taken.
GLP:	This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.
Acceptability:	The study is considered to be acceptable.

Materials and methods:

Tefluthrin technical; batch number P16; analysed purity 95.1 % w/w tefluthrin.

Groups of 6 male and 6 female beagle dogs were dosed with gelatine capsules containing 0, 0.1, 0.5 or 2.0 mg tefluthrin/kg bw/d for 1 year. All dosing solutions were analysed for achieved concentration. Stability of tefluthrin in corn oil had been confirmed in previous studies.

Clinical observations (including cardiac and pulmonary auscultation and ophthalmoscopy), body weights, food consumption, haematology and clinical chemistry were measured during the study. At the end of the scheduled period the animals were killed and given a full examination *post mortem.* Selected organs were weighed and specified tissues were taken for subsequent histopathological examination.

Findings:

General observations: The achieved concentrations of tefluthrin were within 6 % of target levels. The satisfactory stability of tefluthrin in corn oil had been demonstrated in earlier studies.

One male given 2 mg/kg bw/d died during week 36, but in the four weeks preceding death no clinical abnormalities had been observed for this animal.

There was a dose-related increase in fluid faeces for male dogs and a slight increase in fluid faeces in females given 2 mg/kg bw/d. When tefluthrin is administered by diet, even at highly toxic doses, there is no evidence of fluid faeces and, therefore, it is considered that the incidence of fluid faeces is as a result of the method of administration. Ataxia and tremors were seen in 9/12 dogs given 2 mg/kg bw/d and in the majority of instances this was noted in the first few weeks of treatment. The dog found dead had shown signs of neurological effects earlier in the study and lesions on its claws and chin (observed at macroscopic examination *post mortem*) suggest that a neurotoxic event may have preceded death. Ataxia or unsteady gait and body tremors were seen on one occasion in one dog given 0.1 mg/kg bw/d and were accompanied by a distended abdomen, as this was resolved by expulsion of a large quantity of intestinal gas, this was considered not to be treatment-related (please see the table below).

Table 36: Incidence of Ataxia and Body Tremors in One Year Oral Dose in Dogs

Treatment (mg tefluthrin/kg)	Sex	Time Period (Week of Treatment)												
		1-4	5-8	9-12	13-16	17-20	21-24	25-27	29-32	33-36	37-40	41-44	45-48	49-52
0.1	Male						1A(1) 1T(1)							
2.0	Male	1A(1) 3T(2)					1A(1)			1A(1)				
	Female	7A(6) 5T(3)	1A(1) 1T(1)			1A(1) 2T(1)						2T(1)		1T(1)

A - Ataxia or unsteady gait.
T - Tremors.
( ) - Number of dogs affected.

Where blanks are shown, animals were observed, but ataxia or tremors were not seen.

Values are days/group that the observation was made.

Note: No observations of ataxia or tremors were made for dogs given 0.5mg tefluthrin/kg/day, in females given 0.1mg tefluthrin/kg/day or in control animals.

There was no statistically significant, dose-related effect on weight gain in male or female dogs. However, the mean body weight gain of males given 2 mg/kg bw/d was less than would be expected and may represent an effect of tefluthrin (see table below).

Table 37: Intergroup Comparison of Body Weight Gain (kg) - Selected Timepoints

	Concentration of Tefluthrin (mg/kg bw/d)							
	Males				Females			
Week	0 (control)	0.1	0.5	2	0 (control)	0.1	0.5	2
4	1.05	0.82	0.97	0.80	0.40	0.62	0.73**	0.50
20	3.17	2.57	2.55	2.30	1.98	1.90	2.33	1.73
36	3.75	3.03	2.88	2.38	2.67	2.23	2.65	2.15
52	3.97	3.28	3.33	2.67	2.67	2.47	3.00	2.58

** Statistically significant difference from control group mean, 1 % level (Student's t-test, 2-sided)

Food consumption was unaffected by treatment with tefluthrin.

Clinical pathology: There were no treatment-related effects on any haematological or clinical chemistry parameter. Any isolated statistically significant differences from controls were within normal ranges for dogs of this age and strain.

Gross pathology, organ weights, histopathology: The male dog (2 mg/kg bw/d) which died had worn claws, blood staining on the forelegs and a subcutaneous haemorrhage under the chin. A variety of gross pathological changes was observed in control and treated dogs at termination, but none was considered to be treatment-related.

There was a slight, but not statistically significant, increase in liver and kidney weights adjusted for body weight, in males fed 2 mg/kg bw/d.

Histopathological examination revealed congestion of several internal organs in the animal that died. Bilateral optic neuritis, choroiditis and scleritis with focal unilateral retinal degeneration was

seen in one female given 2 mg/kg bw/d. All other changes observed histopathologically are consistent with normal findings for beagles of this age and strain.

Conclusion:

The NOAEL was 0.5 mg/kg bw/d, based on the single death, overt signs of neurotoxicity (tremor, ataxia) and the possible treatment-related single incidence of eye lesions at 2 mg/kg bw/d.

4.7.1.2 Repeated dose toxicity: inhalation

The vapour pressure of tefluthrin is 8 x 10^{-6} kPa at 20 °C. Furthermore, tefluthrin is encapsulated within the liquid formulation and this formulation is then used as a seed pelleting treatment. The vapour pressure of the active ingredient and the use pattern of the product indicate that inhalation exposure is not likely to occur. For this reason, it is not necessary to perform short-term inhalation toxicity studies.

4.7.1.3 Repeated dose toxicity: dermal

Report:	Leah A (1989, TOX2004-2674/2675), Tefluthrin: 21-Day Dermal Toxicity to the Rat. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/2488, study dates November to December 1988 (in-life phase). (Syngenta File No. ICI993/0090 and ICI993/0091)
Guidelines:	92/69/EEC B9 ≅ OECD 410 (1992) The study was performed prior to the above guideline but has been checked for compliance with the above
Deviations:	Animals were given 21 6-hour dermal applications. Chloride, ornithine decarboxylase and gamma glutamyl transpeptidase were not measured. The animals were not fasted prior to measurement of glucose. Adrenals were not weighed. Spleen, testes, adrenals and heart were examined histopathologically only if macroscopic abnormalities had been detected *post mortem*.
GLP:	Yes (laboratory certified by the UK authority)
Acceptability:	The study is considered to be acceptable.

Materials and methods:

Tefluthrin technical; batch number P16; analysed purity 96.5 % w/w tefluthrin.

Groups of ten male and ten female Alpk:AP_fSD rats received 6-hour dermal applications of 0.1, 1.0 or 50 mg/kg bw/d in PEG 300 for 21 consecutive days. A control group of animals was treated with PEG 300 only.

Dosing preparations were analysed for achieved concentration. Stability for a period of up to 13 days was measured.

The animals were assessed daily for any signs of systemic toxicity. Body weights and food consumption were recorded at intervals throughout the study. Twenty-four hours after the final application the animals were killed and cardiac blood samples taken for haematological and biochemical analysis. Each animal was subjected to a macroscopic examination post mortem, selected organs were weighed and selected tissues examined microscopically.

Findings:

General observations: The achieved concentrations and chemical stability of tefluthrin in PEG 300 were satisfactory.

There were no mortalities. Clinical observations (see table below) considered to be related to the administration of tefluthrin included a dose-related incidence of upward or downward curvature of the spine. At the lower doses this was transient and generally seen at decontamination only, and is typical of the known aetiology of paraesthesia. Other observations included tip-toe gait, splayed gait and bizarre behaviour and were also considered to be indicative of paraesthesia rather than systemic toxicity. Animals treated with 50 mg/kg bw/d showed severe skin irritation; on some days the severity was such that the test sample could not be applied. Some of the skin damage, particularly scabbing, is likely to have been self-inflicted as animals were observed to bite and chew the application site. No signs of skin irritation were seen at the lower dose levels.

Table 38: Intergroup Comparison of the Incidence of Selected Clinical Observations

	Dose Level of Tefluthrin (mg/kg bw/d)							
	Males				**Females**			
Observation	0	0.1	1.0	50	0	0.1	1.0	50
Curvature of the spine: Upward Downward	12 (7) 0	56 (10) 4 (4)	138 (10) 15 (6)	341 (10) 206 (10)	16 (9) 0	108 (10) 12 (5)	268 (10) 111 (10)	409 (10) 243 (10)
Tip-toe gait	0	0	2 (2)	11 (3)	0	1 (1)	3 (2)	133 (9)
Splayed gait	0	0	7 (2)	25 (8)	0	0	16 (5)	100 (10)
Bizarre behaviour	0	0	0	3 (3)	0	0	0	9 (6)

The number of animals affected is given in parenthesis

Animals dosed with 50 mg tefluthrin/kg bw/d lost weight after the first application, but thereafter showed a similar daily weight gain to controls. There was no adverse effect of treatment on food consumption.

There were a number of clinical biochemistry and haematology parameters which showed statistically significant differences from control, but none of these changes was considered to be toxicologically significant.

Gross pathology, organ weights, histopathology: There were no toxicologically significant differences in organ weights in treated animals compared with control animals.

Eight males and eight females dosed with 50 mg tefluthrin/kg bw/d had scabs on the treated skin, and the treated skin of one male in this group was thickened. Other macroscopic differences seen were considered not to be treatment-related.

Necrotic areas in the epidermis of males and females dosed with 50 mg tefluthrin/kg bw/d were seen, with surface exudate containing necrotic cells and areas of acanthosis and hyperkeratosis. One male had an epidermal abscess, and focal balloon degeneration occurred within the epidermis of some animals. The irritant nature of these lesions was reflected in the dermis where a minimal to moderate inflammatory cell infiltrate was observed with areas of fibrosis immediately below the epidermis in some animals. There was no evidence of any damage to the peripheral or central nervous system at any of the dose levels tested.

Conclusion:

Behavioural responses, indicative of paraesthesia were seen at all dose levels. Signs of severe skin irritation were observed at 50 mg tefluthrin/kg bw/d, which may have been exacerbated by the animals biting and chewing the application sites. No indication of significant skin irritation was observed at lower dose levels. In this study the systemic NOAEL was considered to be 50 mg/kg bw/d in the absence of true systemic toxicity, whereas for local effects the LOAEL was set at 0.1 mg/kg bw/d covering irritation/paraesthesia and secondary effects (curvature of the spine).

4.7.1.4 Repeated dose toxicity: other routes

No studies submitted by the applicant.

4.7.1.5 Human information

No studies submitted by the applicant.

4.7.1.6 Other relevant information

No studies submitted by the applicant.

4.7.1.7 Summary and discussion of repeated dose toxicity

Tefluthrin was not tested in a 28-day oral toxicity study.
In a 13-week dietary study in rats, a significant reduction in body weight gain was seen of both sexes fed 350 ppm (31.8 mg/kg bw/d), the NOAEL was considered to be 150 ppm (13.6 mg/kg bw/d).

In a 13-week oral study in dogs, via capsule administration, whole body tremors were seen in one female dog at the high dose of 1.5 mg/kg bw/d on day 4, approximately 3 hours after dosing. There was full recovery within one hour and these signs were not observed again in this animal. A slight, statistically significant increase in mean thyroid weight was noted in females at 1.5 mg/kg bw/d. In a one-year dog study, ataxia and tremors (indicative of neurotoxicity) were seen in 9/12 dogs at 2 mg/kg bw/d mostly during the first few weeks of treatment. One male dog at 2 mg/kg bw/d died during week 36. This dog showed signs of neurological effects earlier in the study. A small reduction in body weight gain was also noted in males at 2 mg/kg bw/d.

Dermal administration of tefluthrin to rats for 21 days resulted in behavioural responses indicative of paraesthesia, not systemic toxicity at all dose levels. Signs of severe skin irritation were observed at 50 mg/kg bw/d that may have been exacerbated by the animals biting and chewing the application sited. No indication of skin irritation was observed at lower dose levels. In this study the systemic NOAEL was considered to be 50 mg/kg bw/d in the absence of true systemic toxicity, whereas for local effects the LOAEL was set at 0.1 mg/kg bw/d covering irritation/paraesthesia and secondary effects (curvature of the spine).

4.7.2 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

The repeated dose studies were already summarized under point 4.7.1.7. However, considering a possible classification of tefluthrin with STOT-RE the subchronic neurotoxicity study in rats must also be taken into consideration. This study is presented under point 4.12.1.1.

Signs of neurotoxicity were observed after both single and repeated administration by various routes in animals.

The 90-d neurotoxicity studies in rats revealed the NOAEL of 11.6 mg/kg bw/d (150 ppm) based on diverse clinical signs and increased landing foot splay in female rats and additonally, a change in brain pathology in a single female was observed (supported by 90-d, rat: NOAEL of 13.6 mg/kg bw/d [150 ppm]).

Regarding neurotoxic effects, the dog is considered to be more sensitive compared to rats. The studies in dogs revealed a NOAEL of 0.5 mg/kg bw/d [90-d; 1-yr] based on neurotoxic effects observed at dose levels of 1.5 mg/kg bw/d (90-d) and 2.0 mg/kg bw/d [1-yr]. Indeed, the neurotoxic effects (tremor, ataxia) were more pronounced in the 1-yr dog study, however, these effects were already observed in the first few weeks of treatment.

According to CLP criteria classification with STOT-RE cat. 1; H372 (threshold for classification in cat. 1 $\leq$ 10 mg/kg bw/d) for tefluthrin is proposed based on the overt signs of neurotoxicity in dogs (tremor, ataxia) at 1.5 and 2.0 mg/kg bw/d (90-d; first few weeks of 1-yr).

Consideration for classification due to neurotoxic effects after repeated administration of tefluthrin was already recommended by the PRAPeR Expert Meeting in 2010.

4.7.3 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

CLP criteria: Category 1 (H372):
Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of:
reliable and good quality evidence from human cases or epidemiological studies; or observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations.

Equivalent guidance values for 28-day and 90-day studies:

Oral, rat: 28-day: ≤ 30 mg/kg bw/d; 90-day: ≤ 10 mg/kg bw/d

According to CLP, signs of neurotoxicity in dogs at 1.5 and 2.0 mg/kg bw/d in the 90-d study and in the first few weeks of the 1-yr study meet the criteria for classification with STOT-RE 1; H372 (nervous system).

4.7.4 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

Based on the results of repeated dose studies in dogs classification with STOT-RE 1; H372 (nervous system) is proposed.

RAC evaluation of specific target organ toxicity– repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

Four repeated dose toxicity studies were presented. The studies were conducted via oral and dermal routes.

In a 13-week dietary study (Stonard *et al*., 1984) groups of 20 male and 20 female Alpk:AP rats were fed diets containing 0, 50, 150 or 350 ppm tefluthrin (in accordance with 87/302/EEC B.26 ≅ OECD TG 408). The following findings were reported:

- Significant reduction in body weight gain and food consumption of both sexes at 350 ppm (31.8 mg/kg bw/d).
- Small reductions in haemoglobin, haematocrit and red blood cell count in both sexes at 350 ppm.
- Small increases in plasma urea at weeks 4 and 13 in both sexes at 350 ppm.
- Small increases in plasma cholesterol at weeks 4 and 13 in males at 150 and 350 ppm.
- Dose-related increase in liver weights in males.

NOAEL and LOAEL were considered to be 150 and 350 ppm (13.6 and 31.8 mg/kg bw/d), respectively, based on the reduction in body weight gain.

In a 13-week oral neurotoxicity study (Pinto, 2002) groups of 12 male and 12 female Alpk:APfSD rats were fed diets containing 0, 50, 150 or 350 ppm tefluthrin (in accordance with 96/54/EEC B.38 ≅ OECD TG 424 ≅ OPPTS 870.6200). The following findings were reported:

- Treatment-related findings included increased activity, irregular breathing, increased breathing rate, reduced splay reflex and paw flicking in the 350 ppm males.
- Treatment-related findings included increased activity, ataxia (from week 5), increased breathing rate, reduced splay reflex, upward curvature of the spine, piloerection, increased response to sound, abnormal gait and paw flicking in the 350 ppm females. There was an increase in the incidence and severity as the study progressed for the ataxia, increased activity, upward curvature of the spine and reduced splay reflex.
- Landing foot splay was significantly increased in weeks 5, 9 and 14 in the 350 ppm females.
- At 150 ppm two females had increased breathing rate in week 5, another female in week 14, and one female had upward curvature of the spine from week 9. One female fed 50 ppm had increased breathing rate at week 2 only.
- Change in brain pathology in a single 350 ppm female.
- Significant reduction in body weight and food consumption in the first 5 weeks in the 350 ppm females.
- Significant reduction in food consumption in the first week in the 350 ppm females and a slight reduction in food consumption at all doses for males.

Other observations:

All animals survived to scheduled termination. No effects on motor activity or on brain weights were observed in either sex.

The NOAEL and LOAEL were considered to be 150 and 350 ppm (11.6 and 26.6 mg/kg bw/d for females), respectively.

In a 13-week oral study (Kalinowski *et al*., 1985) groups of 4 male and 4 female Alderley Park beagle dogs were dosed daily with 0, 0.1, 0.5 or 1.5 mg/kg bw/d tefluthrin (in accordance with 87/302/EEC B.27 ≅ OECD TG 409). The following findings were reported:

- Whole body tremors in one female dog in the 1.5 mg tefluthrin/kg bw/d group on day 4, approximately 3 hours after dosing - full recovery occurred within one hour.
- Plasma triglyceride levels of males given 1.5 mg/kg bw/d were slightly raised at weeks 4, 8 and 13.
- Slight increase in the thyroid gland weights in the 1.5 mg/kg bw/d females.

The NOAEL and LOAEL were considered to be 0.5 and 1.5 mg/kg bw/d, respectively, based on the neurotoxicity observed in 1 female at 1.5 mg/kg bw/d on day 4.

In a 1-year oral study (Stonard, 1986) groups of 6 male and 6 female Alderley Park beagle dogs were dosed with gelatine capsules containing 0, 0.1, 0.5 or 2.0 mg/kg bw/d tefluthrin (in accordance with 67/348/EEC B.30 ≅ OECD TG 452). The following findings were reported:

- Ataxia and tremors in 9/12 dogs given 2 mg/kg bw/d; in the majority of instances these effects were noted within the first few weeks of treatment (weeks 1 – 4), but ataxia and tremors were also seen in the middle and the end of the testing period.
- Bilateral optic neuritis, choroiditis and scleritis with focal unilateral retinal degeneration in one female at 2 mg/kg bw/d.
- Mean body weight gain of males at 2 mg/kg bw/d was low.
- Slight, but not statistically significant, increase in liver and kidney weights, in males at 2 mg/kg bw/d.

Other observations:
One 2 mg/kg bw/d male died during week 36, but no clinical abnormalities had been observed in this dog within four weeks preceding death. The dog had shown signs of neurological effects earlier in the study and lesions on its claws and chin suggesting that neurotoxic events may have preceded the death.

The NOAEL and LOAEL were considered to be 0.5 and 2.0 mg/kg bw/d, respectively, based on a single death, signs of neurotoxicity (tremor and ataxia) and the possible treatment-related single incidence of eye lesions at 2 mg/kg bw/d.

In a 21 day dermal study (Leah, 1989) groups of ten male and ten female Alpk:AP$_f$SD rats received 6-hour dermal applications of the test substance at 0, 0.1, 1.0 or 50 mg/kg bw/d in PEG 300 (in accordance with 92/69/EEC B.9 ≅ OECD TG 410). The following findings were reported:

- Dose-related incidence of upward or downward curvature of the spine.
- In both males and females tip-toe gait and splayed gait from 1.0 mg/kg bw/d and bizarre behaviour at 50 mg/kg bw/d - these were considered to be indicative of paraesthesia rather than systemic toxicity.
- Eight males and eight females dosed with 50 mg/kg bw/d had scabs on the treated skin, and the treated skin of one male in this group was thickened.
- Signs of severe skin irritation at 50 mg/kg bw/d.

The systemic NOAEL was considered to be 50 mg/kg bw/d (highest dose) in the absence of true systemic toxicity, whereas for local effects the LOAEL was set at 0.1 mg/kg bw/d covering irritation/paraesthesia and secondary effects (curvature of the spine).

Based on the overt signs of neurotoxicity in dogs (tremor, ataxia) at 1.5 and 2.0 mg/kg bw/d (90-days; first few weeks of 1-year study), the DS proposed that according to CLP criteria tefluthrin should be classified with **STOT-RE 1** (the doses being below the guidance value of ≤ 10 mg/kg bw/d), hazard statement **H372**: Causes damage to organs (nervous system) through

prolonged or repeated exposure.

Comments received during public consultation

Two MSCAs supported the DS proposal for classification of tefluthrin with STOT-RE 1; H372. One MSCA and industry did not agree with the proposed DS classification and were in favour of no STOT-RE classification. One MSCA argued that dermal exposure was also a relevant route of exposure for the STOT-RE 1 classification along with oral exposure.

The MSCA not supporting the STOT RE 1 classification via oral exposure considered the evidence presented in the dossier to be too weak to support classification as STOT RE 1 (for neurotoxicity) and provided extensive comments. In the 90-day study in dogs, whole body tremor was only seen in one female on day 4 at 1.5 mg/kg bw/d and the effect had fully recovered within one hour and was not observed again in this animal. No histological effects were reported and no other effects were observed (clinical, ophthalmological findings or haematological parameters). In the 1-year dog study, ataxia and tremors were seen in 9/12 dogs during the first week but no histological findings were reported. Dogs were more sensitive than the rats. However there were no dose-related effects and the neurotoxic effects were only observed at the beginning of the study. The MSCA questioned the evidence submitted by the DS to support STOT RE 1 and considered it as not sufficient for the classification.

Industry did not support the classification in Category 1 for STOT-RE. Industry argued that the main toxicological effects of tefluthrin in all species are clinical signs of neurotoxicity. This is not unexpected, given the insecticidal mode of action of pyrethroids in interfering with voltage gated sodium channels. The effect is generally seen within a few hours of dosing, and recovers rapidly. It does not get worse with repeated daily dosing. This effect is transient and reversible, and a manifestation of acute toxicity, for which classifications of Acute Tox.2; H300, Acute Tox.2; H310 and Acute Tox.1; H330 (Fatal via oral, dermal and inhalation routes), are being proposed. This position is supported by the following statement from the CLP guidance: "According to CLP Annex I, 3.9.1.1, specific toxic effects covered by other hazard classes are not included in STOT-RE. STOT-RE should only be assigned where the observed toxicity is not covered more appropriately by another hazard class."

The guidance also states that *"STOT-RE is assigned on the basis of findings of "significant" or "severe" toxicity. In this context "significant" means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. "Severe" effects are generally more profound or serious than "significant" effects and are of a considerably adverse nature which significantly impact on health. Both factors have to be evaluated by weight of evidence and expert judgement."*

IND concluded that a STOT-RE classification is not required for tefluthrin, as the signs of neurotoxicity seen very soon after dosing are indicative of interference with voltage gated sodium channels, an effect which is completely reversible, does not get worse on repeated exposure, and which is thus more appropriately covered by the proposed acute classifications. Tefluthrin does not cause any toxicological effects which could be considered "severe" or "significant" according to the CLP guidance.

The MSCA supporting dermal exposure as a relevant route of exposition for STOT-RE 1 along with oral exposure referred to the results obtained in the 21-day repeated dermal study in rats. Clinical observations in this study included a dose-related incidence of upward or downward curvature of the spine, tip-toe gait, splayed gait and bizarre behaviour at 50 mg/kg bw/d, and some of these effects were also observed at 1 and 0.1 mg/kg bw/d (see Table 38 of the CLH report).

In the DS proposal these signs were considered to be indicative of paraesthesia rather than systemic toxicity.

The MSCA noted that during the EFSA Peer Review this issue was discussed [PRAPeR Expert Meeting 76 (31 May -04 June 2010)]. EFSA decided not to regard these effects for systemic toxicity and established a NOAEL in this study of 50 mg/kg bw/d and a LOAEL for local effects (based on signs indicative of paraesthesia and skin irritation) of 0.1 mg/kg bw/d (EFSA Journal 2010;8(12):1709).

However, the MSCA further commented that paraesthesia is a temporary burning, stinging, itching and tingling of the skin and it is a well-known effect that happens after dermal exposure in pyrethroids. Therefore, taking into account that these effects occurred below the cut-off value for STOT-RE 1 and considering that there is reasonable doubt whether these effects are indicative of paraesthesia (local effect) or neurobehavioral effects associated to neurotoxicity (systemic toxicity), the MSCA considers dermal exposure as a relevant route for STOT-RE 1 and concluded that tefluthrin should be classified for STOT RE 1 (H372): Causes damage to nervous system through prolonged or repeated oral and dermal exposure.

Additional key elements

In a 2-year toxicity/oncogenicity study (Stonard *et al*., 1986) groups of 76 male and 76 female Alpk:AP rats were fed diets containing 0, or 400 ppm tefluthrin and groups of 64 male and 64 female Alpk:AP rats were fed diets containing 25 or 100 ppm tefluthrin for up to 105 weeks (in accordance with OECD TG 453). The differences in group sizes were due to extra animals being added to the top dose group due to animal losses early in the study. The following findings were reported:

- Increased response to sound, increased activity, abnormal gait and tremors in the 100 ppm and 400 ppm groups. Observations of abnormal gait were seen mainly during the first few weeks of the study, occasionally throughout the mid phase of the study and increasing in incidence after week 80.
- Body weight gain was reduced in males and females fed 400 ppm and in males fed 100 ppm.
- Reduced food consumption in the 400 ppm groups; females during the first 13 weeks of the study and males during the first year. Reduced food consumption was also seen in males at 100 ppm during the first year, but the effect was statistically significant only during the first 13 weeks.
- Food utilisation values were reduced in both sexes at 400 ppm, and in males at 100 ppm during the first year of the study.

Other observations:

Four male and five female rats fed 400 ppm tefluthrin died during the first three weeks of the study, but this mortality rate did not continue throughout the study. Increased response to sound, increased activity, abnormal gait and tremors were mainly seen within the first three weeks of the study.

There was a minimal increase in brain weight in females fed 400 ppm tefluthrin at 52 weeks and at study termination, but this was not associated with any histopathological changes.

The NOAEL was considered to be 25 ppm (1.5 mg/kg bw/d in males and 1.7 mg/kg bw/d in females). The LOAEL was considered to be 100 ppm (5.9 mg/kg bw/d in males and 7.1 mg/kg bw/d in females).

In a 3-generation reproduction study (Wickramaratne, 1987) groups of 15 male and 30 female (F0 parents) weanling Alpk:AP rats were fed diet containing 0, 15, 50 or 250 ppm tefluthrin (in accordance with OECD TG 416). The following findings were reported:

- Splayed gait, abnormal/high-stepping gait and/or shaking were seen in all 250 ppm parent groups (F0, F1 and F2), but these findings were mostly seen in females.
- Low incidence of shaking and abnormal and/or splayed gait was seen in F1A and F1B pups in the 250 ppm group. In subsequent generations the majority of the litters were affected, and the incidence was high in the F2B and F3A litters (signs became more evident from day 22 *post-partum* onwards).

- Body weight gain prior to mating and during pregnancy was reduced in F0 and F1 parental generations at 250 ppm.
- Food consumption was generally slightly lower in all 250 ppm parent groups.

NOAEL for parental toxicity was considered to be 50 ppm (4.7 mg/kg bw/d) based on neurological effects at the highest dose (LOAEL) of 250 ppm (23.4 mg/kg bw/d).

In a development toxicity study (Kilick *et al*., 1985) groups of 24 female Alpk:AP rats were dosed by gavage with 1, 3 or 5 mg/kg bw/d tefluthrin in corn oil from days 7-16 (inclusive) of gestation (in accordance with OECD TG 414). A group of 18 female rats was similarly dosed with 7.5 mg/kg bw/d. A control group of 30 animals received corn oil alone. The following findings were reported:

- 7/18 females dosed with 7.5 mg/kg bw/d were found dead between days 9 and 14 of gestation.
- Maternal toxicity manifested as abnormal gait, uncoordinated limb movements, involuntary spasms, hypersensitivity to noise, piloerection and subdued behaviour at 7.5 mg/kg bw/d and pyrethroid toxicity, such as abnormal gait, hypersensitivity, piloerection and subdued behaviour at 5 mg/kg bw/d (effects seen within a few hours of exposure).
- Statistically significant dose-related reduction in body weight gain and food consumption from 3 mg/kg bw/d during the dosing period.

NOAEL and LOAEL for maternal toxicity were considered to be 1 and 3 mg/kg bw/d, respectively (LOAEL for maternal neurotoxicity was considered to be 5 mg/kg bw/d).

In a development toxicity study (Kilick *et al*., 1985) groups of 18 female New Zealand White rabbits were dosed by gavage with 0, 3, 6 or 12 mg/kg bw/d tefluthrin in corn oil between days 7-19 (inclusive) of gestation (in accordance with OECD TG 414). The following findings were reported:

- Maternal toxicity manifested as body tremors in one rabbit in the 3 mg/kg bw/d group (day 15), one rabbit in the 6 mg/kg bw/d group (day 16) and six rabbits in the 12 mg/kg bw/d group (days 9-17). Incidences and severities were most marked in the 12 mg/kg bw/d group.
- Statistically significant dose-related reduction in body weight gain in the 12 mg/kg bw/d group between days 7-10 and 16-19.
- Statistically significant dosage-related reduction in food consumption in the 12 mg/kg bw/d group during the dosing period and on days 7-10 in the 6 mg/kg bw/d group

LOAEL for maternal neurotoxicity was considered to be 3 mg/kg bw/d.

Assessment and comparison with the classification criteria

The repeated dose effects of tefluthrin have been studied after oral and dermal exposures with information available on the reversibility of effects.

Neurotoxicological findings such as ataxia or tremor were reported in rats, rabbits and dogs.
Dogs were more sensitive to tefluthrin than rats and rabbits. An overview of the oral studies with neurotoxicological findings is presented in the table below.

Table: Summary of neurotoxicological findings in oral studies

Study	**Neurotoxicity findings**	**Remarks**
Acute oral in Alpk:AP rats. Southwood (1985).	Tremors, splayed gait, loss of stability, salivation and upward curvature of the spine. **LD_{50} = 21.8 mg/kg bw** (males)* 95% confidence interval 10.1 - 47 mg/kg bw	No signs of neurotoxic effects at 10.1 mg/kg bw.

13 weeks oral neurotoxicity study in Alpk:AP rats. Pinto (2002).	Ataxia, reduced splay reflex, upward curvature of the spine, piloerection, increased response to sound, abnormal gait and paw flicking. NOAEL = 11.6 mg/kg bw/d **LOAEL = 26.6 mg/kg bw/d**	Increase in incidence and severity as the study progressed: Ataxia, upward curvature of the spine and reduced splay reflex. LOAEL is almost identical to $LD_{50.}$
105 weeks oral oncogenicity study in Alpk:AP rats. Stonard *et al* (1986).	Increased response to sound increased activity, abnormal gait and tremors - mainly seen within the first three weeks of the study. NOAEL = 1.5 mg/kg bw/d **LOAEL = 5.9 mg/kg bw/d**	Change in severity not reported. Abnormal gait mainly during the first few weeks, occasionally in the mid phase and increasing in incidence after week 80. Approx. 66% of surviving females affected to week 105 at 28.8 mg/kg bw/d (a dose almost identical to LD_{50}). Abnormal gait also seen in 4/64 males and 7/64 females at LOAEL.
13 weeks oral study in Alderley Park beagle dogs. Kalinowski *et al* (1985).	Whole body tremors in one dog on day 4, approximately 3 hours after dosing - full recovery within one hour. NOAEL = 0.5 mg/kg bw/d **LOAEL = 1.5 mg/kg bw/d**	Change in severity not reported.
52 weeks oral study in Alderley Park beagle dogs. Stonard (1986).	Ataxia and tremors. NOAEL = 0.5 mg/kg bw/d **LOAEL = 2.0 mg/kg bw/d**	Change in severity not reported. Majority of instances in the first few weeks (9/12 dogs in week 1 – 4). A few dogs with ataxia and/or tremor also seen in the middle and end of the testing period.
3 generation oral reproduction study in Alpk:AP rats. Duration: 29 - 39 weeks in F0 and F1, 22 - 28 weeks in F2. Wickramaratne (1987).	Splayed gait, abnormal/high-stepping gait and/or shaking were seen in parent groups (F0, F1 and F2) – mostly seen in females. NOAEL = 4.7 mg/kg bw/d **LOAEL = 23.4 mg/kg bw/d**	Incidence was high in the F2B and F3A litters. Signs became more evident from day 22 post-partum onwards. LOAEL is almost identical $LD_{50.}$
Development study in Alpk:AP rats. By gavage, days 7-16 of gestation. Kilick *et al* (1985).	Abnormal gait, hypersensitivity, piloerection and subdued behavior from 5 mg/kg bw/d. NOAEL = 3 mg/kg bw/d **LOAEL = 5 mg/kg bw/d**	Changes in incidence and severity not reported. Hypersensitivity and piloerection in 19/24 rats at LOAEL. In the 7.5 mg/kg bw/d group hypersensitivity was seen in 9/18 rats and piloerection in 6/18 rats - however in this group 7/18 females were found dead between day 9 and 14 of gestation.
Development study in New Zealand White rabbits. By gavage, day 7-19 of gestation. Kilick *et al* (1985).	Body tremor from 3 mg/kg bw/d. **LOAEL = 3 mg/kg bw/d**	Incidence and severity was most marked at 12 mg/kg bw/d were 6/18 rabbits were affected (slight to extreme). At LOAEL 1/18 rabbits were affected (slight to extreme) and at 6 mg/kg bw/d 1/18 rabbits were affected (slight).

* LD_{50} and confidence interval could not be calculated by probit method due to pattern of mortalities.

In the 13-week oral neurotoxicity study (Pinto, 2002) in Alpk:APfSD rats, the Functional Observation Battery (FOB) findings included increased activity, ataxia (from week 5), irregular breathing, increased breathing rate, reduced splay reflex, upward curvature of the spine, piloerection, increased response to sound, abnormal gait and paw flicking in males and/or females. From the table below (Table 87 in the CLH report) it can be seen that these findings were observed/recorded throughout the testing period.

Table (Table 87 in the CLH report): Intergroup comparison of FOB clinical observations for selected parameters

	Dietary Concentration of tefluthrin (ppm)							
	Males				**Females**			
Observation (number of animals affected (week))	**0**	**50**	**150**	**350**	**0**	**50**	**150**	**350**
Increased activity - s				1 (2), 2 (5)				1 (2), 5 (5), 8 (9), 10 (14)
Irregular breathing				1 (2), 1 (5)				
Increased breathing rate				6 (2), 4 (5), 3 (9), 1 (14)		1 (2)	2 (5), 1 (14)	7 (2), 7 (5), 6 (9), 5 (14)
Reduced splay reflex - s		1 (2)		2 (14)	1(9), 2 (14)	1(5), 1 (14)	1 (5), 2(9), 1(14)	2 (5), 2 (9), 7 (14)
Reduced splay reflex - m								3 (5), 3 (9), 4 (14)
Paw flicking				1(5)				1 (2)
Ataxia - s								5 (5), 4 (9), 3 (14)
Ataxia - m								1 (9)
Upward curvature of spine - s							1 (9), 1 (14)	1 (2), 6 (5), 8 (9), 9 (14)
Upward curvature of spine - m								1 (14)
Piloerection								1 (9), 1 (14)
Increased response to sound								1 (2), 1 (5), 1 (9)
Abnormal gait								1 (2)

s = slight, m = moderate

In the study the severity of the neurotoxicological findings is compared over time. It is stated in the CLH report that: *"There was an increase in the incidence and severity as the study progressed for the ataxia, increased activity, upward curvature of the spine and reduced splay reflex"*. Especially in female rats at 350 ppm (31.2 mg/kg bw/d) , tthere was a slightly increased activity , a slightly and moderately reduced splay reflex and a slightly and moderately increased upward curvature of the spine as the study progressed. However, the number of female rats affected with slight ataxia at 350 ppm decreased as the study progressed (from 5 at week 5 and 4 at week 9 to 3 at week 14). One 350 ppm female had moderate ataxia at week 9.

If this exposure time-dependent increase in the incidences and severities of neurological findings in rats is taken as an indication of repeated-dose effects, this study points towards a STOT RE 2 classification (LOAEL = 26.6 mg/kg bw/d is within the range of guidance values for STOT RE 2; $10 < C \leq 100$). However, since the LOAEL is almost identical to the LD_{50} value (21.8 mg/kg bw), it is more likely that the observed neurotoxicological effects are due to repeatedly acute symptoms.

In the 2-year toxicity/oncogenicity study (Stonard *et al*., 1986) in Alpk:AP rats, increased responses to sound, increased activity, abnormal gait and tremors were seen in the 400 ppm (23.2 – 28.8 mg/kg bw/d) group and in a smaller number of rats in the 100 ppm (5.9 – 7.1 mg/kg bw/d) group. Observations of abnormal gait were seen during the first few weeks of the

study, the mid phase of the study and increasing in incidence after week 80 (Table 52 in the CLH report). The increased incidence could probably be explained by a decline in metabolic capacity of the liver (suggested in the report by Stonard *et al*., 1986).

Table (Table 52 in the CLH report): Intergroup comparison of the incidence of selected clinical observations

Dose (ppm)	**0 (control)**	**25**	**100**	**400**
Males / Abnormal gait	0	0	4 (82-97)	7 (2-105)
Shaking	8 (76-105)	6 (93-104)	8 (37-105)	7 (76-105)
Increased response to sound	0	0	3 (7-7)	1 (7-7)
Females / Abnormal gait	2 (90-98)	2 (76-94)	7 (61-105)	60 (1-105)
Shaking	4 (38-105)	5 (97-105)	5 (59-105)	22 (2-105)
Increased response to sound	0	0	0	14 (3-7)

(number) - the number of weeks over which the observation was made

As seen in the table above, the LOAEL of 5.9 mg/kg bw/d is based on a relatively small number of affected rats (4/64 males and 7/64 females with abnormal gait). The effects at LOAEL are seen relatively late in the study, and if this is taken as an indication of repeated dose effects, this study points towards a STOT RE 2 classification (LOAEL is within the range of extrapolated guidance values for STOT RE 2; 1.25 < C ≤ 12.5). The fact that the effects are seen late in the study could probably be explained by the decline in metabolic capacity of the liver.

At 28.8 mg/kg bw/d there was a significant increase in the number of female rats affected. This dose is however close to the LD_{50} value (21.8 mg/kg bw) which indicates that observed neurotoxicological effects at this dose are due to repeatedly acute symptoms.

In the 13-week oral study (Kalinowski *et al*, 1985) with beagle dogs whole body tremor was seen on day 4 in one of the four tested dogs at 1.5 mg/kg bw/d tefluthrin (full recovery within one hour). There were no other treatment-related findings and no indications that the whole body tremor was due to repeated exposure which would warrant classification.

In the 1-year oral study (Stonard, 1986) in beagle dogs, the majority of instances of ataxia and tremors (in 9/12 dogs) were noted between weeks 1-4 of treatment, but they were also seen during weeks 17-24, 33-36, 41-44 and 49-52 at 2.0 mg/kg bw/d (Table below).

Table (Table 36 in the CLH report): Incidences of ataxia and body tremors in one-year oral study in dogs

Treatment (mg/kg bw)	Sex	Time Period (Week of Treatment)									
		1-4	5-8	9-16	17-20	21-24	25-32	33-36	37-44	45-48	49-52
0.1	M					1A(1) 1T(1)					
2.0	M	1A(1) 3T(2)				1A(1)		1A(1)			
	F	7A(6) 5T(3)	1A(1) 1T(1)		1A(1) 2T(1)				2T(1)		1T(1)

A – Ataxia or unsteady gait.
T – Tremors.
( ) – Number of dogs affected.
Where blanks are shown, animals were observed, but ataxia or tremors were not seen.
Values are days/group that the observation was made.
Note: No ataxia or tremors were observed in dogs given 0.5 mg tefluthrin/kg bw/d, in females given 0.1 mg tefluthrin/kg bw/d or in control animals.

If the ataxia and tremor seen in the middle and the end of the 1-year oral study in beagle dogs is taken as an indication of repeated dose effects, this study points towards a STOT RE 1 classification (LOAEL = 2.0 mg/kg bw/d is below the STOT RE 1 Guidance value C ≤ 2.5). However the fact that significantly more dogs are affected in the first 1-4 weeks of the study

indicates that the observed neurotoxicological effects are due to acute toxicity and that no classification for STOT RE is warranted.

In a 3-generation oral reproduction study in Alpk:AP rats (Wickramaratne, 1987) splayed gait, abnormal/high-stepping gait and/or shaking were seen in parent groups (F0, F1 and F2), mostly in females. The incidence was high in the F2B and F3A litters. Signs became more evident from day 22 post-partum onwards (Table below).

Table (Table 63 in the CLH report): Intergroup comparison of the incidence of neurotoxicity signs in offspring

		Dietary Concentration of tefluthrin (ppm)				
	Generation/Observation	**Day**	**0**	**15**	**50**	**250**
F1A:	Shaking	30	0	0	0	0
	Abnormal gait/Splayed gait		0	0	0	12 (1)
F1B:	Shaking	22	0	0	0	1 (1)
	Abnormal gait/Splayed gait	22	0	0	0	0
F2A:	Shaking	22 29	0 0	0 0	2 (2) 0	57 (9) 58 (7)
	Abnormal gait/Splayed gait	22 29	0 0	0 0	0 0	8 (4) 3 (2)
F2B:	Shaking	5 22 29	0 0 0	0 0 0	7 (1) 0 0	0 174 (19) 209 (20)
	Abnormal gait/Splayed gait	5 22 29	0 0 0	0 0 0	0 0 0	0 0 0
F3A:	Shaking	22 29	0 0	0 0	0 0	176 (23) 174 (21)
	Abnormal gait/Splayed gait	22 29	0 0	0 0	0 0	7 (1) 2 (2)

Values shown are the number of pups affected, with the number of litters shown in parentheses.

Assuming that the observed neurotoxicological effects are due to repeated exposure, this study points towards a STOT RE 2 classification (LOAEL = 23.4 mg/kg bw/d is within the range of guidance values for STOT RE 2; $6 < C \leq 60$; Haber's rule used on F2 females that are exposed to tefluthrin for 22 weeks). However, since the LOAEL is almost identical to the LD_{50} value (21.8 mg/kg bw) it is more likely that observed neurotoxicological effects are due to repeatedly acute symptoms.

In a developmental toxicity study (Kilick *et al*., 1985) in Alpk:AP rats (dosing period days 7-16 of gestation, by gavage). In the 7.5 mg/kg bw/d group 7/18 females were found dead between days 9 and 14 of gestation. In the 5 mg/kg bw/d (LOAEL) group maternal toxicity such as abnormal gait (from day 9), hypersensitivity (from day 7), piloerection (from day 9) and subdued behaviour (from day 9) were observed following dosing. Animals were affected in the beginning, middle and end of the dosing period. An increase in severity over time was not reported. The study can therefore not be used to clearly establish if the neurotoxicological effects seen are acute effects or repeated dose effects.

In a developmental toxicity study (Kilick *et al*, 1985) in New Zealand White rabbits (dosing period days 7-19 of gestation, by gavage) maternal toxicity was manifested as body tremors in 1/18 rabbit in the 3 mg/kg bw/d group (day 15 of gestation, by gavage), 1/18 rabbit in the 6

mg/kg bw/d group (day 16, slight) and 6/18 rabbits in the 12 mg/kg bw/d group (days 9-17 of gestation, by gavage). The fact that tremors at 3 and 6 mg/kg bw/d were seen on day 15 and 16 of the dosing period could indicate that the tremors were caused by repeated exposure. However, the effect was seen for one day only at 3 and 6 mg/kg bw/d and in the 12 mg/kg bw/d group the effect was seen for most of the dosing period. From the study it can not be established if the neurotoxicological effects seen are acute effects or repeated dose effects.

An overview of the dermal studies with neurotoxicological findings can be seen in the table below.

Table: Summary of neurotoxicological findings in dermal studies

Type of Study	**Neurotox findings**	**Remarks**
Acute dermal study in Alpk:AP rats. McLean *et al* (1986).	Splayed gait, upward and/or downward curvature of the spine and signs of neuromuscular incoordination in some animals. **LD_{50} = 177 mg/kg bw** 95% confidence interval 76 - 397 mg/kg bw	Effects seen from 50 mg/kg bw in females and from 100 mg/kg bw in males. Males not testet at 50 mg/kg bw.
21 day dermal study in Alpk:AP rats. Leah (1989).	Curvature of the spine, tip-toe gait and splayed gait - considered to be indicative of paraesthesia rather than systemic toxicity*. **Systemic NOAEL = 50 mg/kg bw/d*** **Local LOAEL = 0.1 mg/kg bw/d***	Curvature of the spine observed from day 1 in majority of 0.1 mg/kg bw/d females and from day 2 or 3 in all 0.1 mg/kg bw/d males. Curvature of the spine did not seem to get more severe over time. Tip-toe gait and splayed gait observed in 9 rats at 1.0 mg/kg bw/d - 2 in the middle of the study and 7 at the end of the study.

*Conclusion from the PRAPeR Expert Meeting 76 (31 May – 04 June 2010).

In the 21-day dermal study (Leah, 1989) in Alpk:AP rats curvature of the spine and tip-toe gait was seen from 0.1 mg/kg bw/d. Splayed gait were seen from 1.0 mg/kg bw/d. At the PRAPeR Expert Meeting 76 it was concluded that these effects were indicative of paraesthesia rather than systemic toxicity. However, in the acute dermal study in Alpk:AP rats (McLean *et al*., 1986) curvature of the spine and splayed gait were considered to be signs of neuromuscular incoordination.Regardless of whether the observed effects were to be to be considered as signs of neuromuscular incoordination or as secondary to paraesthesia, they seemed to be due to acute toxicity. This can be seen from the fact that in the 21-day dermal study curvature of the spine was observed from day 1 in the majority of 0.1 mg/kg bw/d females and from day 2 or 3 in all 0.1 mg/kg bw/d males. In the 0.1 mg/kg bw/d groups severity did not seem to change. The picture is not as clear for tip-toe gait and splayed gait since these effects were not observed before the middle and the end of the 21-day study in the 1.0 mg/kg bw/d group. However, in the acute dermal study splayed gait was seen between days 3 – 5 after dosing in the 50 mg/kg bw/d group which indicates that this is a delayed acute effect. Thus it seems more likely that the observed effects (curvature of the spine, tip-toe gait and splayed gait) are due to symptoms of acute toxicity than to repeated dose toxicity effects.

Assessment and comparison with the classification criteria

In general the purpose of STOT RE is to identify the primary target organ(s) of toxicity for inclusion in the hazard statement. The primary target organ of tefluthrin is the nervous system. And since classification as STOT RE includes all significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed (CLP Annex I, 3.9.1.1) it is relevant to evaluate if tefluthrin should be classified for STOT RE.

The key issue is whether the neurotoxicological findings are more appropriately covered by an acute toxicity classification than by STOT RE. None of the above mentioned seven oral studies clearly shows that the neurotoxicological effects are due to repeated dosing. On the contrary,

four oral studies (Pinto, 2002 (90-day rat study), Stonard, 1986 (105-week rat study), Stonard, 1986 (52-weeks dog study) and Wickramaratne, 1987 (3-generation rat study)) indicate that the neurotoxicological effects observed are due to acute toxicity symptoms that are repetedly observed.

Based on these four oral studies, RAC does not support the conclusion of the DS that according to the criteria in the CLP Regulation, tefluthrin should be classified with STOT RE 1. Furthermore, the 21-day dermal study (Leah, 1989) in Alpk:AP rats does not clearly show that the observed effects (curvature of the spine, tip-toe gait and splayed gait) are due to repeated dose toxicity. Curvature of the spine are seen from day one in the study and that splayed gait appears to be a delayed acute effect in both the 21-day dermal study and the acute dermal toxicity study (McLean *et al*, 1986).

RAC concludes that tefluthrin does not meet the criteria for classification with STOT RE.

4.8 Germ cell mutagenicity (Mutagenicity)

Table 39: Summary table of relevant in vitro and in vivo mutagenicity studies

Type of Study	Organism/Cells	Dose Range Tested	Result	Reference
In vitro gene mutation assays				
Bacterial reverse mutation	Salmonella typhimurium	1.6-5000 µg/plate (+/- S9)	Negative (+/- S9)	Callander (1984, TOX2004-2677)
Bacterial reverse mutation	Escherichia coli (WP2 uvrA pKM101)	1.6-5000 µg/plate (+/- S9)	Negative (+/- S9)	Callander (1990, TOX2004-2676)
Mammalian cell gene mutation	Mouse lymphoma L5178Y cells	250-4000 µg/mL (+/- S9)	Negative (+/- S9)	Cross (1986, TOX2004-2678)
In vitro chromosomal aberration assay				
Cytogenetics	Human lymphocytes	250-3000 µg/mL (+/- S9)	Negative (+/- S9)	Randall and Mackay (1993, TOX2004-2679)
In vitro DNA damaging assay				
In vitro UDS assay	Rat hepatocytes	10^{-2}M - 10^{-9}M	Negative	Trueman (1986, TOX2004-2680)
In vivo chromosome aberration assay				
Cytogenetics	Rat bone marrow cells	2.5, 12.5, 25.0 mg/kg	Negative	Howard et al (1985, TOX2004-2681)
Mouse micronucleus	C57BL6J mice bone marrow cells	0, 31, 50 mg/kg	Negative	Sheldon (1985, TOX2004-2683)

4.8.1 Non-human information

The mutagenic and DNA damaging potential of tefluthrin was studied in several *in vitro* test systems using bacteria and mammalian and human cells and *in vivo* test systems using rats and mice. Tefluthrin was negative in two *in vitro* bacterial reverse mutation assays and an *in vitro* gene mutation test in mouse lymphoma cells. No clastogenic effects were seen in an *in vitro* human lymphocyte cytogenectics test, an *in vivo* rat cytogenetics test and an *in vivo* mouse micronucleus test. No evidence of DNA damage or repair was noted in an *in vitro* UDS assay. The weight of the evidence indicates that tefluthrin does not possess significant genotoxicity concern.

4.8.1.1 In vitro data

Report: Callander R (1984, TOX2004-2677), PP993: An Evaluation in the Salmonella Mutagenicity Assay. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/935, study dates: 9 September 1983 to 16 September 1983. (Syngenta File No. ICI993/0625)

Guidelines: 92/69/EEC B.13/B.14 ≅ OECD 471
The study was performed prior to the above guideline but has been checked for compliance with the above

Deviations: The study was performed using 5 strains of *S. typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100. No E.coli strains were included. Consideration was not given to modification of experimental conditions for test 2 as required by the guidelines. The deviations are considered not to compromise the scientific validity of the study.

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin; batch No. P16; analysed purity 95.1 % w/w TS.

Tefluthrin was evaluated in a bacterial mutagenicity assay over a range of concentrations using five strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100).

Tefluthrin was assayed twice using the standard plate incorporation protocol over a dose range of 5000 to 1.6 μg per plate, both in the presence and absence of S9-mix prepared from Aroclor induced Alderley Park rats. The incubation period for each experiment was 3 days (at 37 °C).

For each experiment, positive control substances were tested to validate the bacterial strain and to confirm the activity of the S9-mix. The experimental design is presented in the table below.

Table 40: Experimental Design of the Salmonella Mutagenicity Assay

Compound	Experimental design
Tefluthrin	6 concentrations per strain 3 plates per concentration
Solvent Control: DMSO (100μl)	5 plates
Positive Controls +S9: 2-Aminoanthracene	 3 concentrations per strain
-S9: Acridine Mutagen ICR191(TA1537) Daunomycin HCl (TA98) 4-nitro-0-phenylenediamine (TA1538) N-methyl-N'-nitro-N-nitrosoguanidine (TA1535 and TA100)	 2 plates per concentration

Findings: In two separate experiments, the test substance did not induce any significant, reproducible increases in the observed numbers of revertant colonies in any of the strains used, either in the presence or absence of S9-mix. The precipitate observed at the highest test concentration indicates that the test substance was examined to an adequate limit concentration (as defined in OECD guideline 471).

The sensitivity of the test system, and the metabolic activity of the S9-mix, were clearly demonstrated by the increases in the numbers of revertant colonies induced by positive control substances.

Conclusion: Under the conditions of this assay, tefluthrin gave an unequivocal negative, i.e. non-mutagenic response.

Report:	Callander R (1990, TOX2004-2676), Tefluthrin: An Evaluation of Mutagenic Potential Using E. coli. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/3037, study dates 20 April 1990 to 27 April 1990. (Syngenta File No. ICI993/0144)
Guidelines:	92/69/EEC B.13/B.14 ≅ OECD 471
Deviations:	A single strain of bacteria (*E. coli* , WP2 uvrA pKM101) was used in this study. Consideration was not given to modification of experimental conditions for test 2 as required by the guidelines. The deviations are considered not to compromise the scientific validity of the study.
GLP:	Yes (laboratory certified by the UK authority)

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin; batch No. P22; analysed purity 95.0 % w/w TS.

Tefluthrin was evaluated in a bacterial mutagenicity assay over a range of concentrations using a single strain of *Escherichia coli* (WP2 *uvrA* pKM101). Tefluthrin was assayed twice using the standard plate incorporation protocol over a dose range of 5000 to 1.6 μg per plate, both in the presence and absence of S9-mix prepared from Aroclor induced Alderley Park rats. The incubation period for each experiment was 3 days (at 37° C). For each experiment, positive control substances were tested to validate the bacterial strain and to confirm the activity of the S9-mix. The experimental design is presented in the table below.

Table 41: Experimental Design to Determine the Mutagenetic Potential of Tefluthrin using *E. coli*

Compound	Experimental design
Tefluthrin	6 concentrations per strain 3 plates per concentration
Solvent Control: DMSO (100µl)	5 plates
Positive Controls +S9: 2-Aminoanthracene	 3 concentrations per strain
-S9: N-methyl-N'-nitro-N-nitrosoguanidine	 2 plates per concentration

Findings:

In two separate experiments, the test substance did not induce any significant, reproducible increases in the observed numbers of revertant colonies, either in the presence or absence of S9-mix.

The sensitivity of the test system, and the metabolic activity of the S9-mix, were clearly demonstrated by the increases in the numbers of revertant colonies induced by positive control substances.

Conclusion:

Under the conditions of this assay, tefluthrin gave an unequivocal negative, i.e. non-mutagenic response in both the presence and absence of an auxiliary metabolising system (S9) in one strain of Escherichia coli (WP2 uvrA pKM101), when tested to a limit dose of 5000 µg/plate.

Report: Cross M (1986, TOX2004-2678), Tefluthrin: Assessment of Mutagenic Potential Using L5178Y Mouse Lymphoma Cells. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1363, study dates April 1984 to July 1985. (Syngenta File No. ICI993/0137)

Guidelines: 91/414/EEC ≅ OECD 476 ≅ OPPTS 870.5300

Deviations: 10-20 % survival not achieved in all tests however, the maximum concentration used in all tests produced significant toxicity and was that which produced < 20 % survival in certain tests.
The deviations are considered not to compromise the scientific validity of the study.

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin purity 90.4% [w/w] tefluthrin.

This study was conducted to evaluate the potential of the test substance to cause gene mutation in mammalian cells, L5178Y $TK^{+/-}$ mouse lymphoma cells treated *in vitro*.

Tefluthrin was tested both in the presence and absence of a rat liver derived auxiliary metabolic system (S9-mix) in five independent experiments over a concentration range of 4000 μg/mL to 250 μg/mL. Mutant frequencies were assessed by cell growth in the presence of trifluorothymidine (TFT) after a 48-hour expression time in two experiments and after a 72-hour expression time in three experiments.

Findings:

The positive controls induced appropriate increases in mutant frequency in all mutation experiments thus demonstrating the activity of the S9-mix and that the assay was performing satisfactorily in being capable of detecting known mutagens.

Tefluthrin produced dose-related cytotoxicity at the dose rates tested. Similar levels of cytotoxicity were observed in the presence and absence of S9-mix. On statistical analysis, the results indicated a possible effect of tefluthrin at the 48-hour expression time in the first experiment, however a repeat 48-hour expression time experiment did not substantiate this. In addition no significant increase in mutant frequency at the 72-hour expression time was observed with or without S9-mix in three independent experiments.

Conclusion:

Tefluthrin is non-mutagenic in L5178Y cells when selected in TFT either with or without auxiliary metabolic activation.

Report:	Randall V, Mackay J (1993, TOX2004-2679), Tefluthrin: An Evaluation in the *In vitro* Cytogenetic Assay in Human Lymphocytes. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/4140, study dates 10 May 1993 to 27 July 1993. (Syngenta File No. ICI993/0148)
Guidelines:	92/69/EEC B.10 ≅ OECD 473 (1997) ≅ OPPTS 870.5375 The study was performed prior to the above guideline but has been checked for compliance with the above
Deviations:	The study met all criteria specified in the guidelines detailed in 92/69/EEC B.10
GLP:	Yes (laboratory certified by the UK authority)

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin, purity 92.8 % w/w (batch reference P24).

Tefluthrin was evaluated for clastogenic potential in an *in vitro* cytogenetic assay using human lymphocytes from 2 donors treated in the presence and absence of a rat liver-derived auxiliary metabolic activation system (S9-mix), 48 hours after culture initiation. Cultures from both donors were treated for a period of 3 hours in the presence of S9-mix and 20 hours in the absence of S9-mix, and harvested 68 or 92 (donor 1 only) hours after culture initiation. The test substance was dissolved in dimethylsulphoxide which was used as the negative control. The experimental design is presented in the table below.

Table 42: Concentrations Chosen for Cytogenetic Analysis

Donor 1 (68 hr)		Donor 1 (92 hr)		Donor 2 (68 hr)	
+ S9 mix	- S9 mix	+ S9 mix	- S9 mix	+ S9 mix	- S9 mix
3000 µg/mL	3000 µg/mL	3000 µg/mL	3000 µg/mL	3000 µg/mL	3000 µg/mL
2000 µg/mL	2000 µg/mL	-	-	2000 µg/mL	2000 µg/mL
300 µg/mL	300 µg/mL	-	-	300 µg/mL	250 µg/mL

Frequencies of aberrant metaphases (cells showing one or more aberrations) were calculated for each culture scored, excluding cells with only gap-type aberrations, and mean values were calculated for each concentration. The number of aberrations per cell was also calculated for each culture scored, excluding cells with only gap-type aberrations, as was the mean number of aberrations per cell for each concentration.

Findings:

Concentration related reductions in mitotic activity were observed in cultures from both donors. The highest concentration tested in each case was limited by reductions in mitotic index.

The test system was shown to be sensitive to chromosome damaging effects, by the response given to the positive control substances mitomycin C (a direct-acting clastogen) and cyclophosphamide (a clastogen requiring metabolic activation).

A small but statistically significant increase in the percentage of aberrant cells was observed at the lowest concentration of 300 µg/mL in one donor at the 68-hour harvest time. No increases in chromosomal damage were observed in any other cultures treated with tefluthrin from either donor in either the presence or absence of S9-mix. No such statistically significant increases were observed in the male donor cultures treated with tefluthrin at the higher concentrations of 2000 or 3000 µg/mL in the absence of S9-mix nor in the female donor cultures. The small increase observed in the male donor cultures is therefore not dose related, is not reproducible between donors and is considered to be of no biological significance. At the 92-hour sampling time, no statistically or biologically significant increases in the percentage of aberrant cells, compared to the solvent control values, were recorded in the male donor cultures treated in either the presence or absence of S9-mix.

Conclusion:

Under the conditions of test, tefluthrin is not clastogenic to human lymphocytes in vitro in the presence or absence of auxiliary metabolic activation.

Report: Trueman R (1986, TOX2004-2680), Tefluthrin: Assessment for the Induction of Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1619, study dates April 1986 to June 1986. (Syngenta File No. ICI993/0141)

Guidelines: OECD 486 (1986) ≅ OPPTS 870.5550
The study was performed prior to the above guideline but has been checked for compliance with the above

Deviations: The study met all criteria specified in the guidelines

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods: Tefluthrin, batch No P16. Purity 95.1 % [w/w] tefluthrin.

Tefluthrin was tested in an *in vitro* assay for unscheduled DNA synthesis (UDS) in primary rat hepatocyte cultures. A range of dose levels was examined (10^{-2} M - 10^{-9} M) extending into concentrations that caused overt cytotoxicity to the cell cultures. Two independent experiments were performed.

Findings:

At the higher concentration tested, 10^{-2} M to 10^{-4} M in experiment 1 and 10^{-2} M to 10^{-3} M in experiment 2, a severe cytotoxic response was observed. This resulted in insufficient cells of normal morphology to score at these concentrations. At all the lower concentrations, measurement of the mean net nuclear grain count showed that tefluthrin gave an unequivocal negative response. The concurrent positive controls gave the expected result and confirmed that the test system was responding satisfactorily.

Conclusion:

It is concluded that tefluthrin gave a negative result in this assay and does not induce UDS in primary cultures of rat hepatocytes.

4.8.1.2 In vivo data

Report: Howard C, Richardson C, Banham P *et al* (1985, TOX2004-2681), PP993: An Acute Cytogenetic Study in the Rat. Central Toxicology Laboratory; UK., Syngenta Unpublished Report No. CTL/P/1060, study dates 9 August 1983 to 4 May 1984. (Syngenta File No. ICI993/0134)

Guidelines: OECD 475 (1997)
The study was performed prior to the above guideline but has been checked for compliance with the above.

Deviations: The number of cells analysed for mitotic indices is not reported. Only 50 cells per animal were analysed for chromosomal aberrations.
The deviations are considered not to compromise the scientific validity of the study.

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin; batch No. P14; analysed purity 90.4 % w/w TS.

Tefluthrin was administered by gavage to groups of male and female rats in a single dose, at levels of 25.0, 12.5 and 2.5 mg/kg bodyweight, having previously established 25.0 mg/kg as the maximum tolerated dose (MTD). Chromosome preparations were made from the bone marrow cells in c-metaphase from these animals 12, 24 or 48 hours after dosing in order to determine whether or not tefluthrin had any clastogenic potential.

Findings:

Cyclophosphamide, a well-referenced clastogen, was used as a positive control substance. When administered by gavage, cyclophosphamide induced levels of chromosome damage which were of both statistical and biological significance, thus demonstrating the sensitivity of the test system.

Tefluthrin induced effects on the mitotic index confirming that 25.0 mg/kg was an MTD for this assay. There were no statistically significant increases in percentage aberrant cells (excluding gaps) compared to controls, in any of the tefluthrin treated groups at any of the time points examined. Increases in the incidence of minutes and in the percentage abnormal cells (including gaps) observed in females only, and only at the 48-hour sampling time, were due to a small number of animals (3) and were considered more likely to be due to inter-animal variation rather than to a clastogenic effect of tefluthrin. This interpretation was substantiated in a repeat of this phase of the study when no increase in chromosomal damage due to tefluthrin compared to the control values could be found.

Conclusion:

Tefluthrin is non-clastogenic in the rat bone marrow.

Report:	Sheldon T, Richardson C, Shaw J *et al* (1985, TOX2004-2683), PP993: An Evaluation in the Mouse Micronucleus Test. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1275, study dates 20 November 1984 to 19 February 1985. (Syngenta File No. ICI993/0139)
Guidelines:	92/69/EEC B.12 ≅ OECD 474 (1997) ≅ OPPTS 870.5395
Deviations:	Only 1000 polychromatic erythrocytes were examined from some animals rather than 2000 as specified in the guidelines. Two rather than three dose levels of test compound were administered to the animals at the 24 hour time point. The deviations are considered not to compromise the scientific validity of the study.
GLP:	This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin; batch No. P16, D3140/33; analysed purity 95.1 w/w tefluthrin.

Tefluthrin has been evaluated for its ability to induce micronucleated polychromatic erythrocytes in the bone marrow of C57/BL/6J mice. Tefluthrin was administered as a single intraperitoneal injection and was given to groups of mice as detailed in the table below.

Table 43: Experimental Design of the Mouse Micronucleus Test using Tefluthrin

				Animal Numbers/Time of Kill		
Group	**Treatment**	**Dose**	**Sex**	**24 hours**	**48 hours**	**72 hours**
1	Vehicle Control	10 mL/kg	Male	1-5	41-45	81-85
	(corn oil)		Female	21-25	61-65	101-105
2	Cyclophosphamide	65 mg/kg	Male	6-10	46-50	86-90
			Female	26-30	66-70	106-110
3	Tefluthrin	31 mg/kg	Male	11-15	51-55	91-95
			Female	31-35	71-75	111-115
4	Tefluthrin	50 mg/kg	Male	16-20	56-60	96-100
			Female	36-40	76-80	116-120

The top dose level used was a maximum tolerated dose based on lethalities observed at higher dose levels in a range-finding study. Bone marrow smears were taken from the iliac end of the femur, air dried and stained with polychrome methylene blue and eosin and scored under code.

1000 polychromatic erythrocytes were examined for the presence of micronuclei for each animal. Slides were also examined for evidence of cytotoxicity by determining the ratio of polychromatic to normochromatic erythrocytes.

Findings:

No adverse reactions to treatment were observed for animals dosed with tefluthrin. None of the animals died before the scheduled termination.

A statistically significant increase in the incidence of micronucleated polychromatic erythrocytes, over the vehicle control values, was observed in the tefluthrin treated groups at the 24 hour sampling time. However, as the observed values were only slightly in excess of the control values at the 72-hour sampling time, and are within the laboratory historical control data, the increase is not considered to be biologically meaningful. There were no statistically significant increases in incidence of micronucleated polychromatic erythrocytes at the 48-hour or 72-hour sampling time.

Comparison of the percentage of polychromatic erythrocytes showed no statistically or biologically significant differences at either of the sampling times between the vehicle control animals and those treated with tefluthrin.

The test system positive control, cyclophosphamide, induced statistically significant and biologically meaningful increases in micronucleated polychromatic erythrocytes, compared to the vehicle control values at the 24- and 48-hour sampling times, thus demonstrating the sensitivity of the test system to a known clastogen.

Conclusion:

The results indicate that tefluthrin is not clastogenic in the mouse bone marrow micronucleus test.

4.8.2 Human information

No studies submitted by the applicant.

4.8.3 Other relevant information

No other relevant information available.

4.8.4 Summary and discussion of mutagenicity

The mutagenic and DNA damaging potential of tefluthrin was studied in several *in vitro* test systems using bacteria and mammalian and human cells and in *in vivo* test systems using rats and mice. Tefluthrin was negative in two *in vitro* bacterial reverse mutation assays and an *in vitro* gene mutation test in mouse lymphoma cells. No clastogenic effects were seen in an *in vitro* human lymphocyte cytogenectics test, an *in vivo* rat cytogenetics test and an *in vivo* mouse micronucleus test. No evidence of DNA damage or repair was noted in an *in vitro* UDS assay. Tefluthrin is not genotoxic.

4.8.5 Comparison with criteria

CLP criteria:

The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans.

The classification in Category 1B is based on:

- positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or
- positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or
- positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.

The classification in Category 2 is based on:

- positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from:
- somatic cell mutagenicity tests in vivo, in mammals; or
- other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays.

Note: Substances which are positive in in vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.

No human data are available, hence a classification in Category 1A is not possible. The in-vitro and in vivo-studies revealed no evidence of genotoxicity.

4.8.6 Conclusions on classification and labelling

Classification and labelling is not warranted according to the CLP criteria.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

The mutagenic and DNA damaging potential of tefluthrin was studied in several *in vitro* test systems using bacteria and mammalian and human cells and in *in vivo* test systems using rats and mice. Tefluthrin was negative in two *in vitro* bacterial reverse mutation assays and in an *in vitro* gene mutation test in mouse lymphoma cells. No clastogenic effects were seen in an *in vitro* human lymphocyte cytogenectics test, an *in vivo* rat cytogenetics test or in an *in vivo* mouse micronucleus test. No evidence of DNA damage or repair was noted in an *in vitro* UDS assay.

It was concluded by the DS that no classification of tefluthrin for mutagenicity was required according to the CLP Regulation.

Comments received during public consultation

No comments were received during public consultation

Assessment and comparison with the classification criteria

Mutagenic properties of tefluthrin were negative in several *in vitro* assays (see above), in one *in vivo* micronucleus assay in mice and in one *in vivo* cytogenetics test in rats. RAC supports the conclusion of the DS that classification of tefluthrin for germ cell mutagenicity is not warranted.

4.9 Carcinogenicity

Table 44: Summary table of relevant carcinogenicity studies

Type of Study	Species	Dose Levels Tested	NOAEL	Reference
Oral, 24 months	Rat	0, 25, 100, 400 ppm (0, 1.5, 5.9, 23.2 mg/kg bw/d-males/ 0, 1.7, 7.1, 28.8 mg/kg bw/d-females)	25 ppm (1.5 mg/kg bw/d-males/ 1.7 mg/kg bw/d-females)	Stonard (1986, TOX2004-2686)
Oral, 24 months	Mouse	0, 25, 100, 400 ppm (0, 3.2, 13.1, 51.8 mg/kg bw/d-males/ 0, 3.9, 15.3, 62.8 mg/kg bw/d-females)	25 ppm (3.2 mg/kg bw/d-males/ 3.9 mg/kg bw/d-females)	Wickramaratne (1986, TOX2004-2682)

4.9.1 Non-human information

Tefluthrin was tested in rats and mice for its long-term toxicity and potential for carcinogenicity.

In a 24-month toxicity/oncogenicity study in rats, major effects were seen in animals dosed at the high-dose levels. These effects included mortality (mainly during the first three weeks of the study), clinical signs of toxicity (increased response to sound, increased activity, abnormal gait and tremors), decreased body weight gain, decreased food consumption and food utilisation, changes in clinical chemistry parameters (indicative of a mild toxic effect on the liver), and/or increased relative liver weight. No treatment-related macroscopic or microscopic changes were noted. There

was no increase or decrease in neoplasm that was associated with tefluthrin exposure. The NAOEL was 25 ppm (1.5 mg/kg bw/d in males and 1.7 mg/kg bw/d in females).

In the mouse, decreases in body weight gain were noted in males and females at the high-dose level of 400 ppm and in males at 100 ppm. Decreased food consumption was also noted in males and females at 400 ppm. Substance related effects were confined to the doses of 400 ppm and 100 ppm tefluthrin. There was a positive trend of neoplastic findings in liver, lung, harderian gland and pituitary gland. However, these findings are not considered to be an evidence of carcinogenic activity of tefluthrin. The no effect level of non-neoplastic and neoplastic lesions was 25 ppm tefluthrin (3.2 mg/kg bw/d in males and 3.9 mg/kg bw/d in females).

4.9.1.1 Carcinogenicity: oral

Report:	Wickramaratne G (1986 main study, TOX2004-2682, 1987 and 1990 supplements), Tefluthrin: Lifetime Feeding Study in Mice. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1509, study dates October 1983 to November 1985 (in-life phase). (Syngenta File No. ICI993/0112 main report, ICI993/0108, ICI993/0110 and ICI993/0109 supplements, ICI993/0111 IAD)
Guidelines:	87/302/EEC B.32, OECD 451 (1981), FIFRA § 83-2
Deviations:	Sternum and bone marrow were not examined histopathologically. The deviations are considered not to compromise the scientific validity of the study.
GLP:	This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.
Acceptability:	The study is considered to be acceptable.

Materials and methods:

Tefluthrin technical; batch No. P16; analysed purity 95.1 % w/w.

Groups of 50 male and 50 female Alpk:AP mice were fed diets containing 0 (two groups), 25, 100 or 400 ppm tefluthrin for up to 104 weeks. Achieved concentration was assessed regularly from all the groups (including controls) and stability and homogeneity of tefluthrin in diet was determined in previous and concurrent studies.

Clinical observations, body weights, food consumption and haematological parameters were measured throughout the study. At the end of the scheduled period the animals were killed, terminal blood and bone marrow samples were collected, and they were given a full examination *post mortem.* Selected organs were weighed and specified tissues were taken for subsequent histopathological examination.

Findings:

General observations: The levels of tefluthrin found within most diets analysed were close to those specified for all treatment groups although a small proportion of diets gave values below the target range. Mean dietary levels were within 10% of target concentration for each group. No explanation for the reduced dietary concentrations was evident but they were not of sufficient magnitude to compromise the integrity of the study. There was some evidence for isolated incidences of contamination of control batches of diet with trace amounts of tefluthrin but interpretation of the study was not affected. Stability and homogeneity of tefluthrin in diet was satisfactory. Dose rates

(based on nominal dietary levels of tefluthrin) were calculated in terms of mg tefluthrin/kg bw/d and are shown in the table below.

Table 45: Overall Mean Dose Received (mg/kg bw/d)

Dietary Concentration of Tefluthrin	25 ppm	100 ppm	400 ppm
Male	3.2	13.1	51.8
Female	3.9	15.3	62.8

There was no evidence of any statistically significant effect on mortality in males or females, although female survival was slightly reduced in the 400 ppm tefluthrin group towards the end of the study (please see the table below).

Table 46: Intergroup Comparison of Survival Rate

	Males					Females				
Dose (ppm)	**0**	**0**	**25**	**100**	**400**	**0**	**0**	**25**	**100**	**400**
Week 13	1.00	1.00	0.98	1.00	0.98	1.00	0.98	1.00	1.00	0.98
Week 52	0.88	0.94	0.86	0.92	0.88	0.88	0.98	0.92	0.98	0.90
Week 72	0.68	0.86	0.80	0.86	0.80	0.82	0.83	0.84	0.84	0.78
Week 84	0.56	0.78	0.72	0.71	0.62	0.74	0.63	0.61	0.64	0.64
Week 92	0.46	0.66	0.64	0.63	0.58	0.64	0.46	0.47	0.5	0.44
Week 100	0.36	0.48	0.58	0.41	0.42	0.40	0.31	0.39	0.36	0.24
Week 104	0.32	0.42	0.48	0.33	0.38	0.34	0.18	0.26	0.22	0.15

The clinical findings recorded in this study were of a type and incidence expected for this strain of mouse. There were no treatment-related clinical changes.

At 400 ppm both sexes showed a consistent reduction in body weight gain, particularly during the first week (400 ppm body weights approximately 4 % below control values), but the values continued to diverge slightly so that towards the end of the study they were 6 % lower than controls. Mice fed 100 ppm showed a small but consistent reduction in body weight gain. There was no effect on body weight gain for mice fed with 25 ppm (please see the table below).

Table 47: Intergroup Comparison of Body weight Gain (g) - Selected Timepoints

	Males					Females				
Dose (ppm)	**0**	**0**	**25**	**100**	**400**	**0**	**0**	**25**	**100**	**400**
Week 1	4.7	4.6	4.6	4.1*	3.4**	2.7	2.8	2.5	2.8	1.8**
Week 2	7.5	7.1	7.7	6.9	6.2**	4.3	3.7	4.3	4.4	3.6
Week 4	10.7	10.1	10.9	10.1	9.1**	7.1	7.1	7.3	7.5	6.6*
Week 6	13.3	12.3	12.8	11.8*	11.6**	8.7	8.7	8.5	9.1	7.8**
Week 13	16.5	16.2	16.5	15.3*	15.4	12.3	13.3	12.6	12.9	11.8*
Week 25	19.6	19.3	19.4	18.8	18.5	16.0	17.3	16.4	16.8	15.6*
Week 53	24.0	24.2	23.5	23.4	22.0*	20.2	21.3	20.2	20.9	19.4
Week 77	24.1	25.7	24.5	23.9	22.0*	21.9	22.2	20.6	21.8	20.1*
Week 101	21.0	20.3	21.0	18.9	18.3	19.0	18.0	18.4	18.7	13.1**
Week 104	20.4	19.7	20.8	18.6	17.5	-	-	-	-	-

** Statistically significant difference from control group mean, 1 % level (Student's t-test, 2-sided)
* Statistically significant difference from control group mean, 5 % level (Student's t-test, 2-sided)
- Surviving mice were killed between weeks 102-105. All females dead prior to week 104

At 400 ppm both sexes showed a clear reduction in food consumption during the first two weeks of the study and male mice at this level had a reduced efficiency of food utilisation compared with controls during weeks 1-4 only, but this was due almost entirely to one low value. There was no effect on food consumption or utilisation at the other dose levels (please see the table below).

Table 48: Intergroup Comparison of Food Consumption (g/mouse/day) - Selected Timepoints

	Males					Females				
Dose (ppm)	**0**	**0**	**25**	**100**	**400**	**0**	**0**	**25**	**100**	**400**
Week 1	6.6	6.8	6.6	6.6	6.2**	6.1	6.1	6.0	6.1	5.7**
Week 2	6.4	6.6	6.6	6.6	6.2**	6.0	6.1	6.1	6.1	5.8**
Week 3	6.2	6.4	6.3	6.3	6.2	6.0	6.0	6.0	6.1	6.0

** Statistically significant difference from control group mean, 1 % level (Student's t-test, 2-sided)

Clinical pathology: There were some minor and/or sporadic haematological changes but none were considered to be related to treatment with tefluthrin.

Gross pathology, organ weights, histopathology: Liver weights for males were increased for all treatment groups, but after exclusion of animals with type A or B nodules and histiocytic sarcoma there was no effect. Testis weight of males fed 100 ppm showed a slight increase compared with controls but this did not achieve statistical significance and was due mainly to a lower incidence of testicular atrophy in this group. Any organ weight changes were considered not to be attributable to dosing with tefluthrin.

Incidences of non-neoplastic findings which showed a positive trend are shown in the table below.

Table 49: Incidences of non neoplastic findings with positive trend

Organ and findings	**Sex**	**0 ppm**	**25 ppm**	**100 ppm**	**400 ppm**	**Trend test**
Kindney						
Glomerulonephritis	F	3/100	0/49	2/50	4/50	* p= 0.03
Spleen						
Congestion	M	0/100	0/49	2/48	3/50	** p=0.005
Haemorrhage	F	0/99	0/49	0/50	2/50	** p=0.003
Liver						
Hepatocyte pigmentation	F	1/100	0/49	0/50	2/50	* p=0.03
Hepatocyte necrosis	F	2/100	2/49	4/50	5/50	* p=0.02
Teleangiectasis	F	0/100	1/49	0/50	3/50	**p=0.004
Mammary gland						
Ectasia	F	31/94	15/44	16/47	22/47	* p=0.05
Uterus						
Endometrial Hyperplasia	F	10/99	2/49	7/50	9/48	* p=0.03
Haemangiomatous change	F	3/99	0/49	3/50	6/48	** p=0.002
Ovary						
Ectopic cutaneous adnexa	F	1/98	0/49	2/48	3/50	*p=0.02
Necrosis	F	0/98	0/49	0/48	2/50	**p=0.003
Skin						
Atrophy of hair follicles	F	4/100	1/48	3/50	5/50	*p=0.04
Paraceratosis	F	0/100	0/48	0/50	2/50	**p=0.003

logrank test for positive test with dose (Peto et al., 1980)

Incidences of neoplastic findings with a positive trend are shown in the next table.The incidence of liver adenoma showed a positive trend in females. However, the incidence of liver carcinoma was not increased. There was also a slightly positive trend of lung adenocarcinoma in males. However,

there was absolutely no influence on the number of adenoma. The incidence of adenoma of the harderian gland was also positive. The control group consisted of two subgroups. In one of both subgroups the incidence was 4/49 which is on the same level as the incidences in dose groups 25 and 100 ppm. Furthermore, there was an increased incidence of adenoma of the pituitary gland in males and of adenoma of pars intermedia in females. However, the incidence of carcinoma in males was not increased.

Table 50: Incidences of neoplastic findings (%) with positive trend

Organ and findings	Sex	0 ppm	25 ppm	100 ppm	400 ppm	Trend test	Historical control data
Liver							
Adenoma	F	2/100 (2)	0/49 (0)	3/50 (6)	5/50 (10)	** p=0.004	0-3.4 %
Adenocarcinoma		2/100 (2)	3/50 (6)	1/50 (2)	1/50 (2)		0-8.3 %
Lung							
Adenoma	M	8/100 (8)	3/50 (6)	2/49 (4.1)	4/50 (8)	n.s.	No data
Adenocarcinoma		2/100 (2)	0/50 (0)	1/49 (2)	3/50 (6)	* p=0.03	0-3.3 %
Harderian gland							
Adenoma	M	5/95 (5.3) (4/49 and 1/46)	4/48 (8.3)	4/48 (8.3)	7/49 (14.3)	* p=0.04	0-16 %
Pituitary gland							
Adenoma	M	2/88 (2.3)	0/34 (0)	2/34 (5.9)	4/41 (9.8)	** p=0.01	0-13 %
Carcinoma	M	0/88 (0)	0/34 (0)	1/34 (2.9)	0/41 (0)	n.s.	

logrank test for positive test with dose (Peto et al., 1980); n.s.: not significant

Conclusion:

The data obtained in this study show that substance related effects were confined to the doses of 400 ppm and 100 ppm tefluthrin. There was a positive trend of neoplastic findings in liver, lung, harderian gland and pituitary gland. However, these findings are not considered to be an evidence of carcinogenic activity of tefluthrin since the observed incidences were mainly within historical control data.

The NOAEL was 25 ppm tefluthrin (3.2 mg/kg bw/d in males and 3.9 mg/kg bw/d in females).

Report: Stonard M (1986, TOX2004-2686 main report, 1987 1st supplement, 1990 2nd supplement), Tefluthrin: 2 Year Feeding Study in Rats. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1522, study dates October 1983 to October 1985 (in-life phase). (Syngenta File No. ICI993/0106 main report, ICI993/0104 1st supplement, ICI993/0105 2nd supplement and ICI993/610 IAD)

Guidelines: 87/302/EEC B.33, OECD 453 (1981), FIFRA § 83-5

Deviations: The number of survivors fell slightly below 50 % at 24 months for the male controls and for males and females in the 100 ppm group. Urinalysis determinations did not include appearance, occult blood or microscopy of sediment. Plasma gamma glutamyl transpeptidase and ornithine decarboxylase were not measured. Although bone was examined histopathologically, it was not specified whether or not this was sternum with bone marrow. Adrenals were not weighed.

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

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin technical; batch No. 16; analysed purity 95.1 % w/w tefluthrin.

Groups of 76 male and 76 female Alpk:AP rats were fed diets containing 0 (control), or 400 ppm tefluthrin and groups of 64 male and 64 female Alpk:AP rats were fed diets containing 25 or 100 ppm tefluthrin for up to 104 weeks. (The differences in group size were due to extra animals being added at the top dose due to losses early in the study). Twelve male and 12 female rats from each group were designated for interim clinical pathology investigations after 52 weeks.

Samples from all dietary levels (including controls) were taken at intervals throughout the study and analysed for achieved concentration. Stability and homogeneity of tefluthrin in diet were confirmed in other studies.

Clinical observations (including ophthalmoscopy), body weights, food consumption, haematology and clinical biochemistry (blood and urine) were measured throughout the study. At the end of the scheduled period the animals were killed and subjected to a full examination *post mortem.* Terminal blood and bone marrow samples were taken, selected organs were weighed and specified tissues were taken for subsequent histopathology examination.

Findings:

General observations: Dose rates (based on nominal dietary levels of tefluthrin) were calculated in terms of mg tefluthrin/kg body weight/day and are shown in the table below.

Table 51: Overall Mean Dose Received (mg/kg bw/d)

Nominal dietary level	25 ppm	100 ppm	400 ppm
Male	1.5	5.9	23.2
Female	1.7	7.1	28.8

The achieved concentrations of tefluthrin in the test diets were satisfactory. The satisfactory homogeneity and chemical stability of tefluthrin in diet was demonstrated in other studies at dose levels of 50 and 350 ppm.

Four male and five female rats fed 400 ppm tefluthrin died during the first three weeks of the study but this mortality rate did not continue throughout the study. Changes in clinical condition seen only in rats fed 100 or 400 ppm included an increased response to sound, increased activity, abnormal gait and tremors. These findings were observed during the first 3 weeks of the study only, corresponding to the period during which the mortalities were seen. Abnormal gait was also noted in two females fed 25 ppm tefluthrin and in two control females in the later stages of the study. Observations of abnormal gait were seen mainly during the first few weeks of the study, occasionally throughout the mid phase of the study and increasing in incidence after week 80 (please see the table below).

Table 52: Intergroup Comparison of the Incidence of Selected Clinical Observations

Dose (ppm)	0 (control)	25	100	400
Males / Abnormal gait	0	0	4 (82-97)	7 (2-105)
Shaking	8 (76-105)	6 (93-104)	8 (37-105)	7 (76-105)
Increased response to sound	0	0	3 (7-7)	1 (7-7)
Females / Abnormal gait	2 (90-98)	2 (76-94)	7 (61-105)	60 (1-105)
Shaking	4 (38-105)	5 (97-105)	5 (59-105)	22 (2-105)
Increased response to sound	0	0	0	14 (3-7)

(number) - the number of weeks over which the observation was made

Other minor clinical signs were seen, but these were generally commonly found in rats of this age and strain and none were considered to be related to treatment with tefluthrin. No treatment-related ophthalmoscopic changes were found.

Body weight gain was reduced in males and females fed 400 ppm tefluthrin and, to a lesser extent, in males fed 100 ppm tefluthrin (see table below).

Table 53: Intergroup Comparison of Body weight Gain (Selected Timepoints)

	Males				Females			
	Dose (ppm)				Dose (ppm)			
Week	**0 (control)**	**25**	**100**	**400**	**0 (control)**	**25**	**100**	**400**
1	51.7	51.9	52.0	39.7**	31.5	31.1	31.7	19.9**
4	184.6	184.8	179.7*	170.3**	88.9	87.4	87.3	70.6**
8	276.4	276.1	264.4**	252.3**	129.8	130.3	128.0	105.2**
12	335.9	335.7	319.6**	303.2**	149.5	150.6	147.5	125.8**
16	370.0	369.4	353.6**	336.0**	162.8	164.3	160.1	142.2**
32	452.4	457.3	432.8**	418.5**	188.7	192.5	187.2	178.2**
64	541.0	541.1	516.7*	504.9**	265.1	274.3	254.3	227.5**
80	538.4	543.0	522.7	519.2	292.1	298.0	274.8*	248.8**
104	470.7	455.6	455.8	464.2	284.4	283.4	273.4	238.5**

** Statistically significant difference from control group mean, 1 % level (Student's t-test, 2-sided)
* Statistically significant difference from control group mean, 5 % level (Student's t-test, 2-sided)

Food consumption of females fed 400 ppm tefluthrin was reduced during the first 13 weeks of the study (ranging from approximately 4-17 % below control values). However the food consumption of males fed 400 ppm tefluthrin was consistently about 6 % lower than that of controls for most of the first twelve months of the study. The food consumption of males fed 100 ppm tefluthrin was also generally reduced throughout the first year compared to controls but was small and only attained statistical significance on three occasions in the first 13 weeks. Food utilisation values (see table below) were reduced in both sexes at 400 ppm tefluthrin, and in males at 100 ppm tefluthrin during the first year of the study.

Table 54: Intergroup Comparison of Overall Food Utilisation (g Growth/100 g Food)

	Males				Females			
dose (ppm)	**0 (control)**	**25**	**100**	**400**	**0 (control)**	**25**	**100**	**400**
weeks 1-12	15.34	15.21	14.91**	14.81**	9.36	9.39	9.15	8.69**

**	Statistically significant difference from control group mean, 1 % level (Student's t-test, 2-sided)
*	Statistically significant difference from control group mean, 5 % level (Student's t-test, 2-sided)

Clinical pathology: There were no treatment-related effects on any haematological parameters at the interim kill at 52 weeks.

Males fed 400 ppm tefluthrin (not designated for interim kill), showed reduced haemoglobin and haematocrit at weeks 40 and 53 compared with controls. This was a small reduction, not seen at other weeks and not seen in females. Platelet count was reduced in all treated males at week 79 only. These findings were considered not to be toxicologically significant. Female rats fed 400 ppm tefluthrin showed some reduced plasma albumin, cholesterol and total protein concentrations, and elevated plasma alanine and aspartate transaminase activities compared with control treatments. This could be indicative of a mild toxic effect on the liver, or a reflection of the poorer clinical condition of females at this dose. A similar, but less consistent trend was seen in males fed 400 ppm tefluthrin (see table below).

Table 55: Intergroup Comparison of Selected Clinical Chemistry Parameters

	Males				Females			
Dose (ppm)	**0**	**25**	**100**	**400**	**0**	**25**	**100**	**400**
Plasma albumin (g/100 mL)								
week 5	4.88	4.94	4.97	4.99*	4.89	4.96	5.01*	4.88
week 14	5.02	4.98	5.04	5.10	5.07	5.06	5.12	4.92*
week 27	4.81	4.88	4.88	5.04*	5.11	5.05	5.22	4.93
week 40	4.77	4.75	4.82	4.83	5.48	5.46	5.62	5.15**
Plasma cholesterol (g/100 mL)								
week 14	77.4	74.8	78.2	82.9	74.8	69.8	72.7	63.4**
week 27	84.8	82.6	83.2	99.5**	82.3	85.2	88.5	73.7
week 40	98.6	94.2	96.5	115.5**	95.3	92.1	97.8	81.0*
Total protein (g/100 mL)								
week 5	6.56	6.62	6.71**	6.78**	6.42	6.45	6.52	6.28*
week 40	7.07	7.00	7.02	7.05	7.22	7.18	7.32	6.97*
2. Plasma alanine transaminase (mU/mL)								
week 53	63.8	61.7	63.2	85.2*	63.6	59.5	62.7	72.6
week 79	58.0	58.2	58.3	61.4	58.1	49.6	70.8	88.9**
Aspartate transaminase (mU/mL)								
week 5	60.8	63.1	65.3	65.5	56.0	56.1	59.2	62.3*
week 79	70.4	63.1	65.2	65.0	68.5	69.4	101.3*	140.5**

** Statistically significant difference from control group mean, 1 % level (Student's t-test, 2-sided)
* Statistically significant difference from control group mean, 5 % level (Student's t-test, 2-sided)

There was no evidence of an effect of treatment on urine biochemistry, despite isolated statistically significant differences from control in some parameters in treated groups.

Gross pathology, organ weights, histopathology: There was a minimal increase in brain weight in females fed 400 ppm tefluthrin at 52 weeks and at study termination, but this was not associated with any histopathological change. Liver weight, when adjusted for final body weight, was marginally increased in both males and females fed 400 ppm tefluthrin at 52 weeks; there was no statistically significant difference at study termination (see table below).

Table 56: Intergroup Comparison of Selected Organ Weights (g) - Adjusted for Final Body weight

	Males				Females			
dose (ppm)	**0**	**25**	**100**	**400**	**0**	**25**	**100**	**400**
Brain								
week 52	2.239	2.241	2.262	2.287	2.044	2.051	2.038	2.115*
week 104	2.406	2.365	2.337	2.372	2.081	2.102	2.138	2.176**
Liver								
week 52	21.1	21.3	21.7	23.4**	11.7	11.8	12.1	12.9*

** Statistically significant difference from control group mean, 1 % level (Student's t-test, 2-sided)
* Statistically significant difference from control group mean, 5 % level (Student's t-test, 2-sided)

There were no macroscopic or microscopic changes which could be attributed to treatment with tefluthrin. In particular, tumour incidence, latency and malignancy were not adversely affected by the administration of tefluthrin.

Conclusion:

There was no evidence of a carcinogenic effect of tefluthrin. It was concluded that 25 ppm tefluthrin (1.5 mg/kg bw/d in males and 1.7 mg/kg bw/d in females) was the NOAEL in both sexes.

4.9.1.2 Carcinogenicity: inhalation

No studies submitted by the applicant.

4.9.1.3 Carcinogenicity: dermal

No studies submitted by the applicant.

4.9.2 Human information

No information concerning carcinogenicity in humans.

4.9.3 Other relevant information

No other relevant information available.

4.9.4 Summary and discussion of carcinogenicity

The studies in rats and mice revealed no evidence of carcinogenicity. The relevant long-term NOAEL was 1.5 mg/kg bw/d in rats and 3.2 mg/kg bw/d in mice.

4.9.5 Comparison with criteria

CLP criteria according to CLP regulation:

A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:

Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or

Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.

The classification in Category 1A and 1B is based on strength of evidence together with additional considerations. Such evidence may be derived from:

- human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
- animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen).

In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations. Such evidence

may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

No data from epidemiological studies were submitted by applicant. Hence, no classification with cat.1 A according to CLP regulation is proposed.

The studies in rats and mice revealed no evidence of carcinogenicity. Therefore, tefluthrin does not meet the CLP criteria for classification.

4.9.6 Conclusions on classification and labelling

Tefluthrin has no carcinogenic potential. Classification is not needed.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

The DS presented two long-term oral toxicity studies in the carcinogenicity part of the CLH report.

In a 2-year toxicity/oncogenicity study (Wickramaratne, 1986) groups of 50 male and 50 female Alpk:AP mice were fed diets containing 0, 25, 100 or 400 ppm tefluthrin (in accordance with OECD TG 451). The following findings were reported:

- Body weight gain was reduced in males and females fed 100 ppm and 400 ppm (4 – 6 % below control values).
- Reduced food consumption in the 400 ppm males and females during the first 2 weeks of the study.
- Incidence of liver adenoma showed a positive trend in females. However, the incidence of liver carcinoma was not increased.
- A slightly positive trend of lung adenocarcinoma in males. However, there was no effect on the incidence of adenoma.
- Incidence of adenoma of the harderian gland was positive. The control group consisted of two subgroups. In one of the subgroups the incidence was 4/49 which is similar to the incidences in the 25 and 100 ppm dose groups.
- There was an increased incidence of adenoma of the pituitary gland in males and of adenoma of *pars intermedia* in females. However, the incidence of carcinoma in males was not increased.

The NOAEL was considered to be 25 ppm tefluthrin (3.2 mg/kg bw/d in males and 3.9 mg/kg bw/d in females).

In a 2-year carcinogenicity study (Stonard *et al.*, 1986) groups of 76 male and 76 female Alpk:AP rats were fed diets containing 0 or 400 ppm tefluthrin and groups of 64 male and 64 female Alpk:AP rats were fed diets containing 25 or 100 ppm tefluthrin for up to 104 weeks (in accordance with OECD TG 453). The differences in group sizes were due to extra animals being added at the top dose due to animal losses early in the study. The following findings were reported:

- Four male and five female rats fed 400 ppm tefluthrin died during the first three weeks of the study but this mortality rate did not continue throughout the study.
- Increased response to sound, increased activity, abnormal gait and tremors was mainly seen within the first three weeks of the study in the 100 ppm and 400 ppm groups. Observations of abnormal gait were seen mainly during the first few weeks of the study, occasionally throughout the mid phase of the study and increasing in incidence after week 80.
- Body weight gain was reduced in males and females fed 400 ppm and in males fed 100 ppm.
- Food consumption was reduced in the 400 ppm groups;in females during the first 13

weeks of the study and in males during the first year. Reduced food consumption was also seen in the 100 ppm males for the first year but was statistically significant only for the first 13 weeks.

- Food utilisation values were reduced in both sexes at 400 ppm tefluthrin, and in males also at 100 ppm tefluthrin during the first year of the study.
- Haemoglobin and haematocrit were slightly decreased at weeks 40 and 53 at 400 ppm in males only.
- Plasma albumin, cholesterol and total protein concentrations were reduced, and plasma alanine and aspartate transaminase activities were elevated in 400 ppm females. This could indicate a mild toxic effect on the liver or a poorer clinical condition. A similar, but less consistent trend was seen in 400 ppm males.
- There was a minimal increase in brain weight in females fed 400 ppm tefluthrin at 52 weeks and at study termination, an effect that wasnot associated with any histopathological change.
- Liver weight was marginally increased at 52 weeks in both males and females fed 400 ppm tefluthrin . No statistically significant difference was observed at study termination.

Other observations included no evidence of a treatment-related effect on urine biochemistry, despite isolated statistically significant differences from the control in some parameters in treated groups. There were no macroscopic or microscopic changes which could be attributed to the treatment with tefluthrin. In particular, tumour incidence, latency and malignancy were not adversely affected by the administration of tefluthrin.

According to the DS, there was no evidence of a carcinogenic effect of tefluthrin. No data from epidemiological studies were submitted by applicant. The studies in rats and mice revealed no evidence of carcinogenicity. Therefore, The Ds considered that tefluthrin does not meet the criteria in the CLP Regulation for classification for carcinogenicity.

Comments received during public consultation

One MSCA requested further arguments on the non-carcinogenic potential of tefluthrin. In particular, the MSCA quoted from the CLH report that: "There was a positive trend of neoplastic findings in liver, lung, harderian gland and pituitary gland. However, these findings are not considered to be an evidence of carcinogenic activity of tefluthrin since the observed incidences were mainly within historical control data." The MSCA further noted that at the top dose, the incidence of liver adenoma in female mice and the incidence of lung adenocarcinoma in male mice were outside the historical control data (HCD) range.

Assessment and comparison with the classification criteria

In accordance with the criteria in CLP Regulation EC/1272/2008 classification in Category 1A for carcinogenicity is not justified given that there is no evidence of tefluthrin having caused cancer in humans.

In the 2-year study in rats no data on neoplastic findings were presented in the CLH report but it was concluded that "*tumour incidence, latency and malignancy were not adversely affected by the administration of tefluthrin*".

In the 2-year study in mice the neoplastic findings are summarized in the Table below.

Table (Table 50 in the CLH report): Incidences of neoplastic findings (%) with positive trend

Organ and findings	Sex	0 ppm	25 ppm	100 ppm	400 ppm	Trend test	HCD
Liver							
Adenoma	F	2/100 (2)	0/49 (0)	3/50 (6)	5/50 (10)	** p=0.004	0-3.4 %
Adenocarcinoma		2/100 (2)	3/50 (6)	1/50 (2)	1/50 (2)		0-8.3 %
Lung							

Adenoma Adenocarcinoma	M	8/100 (8) 2/100 (2) (0/50 & 2/50)	3/50 (6) 0/50 (0)	2/49 (4.1) 1/49 (2)	4/50 (8) 3/50 (6)	n.s. * p=0.03	No data 0-3.3 %
Harderian gland Adenoma	M	5/95 (5.3) (4/49 & 1/46)	4/48 (8.3)	4/48 (8.3)	´7/49 (14.3)	* p=0.04	0-16 %
Pituitary gland Adenoma Carcinoma	M M	2/88 (2.3) 0/88 (0)	0/34 (0) 0/34 (0)	2/34 (5.9) 1/34 (2.9)	4/41 (9.8) 0/41 (0)	** p=0.01 n.s.	0-13 %

logrank test for positive test with dose (Peto *et al*., 1980); n.s.: not significant

As can be seen from the Table above the incidences of liver adenoma were increased and outside the historical range in both 100 ppm and 400 ppm females. Since liver adenocarcinomas were not increased, tefluthrin does not seem to have a potential to progress to malignant tumours. The incidence of liver adenocarcinoma was at the same level as in controls and within the range of historical control data.

The increased incidence of lung adenocarcinoma in male mice was not significant. The incidences in the control groups were 0/50 and 2/50 (*ie*. 2/100). In comparison with 3/50 in 400 ppm males this is not significant. The incidence of lung adenocarcinoma was outside the historical control range in the 400 ppm males, but so was one of the control groups (2/50). The lack of significant increases in tumours and no dose-response relationship will usually lead to no classification if this was the only tumour type seen according to CLP Guidance (Version 4.0, section 3.6.2.3.2 a).

The incidence of Harderian gland adenoma was within the range of historical control data. In addition, according to the CLP Guidance (*V*ersion 4.0, section 3.6.2.3.2 a) tumours in the Harderian gland are of no relevance to humans (although it cannot automatically be ruled out that the substance could cause similar tumours in humans), and therefore Harderian gland adenoma on its own is unlikely to lead to classification.

The incidence of Pituitary gland adenoma was within the range of historical control data. Since pituitary gland carcinomas were not increased there does not seems to be a potential to progress to malignant tumours. According to the CLP Guidance (Version 4.0, section 3.6.2.3.2 c) benign brain tumours may be of concern and could support a classification in category 2. In this case however, the fact that Pituitary gland adenoma are within the range of historical control data supports no classification according to CLP Guidance.

RAC agrees with the DS that the studies in rats and mice revealed no evidence of carcinogenicity. Therefore, tefluthrin does not meet the CLP criteria for classification for carcinogenicity.

4.10 Toxicity for reproduction

Table 57: Summary table of relevant reproductive toxicity studies

Type of Study	Species	Dose Levels Tested	NOAEL	Reference
Three-generation reproduction	Rat	0, 15, 50, 250 ppm	Pup: 15 ppm (1.4 mg/kg bw/d) Parental and Reproductive: 50 ppm (4.7 mg/kg bw/d)	Wickramaratne (1987, TOX2004-2687)
Teratology	Rat	0, 1, 3, 5, 7.5 mg/kg bw/d	Maternal: 1 mg/kg bw/d Foetotoxicity: 3 mg/kg bw/d Teratogenicity: 5 mg/kg bw/d	Killick et al (1985, TOX2004-2689)

Type of Study	Species	Dose Levels Tested	NOAEL	Reference
			No evidence of teratogenicity	
Teratology	Rabbit	0, 3, 6, 12 mg/kg bw/d	Maternal: < 3 mg/kg bw/d Foetotoxicity: < 3 mg/kg bw/d Teratogenicity: 12 mg/kg bw/d No evidence of teratogenicity	Killick et al (1985, TOX2004-2690)

4.10.1 Effects on fertility

4.10.1.1 Non-human information

Parental toxicity in a three-generation rat reproduction study conducted with tefluthrin consisted of splayed gait, abnormal or high-stepping gait and shaking, decreased body weight gain in all parental generations in both sexes, decreased food consumption and increased food utilisation in each generation at the high-dose level (250 ppm, equivalent to 23.4 mg/kg bw/d). There were no treatment-related effects on fertility, length of gestation, the incidence of whole litter losses in any groups and percentage of pups born live or pup survival. A low incidence of shaking and abnormal and/or splayed gait was seen in F_1A and F_1B pups in the 250 ppm group. In subsequent generations the incidence in the 250 ppm group was high and in the F_2B and F_3A litters, the majority of the litters were affected. These signs became more evident from day 22 *post partum* onwards, as the pups ate more diet. The incidence of shaking was also slightly increased in F2A (2 litters) and F2B pups (1 litter) of dose group 50 ppm (4.7 mg/kg bw/d), but was considered as an incidental finding. Pup body weight gain and total litter weight were consistently reduced at 250 ppm.

Report: Wickramaratne G (1987, TOX2004-2687), Tefluthrin: Multigeneration Reproduction Study in Rats. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1755, study dates March 1984 to January 1986 (in-life phase). (Syngenta File No. ICI993/0126 and ICI993/0127)

Guidelines: 87/302/EEC B.35, OECD 416 (1983)

Deviations: If there was no evidence of mating after 10 days, the male was removed and replaced, after 3 days, with a second male. Food consumption and utilisation was measured only during the pre-mating periods. Live pups were counted and weighed on the morning after birth and on days 4, 7 and weekly thereafter. Pituitary glands of all P and F1 animals selected for mating were not preserved for possible microscopic examination. The deviations are considered not to compromise the scientific validity of the study.

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin technical; batch No P16; analysed purity 95.1 % w/w tefluthrin.

Groups of 15 male and 30 female (F_0 parents) weanling rats were fed diet containing 0 (control), 15, 50 or 250 ppm tefluthrin. After 12 weeks, the animals were mated to produce the first (F_1A) litter and subsequently re-mated to produce a second (F_1B) litter. The breeding program was repeated with the F_1 parents selected from the F_1B offspring to produce the F_2A and F_2B litters and F_2 parents selected from the F_2B offspring to produce the F_3A litters. Test diets were fed continuously throughout the study. Parental food and body weights were measured throughout the study. Reproductive performance and selected offspring parameters were measured.

Samples from all dietary levels (including controls) were taken at intervals throughout the study and analysed for achieved concentrations, and for chemical stability for a period of up to 6 weeks. Homogeneity of tefluthrin in diet was confirmed in a previous study.

Findings:

General observations: Analysis of the diets showed that the achieved concentrations, homogeneity and stability of tefluthrin in diet were satisfactory overall (although some diet batches were inexplicably outside the 10 % of the target concentration). The mean dose received (based on nominal dietary levels of tefluthrin) during the premating period is shown in the table below.

Table 58: Overall Mean Dose Received During the Pre-Pairing Period (mg/kg bw/d)

Dose (ppm)	15	50	250
F0 Parents: Males	1.4	4.7	23.4
Females	1.5	5.0	25.2
F1 Parents: Males	1.4	4.7	23.5
Females	1.5	5.0	25.5
F2 Parents: Males	1.4	4.7	23.6
Females	1.4	4.9	25.5

A small number of parental animals were killed due to poor clinical condition. Clinical abnormalities which could be related to treatment were seen in animals fed 250 ppm tefluthrin in all generations, during the early part of the pre-mating period. These findings included splayed gait, abnormal or high-stepping gait and shaking (please see the table below).

Table 59: Intergroup Comparison of the Total Incidence of Selected Clinical Observations

	Males				Females			
Dose (ppm)	**0**	**15**	**50**	**250**	**0**	**15**	**50**	**250**
F0 Parents								
Killed or found dead	0	1	0	0	1	0	0	0
High stepping/splayed gait	0	0	0	1	0	0	0	11
Unsteady gait	0	0	0	0	1	0	0	0
F1 Parents								
Killed or found dead	0	0	0	0	2	0	1	3
Abnormal/splayed gait	0	0	0	0	0	0	0	2
F2 Parents								
Killed or found dead	0	0	0	0	0	0	0	1
Shaking	0	0	0	3	0	0	0	11
Abnormal/splayed gait	0	0	0	0	0	0	0	6

Body weight gain was reduced in F0 and F1 parental generations fed 250 ppm tefluthrin. Reduction in weight gain compared to the control group was also evident during pregnancy in the F_0 and F_1 females (please see next two tables).

Table 60: Intergroup Comparison of Body weight (g) - Prior to Mating

	Males				Females			
Dose (ppm)	**0**	**15**	**50**	**250**	**0**	**15**	**50**	**250**
F0 Parents	475.0	485.1	478.9	467.2	269.0	263.2	270.7	257.4*
F1 Parents	485.7	488.0	497.2	451.2**	273.6	282.0	274.1	254.7**
F2Parents	451.8	493.2**	493.6**	450.6	251.8	261.5	274.0**	250.9

* statistically significantly difference from the control group mean at the 5 % level
** statistically significantly difference from the control group mean at the 1 % level

Table 61: Intergroup Comparison of Day 22 Pregnancy Body weight (g) - Females

Dose (ppm)	**0**	**15**	**50**	**250**
F0 Parents/ A litter	393.3	389.9	395.5	365.3**
B litter	443.0	431.5	445.5	419.7**
F1 Parents/ A litter	408.0	423.5*	422.9	385.1**
B litter	444.8	462.1	447.9	413.6**
F2 Parents/ A litter	384.1	393.9	416.2**	394.1

* statistically significantly difference from the control group mean at the 5 % level

** statistically significantly difference from the control group mean at the 1 % level

Food consumption was generally slightly lower and utilisation values increased in the F1 and F2 females of 250 ppm tefluthrin groups compared to controls. In the F0 females food utilisation was decreased in the 250 ppm group (see table below).

Table 62: Intergroup Comparison of Food Utilisation (g growth/100 g food) - Pre-Mating Period Overall

	Males				Females			
Dose (ppm)	**0**	**15**	**50**	**250**	**0**	**15**	**50**	**250**
F0 Parents	16.11	16.63*	16.37	16.16	11.59	11.25	11.41	11.09*
F1 Parents	14.06	13.98	13.74	13.88	9.17	9.21	8.99	9.65*
F2Parents	14.30	14.16	14.45	14.78	9.18	9.33	9.52	9.87**

* statistically significantly difference from the control group mean at the 5 % level
** statistically significantly difference from the control group mean at the 1 % level

There was no evidence for any adverse effect on fertility, length of gestation or on the incidence of whole litter losses in any group fed tefluthrin for either A or B litters.

Litter data: There was no evidence of a treatment-related effect on the percentage of pups born live or pup survival. Whole litter losses were seen in all groups, including control, particularly in the A litters and is considered to be due to maternal neglect (which is not uncommon in this strain of rat).

Pups in the F_1A and F_1B litters generally remained in good clinical condition in each generation. However, there was a very low incidence of shaking and abnormal and/or splayed gait seen in pups in the 250 ppm tefluthrin group. In subsequent generations the incidence was high and in the F_2B and F_3A litters, the majority of the litters were affected. These signs became more evident from day 22 *post partum* onwards, as the pups ate more diet. The incidence of shaking was also slightly increased in F2A and F2B pups of dose group 50 ppm (see table below), however considered to be an incidental finding: The effects in two pups out of two litters in the F2A-generation seems to be an acute neurotoxic effect rather than a developmental effect. These effects were observed at weaning when pups generally consume more food than adults compared to their body weight. Therefore, one may assume that the intake of tefluthrin at 50 ppm was twice as high in pups compared to the adults at weaning. Furthermore, the findings in seven pups out of one litter in the F2B-generation at day 5 p.n. were without any dose response relationship.

Table 63: Intergroup Comparison of the Incidence of Neurotoxicity Signs in Offspring

		Dietary Concentration of Tefluthrin (ppm)			
Generation / Observation	**Day**	**0**	**15**	**50**	**250**
F1A: Shaking	30	0	0	0	0
Abnormal gait/Splayed gait		0	0	0	12 (1)
F1B: Shaking	22	0	0	0	1 (1)
Abnormal gait/Splayed gait	22	0	0	0	0
F2A: Shaking	22	0	0	2 (2)	57 (9)
	29	0	0	0	58 (7)
Abnormal gait/Splayed gait	22	0	0	0	8 (4)
	29	0	0	0	3 (2)
F2B: Shaking	5	0	0	7 (1)	0
	22	0	0	0	174 (19)
	29	0	0	0	209 (20)
Abnormal gait/Splayed gait	5	0	0	0	0
	22	0	0	0	0
	29	0	0	0	0
F3A: Shaking	22	0	0	0	176 (23)
	29	0	0	0	174 (21)
Abnormal gait/Splayed gait	22	0	0	0	7 (1)
	29	0	0	0	2 (2)

values shown are the number of pups affected, with the number of litters shown in parentheses

Pup body weight gain and total litter weight were consistently reduced at 250 ppm tefluthrin (see next table).

Table 64: Intergroup Comparison of Day 29 Pup Body weight (g)

	Males				Females			
Dose (ppm)	**0**	**15**	**50**	**250**	**0**	**15**	**50**	**250**
F1A	76.3	78.2	75.7	62.5**	71.1	73.5	70.8	58.9**
F1B	82.3	87.8*	85.7	71.0**	76.5	81.4*	80.4	64.5**
F2A	79.4	77.9	79.8	66.5**	76.0	73.4	74.6	62.4**
F2B	79.7	84.3	85.2	67.2**	74.7	77.4	79.4	62.0**
F3A	81.5	81.2	76.4	63.4**	75.7	75.1	73.5	59.4**

* statistically significantly difference from the control group mean at the 5 % level
** statistically significantly difference from the control group mean at the 1 % level

Gross pathology, histopathology: A variety of histopathological changes were seen in both parents and offspring in each generation, at all dose levels, but none of these changes was considered to be related to treatment with tefluthrin.

Conclusion:

The NOAEL of parental and offspring toxicity was considered to be 50 ppm (4.7 mg/kg bw/day) based on neurological effects at highest dose of 250 ppm (23.4 mg/kg bw/d) and additionally in offspring reduced total litter weight and pup weight gain.

Since no treatment-related effects on fertility, length of gestation, the incidence of whole litter losses in any groups and percentage of pups born live or pup survival were observed, the NOAEL for reproductive toxicity was 250 ppm (23.4 mg/kg bw/d).

4.10.1.2 Human information

No studies submitted by the applicant.

4.10.2 Developmental toxicity

4.10.2.1 Non-human information

In the developmental toxicity studies in rats and rabbits, there was no evidence of teratogenicity. The relevant maternal NOAEL is 1 mg/kg bw/d for the rat and < 3 mg/kg bw/d for the rabbit. Based on reduced foetal ossification (rat) and skeletal variations (rat, rabbit), the developmental NOAEL is 3 mg/kg bw/d for the rat and < 3 mg/kg bw/d for the rabbit.

Report: Killick M, Wickramaratne G, Banham P *et al* (1985, TOX2004-2689), PP993: Teratogenicity Study in the Rat. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1134, study dates April 1984 to May 1984 (in-life phase). (Syngenta File No. ICI993/0116)

Guidelines: 87/302/EEC B.31, OECD 414 (1981), FIFRA § 83-3

Deviations: There were 7 animals found dead in the group dosed with 7.5 mg/kg and therefore the surviving animals in this group were removed from the study and no teratological assessments were made. The experimental design was

therefore modified to include an additional group of 24 rats, which was dosed with 5 mg/kg. (A further six animals were allocated to the control group to provide a concurrent control group, as the additional animals commenced treatment at a later date than the original animals on study).

GLP: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin (PP993) technical; batch number P14; analysed purity 93 % w/w tefluthrin.

Groups of 24 female rats were dosed by gavage with 1, 3 or 5 mg tefluthrin/kg bw/d in corn oil from days 7-16 (inclusive) of gestation which thus included the period of organogenesis. A group of 18 female rats was similarly dosed with 7.5 mg tefluthrin/kg bw/d. A control group of 30 animals received corn oil alone. The day of confirmation of mating (when spermatozoa were detected) was designated day 1 of gestation. The achieved concentration of tefluthrin in corn oil was measured at all dose levels and the chemical stability of tefluthrin in corn oil was determined by re-analysis of the dosing formulations at the lowest and highest concentrations (nominally containing 0.1 or 0.75 mg/mL) after an interval of 38 days. On day 22 of gestation, the females were killed and their uteri examined for live foetuses and intra-uterine deaths. The foetuses were weighed, examined for external/visceral abnormalities, sexed, eviscerated and stained for skeletal examination.

Findings:

General observations: Analysis of the dosing formulations showed that the achieved concentrations of ± 10 % of nominal values and the chemical stability of tefluthrin in corn oil at the lowest and highest concentrations were satisfactory.

Maternal findings: Seven of the eighteen females dosed with 7.5 mg tefluthrin/kg bw/d were found dead between days 9 and 14 of gestation, therefore the remaining animals in this group were killed. Administration of 7.5 mg tefluthrin/kg bw/d was associated with maternal toxicity manifest as abnormal gait, uncoordinated limb movements, involuntary spasms, hypersensitivity to noise, piloerection and subdued behaviour. The observations were generally apparent within a few hours after dosing and were of the type associated with pyrethroid toxicity. This dose was also associated with reduced maternal weight gain and food consumption.

There were no mortalities in the 0 (control), 1, 3 or 5 mg tefluthrin/kg mg/d groups. Administration of 5 mg tefluthrin/kg bw/d was associated with some maternal toxicity characteristic of pyrethroid toxicity, such as abnormal gait, hypersensitivity, piloerection and subdued behaviour following dosing. Two animals dosed with 3 mg tefluthrin/kg bw/d showed occasional signs of subdued behaviour (see table below).

Table 65: Summary of Selected Clinical Observations

Dose (mg/kg bw/d)	0	1	3	5	7.5
Number of females examined	30	24	24	24	18
Abnormal gait	0	0	0	7	15
Hypersensitivity	0	0	0	19	9
Piloerection	6	4	7	19	6
Subdued behaviour	0	0	2	24	11

Administration of 3 or 5 mg tefluthrin/kg bw/d was associated with a statistically significant reduction in body weight gain during the dosing period when compared with the control group. The effect on weight gain was most apparent between days 7 and 10 of gestation and was dosage-related (see table below).

Table 66: Intergroup Comparison of Body weight Gain (g)

Dose (mg/kg bw/d)	0 (control)	1	3	5
Initial Body weight (day 1)	243.1	245.7	239.0	246.5
Pre-dosing period (days 1-7)	31.6	28.7	31.2	33.9
Dosing period (days 7-16)	45.8	45.9	38.3**	18.4**
(days 7-10)	10.9	9.3	6.3**	-6.0**
(days 10-13)	16.5	18.3	14.7	9.9**
(days 13-16)	18.4	18.3	17.3	14.5**
Post-dosing (days 16-22)	57.5	59.1	60.0	58.3
Overall (days 1-22)	134.9	133.7	129.4	110.7**
Number of females with live foetuses in utero	30	23	23	24

** Statistically significantly different from the control group mean at the 1 % level

Administration of 3 or 5 mg tefluthrin/kg bw/d was associated with a statistically significant and dosage-related reduction in food consumption during the dosing period when compared with the control group. Maternal food consumption in the 5 mg tefluthrin/kg bw/d was also reduced in the post-dosing period (see next table).

Table 67: Intergroup Comparison of Mean Maternal Food Consumption (g/day)

	Dose Level of Tefluthrin (mg/kg bw/d)			
Period (Days)	0 (control)	1	3	5
Pre-dosing period (days 1-7)	23.6	23.5	23.2	24.6
Dosing period (days 7-16)	22.7	22.5	20.5**	16.6**
(days 7-10)	20.9	20.1	18.6**	14.8**
(days 10-13)	22.5	22.8	20.6**	16.5**
(days 13-16)	24.7	24.5	22.2**	18.3**
Post-dosing (days 16-22)	28.8	29.8	28.2	25.4**
Overall (days 1-22)	24.7	24.9	23.5	21.4**

** Statistically significantly different from the control group mean at the 1% level

Gross pathology, organ weights, histopathology: Macroscopic changes seen in the dams at examination *post mortem* were of a type and incidence commonly seen in the strain of rat used in this study and were considered not to be related to treatment.

Foetal data: There was no evidence of any difference in the number, growth or survival of the foetuses *in utero* at any dose level, when compared with control values.

The incidence of foetuses with major defects was 1, 1, 0 and 2 in the control, 1, 3 and 5 mg tefluthrin/kg bw/d groups respectively. The defects were considered to be spontaneous and not a result of treatment with tefluthrin.

There was no evidence of any effect of treatment on the incidence of minor external/visceral defects. One skeletal variation, the occurrence of 25 pre-sacral vertebrae, was seen in the 5 mg tefluthrin/kg bw/d group and attained statistical significance when compared with the control group where it did not occur (see table below). Most of the foetuses have 26 pre-sacral vertebrae which is normal in rats. 27 pre-sacral vertebrae is considered to be in the range of ‘normal’ however, there is

a shift towards a decrease at the high dose. In the highest dose group one foetus was observed with 6 cervical vertebrae.

Table 68: Incidence of 25 or 27 pre-sacral vertebrae and of 6 cervical vertebrae

Dose (mg/kg bw/d)	0	1	3	5
Incidence of 25 pre-sacral vertebrae	0	0	0	5* (3)
Incidence of 27 pre-sacral vertebrae	2 (2)	1 (1)	0	0
Incidence of 6 cervical vertebrae	0	0	0	1 (1)

number of foetuses (number of litters); *=Fisher`s exact test, p≤ 0.05

The incidence of foetuses with extra 14th (short length) ribs in the 1 mg tefluthrin/kg bw/d group and the incidences of foetuses with fully ossified transverse processes on the 4th lumbar vertebra in the 3 mg tefluthrin/kg bw/d group were statistically significantly increased compared with the control group. However, neither of these defects was increased in the 5 mg tefluthrin/kg bw/d group and in the absence of a dosage-related effect, this finding was considered to be unrelated to treatment with tefluthrin.

The mean *manus* and *pes* scores for the tefluthrin treated groups were not statistically significantly different from the control group. The *pes* scores for the 5 mg tefluthrin/kg bw/d group did however reflect a very slight reduction in ossification compared to the control group.

Conclusion:

There was no evidence of teratogenicity in this study. Administration of 7.5 mg/kg bw/d was associated with maternal mortality and in dose groups of 5 and 3 mg/kg bw/d maternal toxicity was observed. In addition, 5 mg tefluthrin/kg bw/d was associated with a minimal effect on foetal ossification and an increased incidence of 25 pre-sacral vertebrae. The dose level of 3 mg tefluthrin/kg bw/d was established as the NOAEL for developmental toxicity and 1 mg tefluthrin/kg bw/d the NOAEL for maternal toxicity.

Report:	Killick M, Wickramaratne G, Banham P *et al* (1985, TOX2004-2690), PP993: Teratogenicity Study in the Rabbit. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/P/1082, study dates July 1983 to August 1983 (in-life phase). (Syngenta File No. ICI993/0120)
Guidelines:	87/302/EEC B.31, OECD 414 (1981), FIFRA § 83-3
Deviations:	None
GLP:	This study was performed prior to the GLP certification of Laboratories but was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.
Acceptability:	The study is considered to be acceptable

Materials and methods:

Tefluthrin (PP993) technical; batch number P14; analysed purity 90.4 % w/w subsequent analysis 93 % w/w tefluthrin. Groups of 18 female New Zealand White rabbits were dosed by gavage with 3, 6 or 12 mg tefluthrin/kg bw/d in corn oil from days 7-19 (inclusive) of gestation which thus included the period of organogenesis. A control group of 18 animals received corn oil alone. The day of insemination was designated day 1 of gestation. Two preparations of each dose level were made and the achieved concentration of tefluthrin in corn oil was measured at all dose levels. The chemical stability of tefluthrin in corn oil was determined by re-analysis of the dosing formulations after an interval of 8 days, which covered the period of use in this study. On day 30 of gestation, the females were killed and their uteri examined for live foetuses and intra-uterine deaths. The foetuses were weighed, examined for external/visceral abnormalities, sexed, eviscerated and stained for skeletal examination.

Findings:

General observations: Analysis of the dosing formulations showed that the achieved concentrations of ± 7 % of nominal values and the chemical stability of tefluthrin in corn oil at all concentrations were satisfactory.

Maternal findings: One, one, two and two animals in the control, 3, 6 and 12 mg tefluthrin/kg bw/d groups died or were killed prior to study termination.

One animal from each of the control, 6 and 12 mg tefluthrin/kg bw/d groups was killed following abortion. Administration of 12 mg tefluthrin/kg bw/d was associated with maternal toxicity manifest as body tremors, typical of those known to be associated with pyrethroid toxicity. One animal from the 6 mg tefluthrin/kg bw/d group and one from the 3 mg tefluthrin/kg bw/d group also exhibited body tremors. The incidence and severity of this maternal toxicity was most marked at 12 mg tefluthrin/kg bw/d (see table below).

Table 69: Summary of the Incidence of Animals Exhibiting Body Tremors

Dose level (mg/kg bw/d)	0	3	6	12
Incidence (day)	0	1 animal (day 15)	1 animal (day 16)	6 animals (days 9-17)
degree	-	slight to extreme	slight	slight to extreme

Administration of 12 mg tefluthrin/kg bw/d was associated with a statistically significant reduction in body weight gain between days 7-10 and 16-19 of gestation (see table below).

Table 70: Intergroup Comparison of Body weight Gain (g)

Dose level (mg/kg bw/d)	0 (control)	3	6	12
Initial Body weight (day 1)	3554.0	3523.4	3553.6	3675.5
Pre-dosing period (days 1-7)	191.6	143.3	172.1	178.0
Dosing period (days 7-19)	194.4	192.7	140.9	151.4
(days 7-10)	-12.5	22.7	-33.8	-71.0*
(days 10-13)	53.6	46.7	63.2	106.8*
(days 13-16)	100.1	86.4	93.1	121.7
(days 16-19)	53.2	36.8	18.3	-6.1*
Post-dosing (days 19-30)	259.1	234.9	266.2	254.0
Overall (days 1-30)	645.1	570.9	579.2	583.4

* Statistically significantly different from the control group mean at the 5 % level

Maternal food consumption in the 6 and 12 mg tefluthrin/kg bw/d groups was slightly reduced during the dosing period when compared with the control group. These reductions were statistically significant on days 7-10 of gestation for the 6 mg/kg bw/d group and over the total dosing period of days 7-19 of gestation for the 12 mg/kg bw/d group (see table below).

Table 71: Intergroup Comparison of Mean Maternal Food Consumption (g/day)

Dose level (mg/kg bw/d)	0 (control)	3	6	12
Pre-dosing period (days 1-7)	180.8	178.3	177.4	188.4
Dosing period (days 7-19)	131.9	128.6	112.3	110.0*
(days 7-10)	120.7	109.5	89.6*	94.1
(days 10-13)	148.4	139.6	132.4	122.3
(days 13-16)	123.4	124.2	115.1	118.0
(days 16-19)	136.5	141.2	112.2	120.9
Post-dosing (days 19-30)	156.6	147.5	154.9	167.0
Overall (days 1-30)	150.7	146.0	141.0	144.7

* Statistically significantly different from the control group mean at the 5 % level

Gross pathology: Macroscopic changes seen in the dams at examination *post mortem* were of a type and incidence commonly seen in the strain of rabbit used in this study and were considered not to be related to treatment.

Foetal data: There was no evidence of any difference in the number, growth or survival of the foetuses *in utero* at any dose level, when compared with control values.

The incidence of foetuses with major defects was 4, 2, 4 and 1 in the control, 3, 6 and 12 mg tefluthrin/kg bw/d groups respectively. Neither the type nor the incidence provided any evidence of an association with administration of tefluthrin.

There was no evidence of any effect of treatment on the incidence of minor external/visceral or skeletal defects.

Almost all foetuses showed one or more skeletal variant. The incidence of foetuses with extra 13^{th} thoracic ribs, unilateral or bilateral, short or normal length was statistically significantly increased in the 6 and 12 mg tefluthrin/kg bw/d groups compared with the control group. However, the incidence was not dose-related. The incidence of foetuses with 27 pre-sacral vertebra was statistically significantly increased in all the tefluthrin treated groups compared with the control group (see table below).

Table 72: Incidence of specific skeletal variations

Dose (mg/kg bw/d)	0	3	6	12
Incidence of extra 13^{th} ribs (any qualification)	85	89	110**	94**
Incidence of 27 pre-sacral vertebrae	45	59*	59*	62**

number of foetuses (number of litters); *=Fisher`s exact test, p≤ 0.05; **=Fisher`s exact test, p≤ 0.01

Conclusion:

Administration of tefluthrin was associated with maternal toxicity in all dose groups. Tefluthrin was not teratogenic. However, the incidence of skeletal variations (27 pre-sacral vertebrae) was increased in all dose groups. The NOAEL of teratogenicity was 12 mg/kg bw/d, whereas the NOAEL's of maternal and developmental toxicity were < 3 mg/kg bw/day.

4.10.2.2 Human information

No information submitted by the applicant.

4.10.3 Other relevant information

No other relevant information submitted by the applicant.

4.10.4 Summary and discussion of reproductive toxicity

In the reproductive toxicity study (3-generation), the neurological effects in the offspring were attributed to a direct systemic exposure after oral ingestion. No adverse effects were observed in the fertilitiy parameters. The agreed parental and offspring NOAELs were 4.7 mg/kg bw/d (50 ppm), whereas the agreed reproductive NOAEL was 23.4 mg/kg bw/d (250 ppm)

In a rat developmental study, maternal toxicity consisted of increased mortality, clinical signs of maternal toxicity (abnormal gait, uncoordinated limb movements, involuntary spasms, hypersensitivity to noise, piloerection and subdued behaviour) and decreased maternal body weight gain and food consumption at the high dose of 7.5 mg/kg bw/d. Some maternal toxicity was also noted at 5 mg/kg bw/d. Decreases in maternal body weight gain and food consumption during the dosing period were noted in females at 3 and 5 mg/kg bw/d. Maternal food consumption was also decreased at 5 mg/kg bw/d in the post-dosing period. At 5 mg/kg bw/d a slight reduction in ossification of the foetuses and increased incidence of 25 pre-sacral vertebrae was observed. No evidence of a teratogenic effect was noted.

In a rabbit developmental study, maternal toxicity consisted of body tremors in all treatment groups (the incidence and severity of this finding was most marked at the high-dose level of 12 mg/kg bw/d), decreased body weight gain during dosing at 12 mg/kg bw/d and decreased food consumption at 6 and 12 mg/kg bw/d. No evidence of a teratogenic effect was noted. However, the incidence of skeletal variations (27 pre-sacral vertebrae) was increased in all dose groups. The NOAEL of teratogenicity was 12 mg/kg bw/d. The NOAEL`s of maternal toxicity and foetotoxicity were < 3 mg/kg bw/d.

Overall, based on the results of the multi-generation study and the developmental toxicity studies classification for reproductive toxicity is not proposed.

4.10.5 Comparison with criteria

<u>Adverse effects on sexual function and fertility (CLP criteria):</u>

There are no epidemiological data to evaluate effects on sexual function and fertility, hence tefluthrin cannot be placed in category 1A according to CLP regulation.

No specific information regarding effects on or via lactation was provided.

No effects were observed in the multi-generation study, therefore comparison to the CLP criteria is not relevant.

<u>Adverse effects on development:</u>

Category 1A: Known human reproductive toxicant

Category 1B: Presumed human reproductive toxicant largely based on data from animal studies

- clear evidence of an adverse effect on development in the absence of other toxic effects, or
- the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects

Category 2: Suspected human reproductive toxicant

- some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on development and
- the evidence is not sufficiently convincing to place the substance in Category 1 (deficiencies in the study).
- the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects

There are no appropriate epidemiological studies available on developmental effects in humans. Hence, classification with Category 1A according CLP regulation is not possible.

The developmental toxicity studies revealed only minimal effects on foetal ossification in rats and an increased incidence of one skeletal variation in rats (25 pre-sacral vertebrae) and rabbits (27 pre-sacral vertebrae) at maternal toxic dose levels. No evidence of teratogenicity was observed in both species.

Based on the results of developmental toxicity studies in rats and rabbits, the substance does not meet the criteria for classification.

4.10.6 Conclusions on classification and labelling

Classification is not proposed.

RAC evaluation of reproductive toxicity
Summary of the Dossier submitter's proposal In the reproductive toxicity study (3-generation), the neurological effects in the offspring were attributed to a direct systemic exposure after oral ingestion. No adverse effects were observed in the fertility parameters. The parental and offspring NOAELs were 4.7 mg/kg bw/d (50 ppm), whereas the reproductive NOAEL was 23.4 mg/kg bw/d (250 ppm). In a rat developmental study, maternal toxicity consisted of increased mortality, clinical signs of maternal toxicity (abnormal gait, uncoordinated limb movements, involuntary spasms, hypersensitivity to noise, piloerection and subdued behaviour) and decreased maternal body weight gain and food consumption at the high dose of 7.5 mg/kg bw/d. Some maternal toxicity was also noted at 5 mg/kg bw/d. Decreases in maternal body weight gain and food consumption during the dosing period were noted in females at 3 and 5 mg/kg bw/d. Maternal food consumption was also decreased at 5 mg/kg bw/d in the post-dosing period. At 5 mg/kg bw/d a slight reduction in ossification of the foetuses and increased incidence of 25 pre-sacral vertebrae were observed. No evidence of a teratogenic effect was noted. In a rabbit developmental study, maternal toxicity consisted of body tremors in all treatment groups (the incidence and severity of this finding was most marked at the high-dose level of 12 mg/kg bw/d), decreased body weight gain during dosing at 12 mg/kg bw/d and decreased food

consumption at 6 and 12 mg/kg bw/d. No evidence of a teratogenic effect was noted. However, the incidence of skeletal variations (27 pre-sacral vertebrae) was increased in all dose groups. The NOAEL of teratogenicity was 12 mg/kg bw/d. The NOAELs for maternal toxicity and foetotoxicity were < 3 mg/kg bw/d.

It was concluded by the DS that based on the results of the multi-generation study and the developmental toxicity studies **classification for reproductive toxicity is not proposed**.

Comments received during public consultation

No comments were received during the public consultation for this endpoint.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility:

There were no epidemiological data to evaluate effects on sexual function and fertility.No specific information regarding effects on or via lactation was provided. No effects were observed in the 3-generation study; therefore no classification for adverse effects on sexual function and fertility is warranted.

Adverse effects on development:

There were no appropriate epidemiological studies available on developmental effects in humans. The developmental toxicity studies revealed only minimal effects on foetal ossification in rats and an increased incidence of a skeletal variation in rats (25^{th} pre-sacral vertebra) and rabbits (27^{th} pre-sacral vertebra) at maternal toxic dose levels. No evidence of teratogenicity was observed in either species. Hence, no classification for adverse effects on development is warranted.

RAC supports the conclusion of the DS that based on the results of reproductive toxicity studies in rats and rabbits, the substance does not meet the criteria for classification for reproductive toxicity.

4.11 Other effects

4.11.1 Non-human information

4.11.1.1 Neurotoxicity

In a delayed neurotoxicity study, oral administration of a single dose of tefluthrin at 3605 mg/kg, followed by a repeat dose after 21 days, to the domestic hen, did not produce any clinical signs of acute delayed neurotoxicity. However, in 5 out of 13 hens, histopathological examination showed minimal axonal degeneration at different levels of the spinal cord, without any damage to the sciatic or tibial nerves. This result was not typical of that normally occurring as a result of acute delayed neurotoxicity. However, since the incidence of spinal cords with minimal axonal degeneration was greater than that usually encountered in untreated hens, the possibility of a mild neurotoxic effect exerted by tefluthrin cannot be ruled out.

In a rat acute neurotoxicity study, 10 mg/kg showed clinical signs of toxicity and a decreased landing foot splay 6-7 hours post dosing. Although most of the changes showed rapid recovery, increased breathing rate was noted for some males throughout the rest of the study. Fore-limb grip strength was increased in both sexes on day 15 only.

At 5 mg/kg few effects were observed and these showed full recovery by the end of the study. The observations at this dose level are considered to be of no toxicological significance.

The no-observed-adverse-effect-level for this study was 5 mg/kg.

In a sub-chronic neurotoxicity study, 350 ppm in the diet for 90 days resulted in clinical signs of toxicity and increased landing foot splay in female rats. There were no neuropathological findings with the exception of a change in brain pathology in a single female rat at this highest dose level. Male rats were much less affected at this dose level with only some clinical signs in a few animals. Transient clinical signs in a small number of animals and decreased group mean food consumption in week 1 were the only findings noted for females fed 150 ppm; these were considered not to be toxicologically significant.

The no-observed effect level for toxicologically significant findings is considered to be 150 ppm.

In a research study to evaluate the methodology for neurotoxicity, 2,5-hexanedione and tefluthrin showed no consistent effects on motor or sensory nerve electrophysiology or function, clinical or histopathological signs of neurotoxicity were observed in male or female rats treated chronically with near lethal doses of tefluthrin for eight weeks. Animals surviving this dosing regimen were indistinguishable from control animals in all respects.

Table 73: Summary table of relevant neurotoxicity studies

Method	Results	Remarks	Reference
Acute Delayed Neurotoxicity, Domestic Hen	Single dose 3605 mg/kg bw: no delayed neurotoxicity	Clinical signs of acute toxicity; minimal axonal degeneration of spinal cord without damage of sciatic or tibial nerve	Roberts et al. (1986, TOX2004-2691)
Acute Neurotoxicity, rat	NOAEL: 2.5 mg/kg bw	Decreased landing foot splay, increased breathing rate	Pinto P (2002, TOX2004-2692),
90-d Neurotoxicity, rat	NOAEL: 150 ppm (11.6 mg/kg bw/d)	Increased landing foot splay, clinical signs	Pinto P (2002, TOX2004-2693)

Report: Roberts N, Fairley C, Gopinath C *et al* (1986, TOX2004-2691), Acute Delayed Neurotoxicity Study With PP993 in the Domestic Hen. Huntingdon Research Centre Ltd., Huntingdon, UK., Syngenta Unpublished Report No. CTL/C/1805, study dates 16 December 1985 to 26 June 1986. (Syngenta File No. ICI993/0163)

Guidelines: FIFRA § 81-7

Deviations: There were 10 hens per group. No biochemical determinations were made. Hens were between 13 and 14 months of age at the start of the study. They were acclimatised for only two days prior to neurotoxicity assessment. Hens were given a single oral dose followed by a repeat dose after 21 days if they were showing a negative clinical neurotoxic response. It is stated in the methodology only that hens were examined daily, but it can be assumed that several observations were made per day. There was no analysis for NTE activity. Any hen which died within 4 days of dosing was not given a gross necropsy.

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

GLP: This study was performed prior to the GLP certification of Laboratories but was conducted according to the principles and practices of GLP. A Quality Assurance Statement is included in the report.

Acceptability: The study is considered to be acceptable.

Materials and methods:

Tefluthrin (PP993) technical; batch No. P22; analysed purity 94.4 % w/w tefluthrin.

The acute hen toxicity of tefluthrin was evaluated in groups of 10 adult domestic hens given a single oral dose of 0 (control), 2048, 2560, 3200, 4000 or 5000 mg/kg tefluthrin at a dose volume of 12.5 mL/kg in corn oil. The hens were observed for 14 days after dosing and body weights were recorded at intervals.

The acute delayed neurotoxicity test consisted of six groups of 10 adult domestic hens. The groups received a single oral dose of corn oil only (negative control) or 500 mg/kg tri-ortho-cresyl phosphate (TOCP) (positive control), the remaining four groups all received 3605 mg/kg tefluthrin. Positive controls were dosed at 2.5 mL/kg, test and negative control birds were dosed at 10 mL/kg and corn oil was used as the vehicle in all cases. All negative control and all tefluthrin-treated birds were re-dosed at the same dose levels on day 21.

Bird health, abnormal behaviour, clinical signs of toxicity, mortalities and assessment of ataxia were checked daily for 21 days post-dose. Body weights and food consumption were recorded weekly. Any bird which died within 4 days of dosing was not examined *post mortem* but all other birds which died or were sacrificed, either during the study or at scheduled termination, were given a macroscopic examination *post mortem***.** Selected tissues from 8 negative controls, 10 positive controls and 13 hens dosed with tefluthrin were examined histopathologically for treatment-related changes to the brain, spinal cord and peripheral nerve.

Findings:

Acute toxicity study: There were no mortalities in controls or in hens dosed at 2048 mg/kg tefluthrin, but there were a number of hens found dead or killed within four days of dosing in all the other groups (see table below).

Table 74: Acute Toxicity of Tefluthrin in the Hen (Cumulative Mortality)

Dose Level (mg/kg)	**Time after Dosing** (Days)	**Number of Deaths**
0 (control)	14 (total)	0/10
2048	14 (total)	0/10
2560	1	3/10
	2	5/10
	14 (total)	5/10
3200	1	1/10
	2	2/10
	3	4/10
	14 (total)	4/10
4000	1	4/10
	2	6/10
	4	7/10
	14 (total)	7/10
5000	1	3/10
	2	4/10

Dose Level (mg/kg)	**Time after Dosing** (Days)	**Number of Deaths**
	4	5/10
	14 (total)	5/10

Clinical signs observed in hens dosed with tefluthrin included varying degrees of unsteadiness, stumbling, trembling, lying or sitting on the pen floor and twitching. Signs first became apparent within 2 to 4 hours following dosing and surviving birds had recovered by the end of day 4. There were no abnormalities observed in the controls. During days 0 to 7 decreases in body weight were observed in all groups and these were more marked in the tefluthrin-treated hens but thereafter all groups showed increases in body weight.

The acute oral median lethal dose was calculated to be 3605 mg/kg.

Neurotoxicity Assessment: There were mortalities in each group as shown in the table below.

Table 75: Neurotoxicity of Tefluthrin in the Hen (Cumulative Mortality)

Dose Level (mg/kg)	**Time After Dosing (days)**	**Number of Deaths**
0 (Control)	6	1/10
	18	2/10
	21 (total)	2/10
	42 (total)	2/10
500 (TOCP)	15	2/10
	19	4/10
	21 (total)	4/10
3605 (group 3)	1	4/10
	2	5/10
	3	7/10
	21 (total)	7/10
	24	8/10
	42 (total)	8/10
3605 (group 4)	1	3/10
	3	4/10
	21(total)	4/10
	22	6/10
	42 (total)	6/10
3605 (group 5)	1	2/10
	9	3/10
	16	4/10
	21 (total)	4/10
	22	5/10
	24	6/10
	42 (total)	6/10
3605 (group 6)	1	2/10
	2	4/10
	3	5/10
	21 (total)	5/10
	25	6/10
	27	7/10
	42 (total)	7/10

Day 21 (total) is total number of mortalities after first dose
Day 42 (total) is total number of mortalities following first and second doses. The second dose was administered on day 22.

Hens dosed with tefluthrin showed clinical signs (see table below) which included subdued behaviour, unsteadiness, stumbling, trembling, wing-flapping, inability to stand, lying on one side unable to walk, eyes closed with head and neck rotating. These signs were seen within approximately one hour of dosing and were most frequent and severe on days 1 and 2. The majority of survivors had recovered by day 5. Following the second dose (see table after next), similar clinical signs were seen. All of the surviving hens, except one, had recovered by the end of day 26.

No treatment-related abnormalities were seen in the negative control hens and the positive control hens showed no immediate signs of toxicity following dosing.

Table 76: Summary of the Incidence of Clinical Signs (Selected Parameters) Following the First Dose

Observation	Number of Hens Showing Each Clinical Sign		
	Corn Oil (negative control)	500 mg/kg TOCP (positive control)	3605 mg/kg Tefluthrin
Subdued Behaviour	0/10	0/10	39/40
Unsteadiness	0/10	0/10	34/40
Stumbling	0/10	0/10	5to15/40
Trembling	0/10	0/10	23to33/40
Wing-flapping	0/10	0/10	6to10/40
Inability To Stand	0/10	0/10	14to18/40
Lying On Side Unable To Walk	0/10	0/10	5/40
Eyes Closed With Head And Neck Rotating	0/10	0/10	6-11/40

Table 77: Summary of the Incidence of Clinical Signs (Selected Parameters) Following the Second Dose

Observation	Number of Hens Showing Each Clinical Sign		
	Corn Oil (negative control)	500 mg/kg TOCP (positive control)	3605 mg/kg Tefluthrin
Subdued Behaviour	0/8	-	20/20
Unsteadiness	0/8	-	16/20
Stumbling	0/8	-	2/20
Trembling	0/8	-	11/20
Wing-flapping	0/8	-	-
Inability To Stand	0/8	-	3/20
Lying On Side Unable To Walk/Stand	0/8	-	5/20
Eyes Closed With Head And Neck Rotating	0/8	-	-

- TOCP birds not dosed a second time

No signs of delayed neurotoxicity were observed in any negative controls or hens given tefluthrin either after the first or second dose. Nine out of ten hens dosed with TOCP at 500 mg/kg developed signs of ataxia. It was not possible to test all birds dosed with tefluthrin for ataxia for several days after dosing as the birds were still exhibiting clinical signs of acute toxicity. After recovery none of these birds showed signs which could be related to delayed neurotoxicity.

Following the first dose all groups dosed with tefluthrin showed mean body weight decreases. The positive control group also showed a mean body weight decrease which was more marked than the tefluthrin-treated groups. The negative control group showed a small mean body weight increase.

Following the second dose, tefluthrin-treated and the negative control groups showed mean body weight increases (see table below).

Table 78: Group Mean Body weight Changes (g/bird)

Group	Treatment	Days 0 to 21	Days 21 to 42
1	Corn Oil (Negative Control)	+ 19	+ 49
2	TOCP 500 mg/kg (Positive Control)	-328	-
3	Tefluthrin 3605 mg/kg	-105	+215
4	Tefluthrin 3605 mg/kg	-134	+104
5	Tefluthrin 3605 mg/kg	- 54	+ 68
6	Tefluthrin 3605 mg/kg	- 70	+196

Mean food consumption was lower in the test groups and positive control group over days 1 to 21 and in the test groups over days 22 to 42 in comparison with the negative control (see table below).

Table 79: Group Mean Food Consumption (g/bird/day)

Group	Treatment	Days 1 to 21	Days 22 to 42
1	Corn Oil (Negative Control)	144	216a
2	TOCP 500 mg/kg (Positive Control)	82	-
3	Tefluthrin 3605 mg/kg	96	118
4	Tefluthrin 3605 mg/kg	88	105
5	Tefluthrin 3605 mg/kg	86	109
6	Tefluthrin 3605 mg/kg	112	113

a excluding days 36 to 42

Gross pathology, histopathology: No macroscopic abnormalities were seen which were considered to be treatment-related.

Any histopathological changes seen were graded on a 1 (no degeneration) to 5 (widespread degeneration) scale. In the negative controls at least two levels of spinal cord were recorded as grade 2, thus indicating the presence of a few degenerating axons as normal background. There were no axonal changes in peripheral nerve or brain. All except one negative control hen showed grade 3 or worse changes in at least one level of spinal cord. The majority of these birds also showed grade 3 or 4 changes in all levels of peripheral nerve. Five hens showed grade 2 changes in the brain. All of the tefluthrin-treated hens showed grade 2 changes in at least two levels of spinal cord and five of these also showed grade 3 changes in at least one level of spinal cord. One hen showed grade 2 changes in one level of peripheral nerve and two showed grade 2 changes in the brain. The grade 3 changes observed in the spinal cord indicate axonal degeneration probably related to treatment with tefluthrin However, the acute delayed neurotoxic effect was not clear cut, since no significant axonal degeneration was seen in peripheral nerve and the distribution of the lesions in spinal cord was not typical in some of the affected birds (namely, not confined to the upper cervical region in all the affected birds).

Conclusion: Under the conditions of this test, oral administration of a single dose of tefluthrin at 3605 mg/kg, followed by a repeat dose after 21 days, to the domestic hen, did not produce any clinical signs of acute delayed neurotoxicity. However, in 5 out of 13 hens, histopathological examination showed minimal axonal degeneration at different levels of the spinal cord, without any damage to the sciatic or tibial nerves. This result was not typical of that occurring in acute delayed neurotoxicity. However, since the incidence of spinal cords with minimal axonal degeneration was

greater than that usually encountered in untreated hens, the possibility of a mild neurotoxic effect exerted by tefluthrin cannot be ruled out.

Report:	Pinto P (2002, TOX2004-2692), Tefluthrin: Acute Neurotoxicity Study In Rats. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/AR6767/REGULATORY/REPORT, study dates 19 June 2000 (study initiated), 4 July 2000 to 14 December 2000 (experimental phase). (Syngenta File No. ICI993/0626)
Guidelines:	96/54/EC B.37 (1996) ≅ OECD 424 (1997) ≅ OPPTS 870.6200 (1998)
Deviations:	No justification reported for the choice of corn oil as the vehicle. All rats were checked at least once a day for general clinical condition but it was not reported that twice daily checks for mortality were done. Detailed clinical observations and function tests were carried out - prior to the first exposure, within 8 hours of dosing at estimated time of peak effect and then at day 8 and 15 after dosing. The report does not mention homogeneity of the dose preparations. The deviations are considered not to compromise the scientific validity of the study.
GLP:	Yes (laboratory certified by the UK authority).

Acceptability: The study is considered to be acceptable

Materials and methods:

Tefluthrin; batch P25 (R151993:TSC 0295/05989); purity 92.4 % w/w.

Groups of ten male and ten female Alpk:AP_fSD (Wistar-derived) rats were administered single oral doses of 0 (control), 2.5, 5 or 10 mg tefluthrin/kg body weight and were observed for the following 14 days.

All animals were observed prior to the study start and daily throughout the study for any changes in clinical condition. In addition, a function observation battery (FOB), including quantitative assessments of landing foot splay, sensory perception and muscle weakness, was performed in week –1, and on days 1, 8 and 15. Locomotor activity was also monitored in week –1, and on days 1, 8 and 15. Body weights and food consumption were measured weekly throughout the study. At the end of the scheduled period, 5 rats/sex/group were perfused *in situ*, and the brains were removed and weighed. Selected nervous system tissues were removed, processed and examined microscopically.

Findings:

General observations: Samples of each dose preparation were analysed prior to the start of dosing to verify the achieved concentrations of tefluthrin in the vehicle (corn oil). The mean achieved concentrations were within 10% of the nominal concentration and were considered to be satisfactory. The chemical stability of tefluthrin in corn oil was determined for the low (2.5 mg/kg) and high (10 mg/kg) dose levels at room temperature over a period of up to 10 days and found to be satisfactory. This covered the period of use in the present study.

All rats survived for the duration of the study. The following clinical signs observed during daily observations are considered not to be related to treatment with tefluthrin based on the lack of a dose-response, findings in control animals and/or type of clinical sign: annular constriction of the tail, diarrhoea, dry sores, torn ear, scabs, signs of diarrhoea, reduced splay reflex and tail damage. The treatment-related findings are described in the clinical observation results of the FOB section.

There were no effects of treatment on body weights or food consumption of either sex throughout the study.

Functional observation battery (FOB):

Clinical observations: All of the animals were physically normal and displayed normal behaviour prior to dosing (day -7). In the 10 mg/kg group, six to seven hours post-dosing on day 1, 4/10 males and 2/10 females had slight ataxia, tremors were recorded in 2/10 male rats, increased breathing rate was noted in 6/10 males and in 9/10 females, and one female had upward curvature of the spine. On day 8, the only clinical abnormalities noted in this group were increased breathing rate (2/10 males and 2/10 females) and irregular breathing (2/10 males). On day 15, there were no treatment-related findings in the females and 2/10 males had increased breathing rate. In the 5 mg/kg group, at six to seven hours post-dosing on day 1, the only clinical observation noted was increased breathing rate in 4/10 males and 7/10 females. One male rat had an irregular breathing rate on day 8. There were no treatment-related findings in either sex on day 15 post-dosing. There were no treatment-related clinical abnormalities in either sex in the 2.5 mg/kg group during the study (see table below).

Table 80: Intergroup comparison of FOB treatment-related clinical observations – selected parameters -number of animals affected (day)

	Dose level of tefluthrin (mg/kg)							
	Males				Females			
Observation	**0**	**2.5**	**5**	**10**	**0**	**2.5**	**5**	**10**
Slight ataxia				4 (1)				2 (1)
Tremors				2 (1)				
Increased breathing rate			4 (1)	6(1), 2 (8)			7 (1)	9 (1), 2 (8)
Upward curvature of the spine								1 (1)
Irregular breathing			1 (8)	2 (8), 2 (15)				

Landing foot splay: Six to seven hours post dosing, landing foot splay was significantly smaller than the controls for both sexes in the 10 mg/kg group and for males in the 5 mg/kg group. There were no differences from control in landing foot splay measured on days 8 and 15 of the study in either sex in any dose group (see table below).

Table 81: Intergroup comparison of landing foot splay (mm) (selected timepoints)

	Dose level of tefluthrin (mg/kg)							
	Males				Females			
days	**0**	**2.5**	**5**	**10**	**0**	**2.5**	**5**	**10**
-7	67.8	62.7	60.4	56.9	49.8	50.6	50.4	48.0
1	61.4	52.0	44.6**	46.6*	46.4	44.3	39.4	35.7*
8	70.3	72.0	66.1	67.2	49.6	45.4	53.2	58.2
15	66.5	67.6	64.1	68.6	50.5	47.7	57.3	60.2

* Statistically significant difference from control group mean, $p < 0.05$ (Student's t-test, 2-sided)
** Statistically significant difference from control group mean, $p < 0.01$ (Student's t-test, 2-sided)

Time to tail flick: There were no effects of treatment on time to tail flick in either sex at any dose level.

Fore-limb and hind-limb grip strength measurements: On days 1 and 8, there were no effects of treatment on fore-limb grip strength in either sex at any dose level. Fore-limb grip strength was statistically significantly higher than controls in both sexes in the 10 mg/kg group on day 15 (see table below).

There were no effects of treatment on fore-limb grip strength on day 15 for the 2.5 and 5 mg/kg groups. There were no effects of treatment on hind-limb grip strength in either sex at any dose level.

Table 82: Intergroup comparison of fore-limb grip strength (g) (selected timepoints)

	Dose level of tefluthrin (mg/kg)							
	Males				Females			
days	**0**	**2.5**	**5**	**10**	**0**	**2.5**	**5**	**10**
-7	370	368	343	335	358	388	338	365
15	800	820	943	998*	653	663	755	805*

* Statistically significant difference from control group mean, $p < 0.05$ (Student's t-test, 2-sided)

Motor activity measurements: There were no effects of treatment on motor activity in either sex.

Brain weights, histopathology: There were no treatment-related effects on brain weight in either sex. Brain weight adjusted for body weight was statistically significantly higher for males in the 5 mg/kg group, but absolute brain weights were similar to controls. The statistical significance after adjusting for body weight is due to a slightly lower body weight for this group, but it does not reflect an effect of treatment on brain weight. There were no treatment-related microscopic findings in the selected nervous system tissues after examination of the control and 10 mg/kg groups.

Conclusion:

Single oral administration of 10 mg/kg tefluthrin to male and female rats resulted in clear treatment-related clinical signs and decreased landing foot splay 6-7 hours post dosing. Although most of the changes showed rapid recovery, increased breathing rate was noted for some males throughout the rest of the study. Fore-limb grip strength was increased in both sexes on day 15 only.

At 5 mg/kg few effects were observed and these showed full recovery by the end of the study. The observations at this dose level are considered to be of no toxicological significance.

The no-observed-adverse-effect-level for this study was 5 mg/kg.

Report: Pinto P (2002, TOX2004-2693), Tefluthrin: Subchronic Neurotoxicity Study In Rats. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/PR1145/REGULATORY/REPORT, study dates 19 April 2000 (study initiated), 26 April 2000 to 28 February 2001 (experimental phase). (Syngenta File No. ICI993/0627)

Guidelines: 96/54/EC B.38 (1996) ≅ OECD 424 (1997) ≅ OPPTS 870.6200 (1998)

Deviations: Animals were observed daily for general health condition but the report does not state that they were observed twice daily for mortality/morbidity. No justification reported for the choice of corn oil as the vehicle. The

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

GLP: Yes (laboratory certified by the UK authority).

Acceptability: The study is considered to be acceptable

Materials and methods:

Tefluthrin; batch P25 (R151993:TSC 0295/05989); purity 92.4 % w/w.

Groups of twelve male and twelve female Alpk:AP$_f$SD (Wistar-derived) rats were fed diets containing 0 (control), 50, 150 or 350 ppm tefluthrin for at least 90 consecutive days.

All animals were observed prior to the study start and daily throughout the study for any changes in clinical condition. In addition, detailed clinical observations, including quantitative assessments of landing foot splay, sensory perception and muscle weakness, were performed in weeks –1, 2, 5, 9 and 14. Locomotor activity was also monitored in weeks –1, 2, 5, 9 and 14. Body weights and food consumption were measured weekly throughout the study. Eyes were examined prior to dosing and during week 13 of the study. At the end of the scheduled period, 5 rats/sex/group were killed by *in situ* perfusion fixation, and brains were removed and weighed. Selected nervous system tissues were removed, processed and examined microscopically.

Findings:

General observations: Samples from all dietary levels (including controls) were taken prior to the start of the study and once during the study and analysed quantitatively for tefluthrin. The mean achieved concentrations of tefluthrin in each dietary preparation were found to be satisfactory. Prior to feeding of the experimental diets, the homogeneity of tefluthrin in the diet was determined by analysing samples from the 50 and 350 ppm dose levels and found to be satisfactory with percentage deviations within 11 % of the overall mean for both these dose levels. The chemical stability of tefluthrin in diet (when stored at room temperature and at approximately –20 ^{o}C) was determined at the 50 and 350 ppm dose levels over a period of up to 36 days. Stability at room temperature was shown to be satisfactory for 7 days and stability at –20 ^{o}C was shown to be satisfactory for at least 36 days. These times covered the period of storage in this study.

The mean dose received (based on nominal dietary levels of tefluthrin) was calculated in terms of mg tefluthrin/kg body weight/day (see table below).

Table 83: Overall mean dose received (mg/kg bw/day)

Sex	Dietary concentration of tefluthrin (ppm)		
	50	150	350
Males	3.8	11.6	26.6
Females	4.4	13.4	31.2

All animals survived to scheduled termination. From week 4 of the study, ataxia, upward curvature of the spine, increased breathing rate and increased response to sound were recorded for 5, 6, 4 and 1 female rat respectively, in the 350 ppm group. One male fed 350 ppm had irregular breathing from week 6 to 8. There were no other treatment-related clinical findings in male rats fed tefluthrin in the diet. A single female in the 150 ppm group was noted to have an increased breathing rate and

upward curvature of the spine from week 10 of the study. There were no treatment-related clinical findings in rats fed 50 ppm tefluthrin in the diet.

All animals had normal eyes prior to the start of the study. All animals in the control and 350 ppm groups had normal eyes in week 13.

Body weights for female rats in the 350 ppm group were significantly lower than controls throughout the study, with a maximum effect of approximately 11 %. There were no effects in females at the lower dose levels. Body weights for males were slightly lower than concurrent controls in all dose groups. However, in the absence of a dose-response and lack of statistical significance at 350 ppm, the differences in males are considered to be incidental to treatment with tefluthrin (see table below).

Table 84: Intergroup comparison of body weights (g) - (selected timepoints; adjusted mean values shown after week 1)

	Dietary Concentration of tefluthrin (ppm)							
	Males				Females			
week	0	50	150	350	0	50	150	350
1	224.0	219.9	219.8	217.8	162.2	163.3	160.5	164.9
5	373.4	360.3	352.7*	361.0	225.1	220.1	220.5	199.9**
10	476.5	450.8	442.0*	452.8	260.8	255.9	258.6	242.1**
14	525.7	493.2*	489.8*	499.2	278.9	274.2	277.8	255.2**

* Statistically significant difference from control group mean, $p < 0.05$ (Student's t-test, 2-sided)
** Statistically significant difference from control group mean, $p < 0.01$ (Student's t-test, 2-sided)

Food consumption for female rats fed 350 ppm was significantly reduced for the first 5 weeks of the study. Food consumption for female rats fed 150 ppm was significantly reduced for the first week only of the study. Food consumption for females fed 50 ppm was similar to controls throughout the study. Food utilisation was reduced for female rats fed 350 ppm for weeks 1-4. There were no treatment-related effects on food utilisation in the female rats exposed to tefluthrin at 150 or 50 ppm in the diet.

Food consumption was slightly lower than controls for the first 7 weeks of the study for male rats in all dose groups compared with controls and the differences achieved statistical significance on occasion. There were isolated statistical significant differences in food utilisation in males fed 5 and 150 ppm. These sporadic differences in food consumption and utilisation in males showed no dose-response and are considered to be incidental (see next two tables).

Table 85: Intergroup comparison of food consumption (g/rat/day) - (selected timepoints)

	Dietary Concentration of tefluthrin (ppm)							
	Males				Females			
week	0	50	150	350	0	50	150	350
1	29.5	28.1*	28.7	27.0**	21.7	20.2	18.4*	18.1*
3	30.7	28.7	29.3	28.3*	21.4	20.0	20.5	17.6*
5	31.0	28.9	29.5	28.3	21.4	20.7	20.4	19.5**
7	32.0	29.5*	29.0**	29.2**	21.6	21.7	21.4	20.4
10	30.9	29.3	28.7*	29.2	20.8	19.8*	20.2	20.0
13	31.9	29.8	30.2	30.3	21.7	21.3	21.7	21.4

* Statistically significant difference from control group mean, $p < 0.05$ (Student's t-test, 2-sided)
** Statistically significant difference from control group mean, $p < 0.01$ (Student's t-test, 2-sided)

Table 86: Intergroup comparison of food utilisation (g growth/100g food)

	Dietary Concentration of tefluthrin (ppm)							
	Males				Females			
Weeks	**0**	**50**	**150**	**350**	**0**	**50**	**150**	**350**
1-4	18.03	17.43	16.41*	17.89	10.46	10.24	10.42	7.58**
5-8	9.59	9.67	8.79	8.89	4.91	5.64	4.84	5.14
9-13	6.42	5.20*	6.43	6.26	3.53	2.90	3.88	3.74
1-13	10.93	10.31	10.22	10.55	6.27	5.99	6.10	5.27**

* Statistically significant difference from control group mean, $p < 0.05$ (Student's t-test, 2-sided)
** Statistically significant difference from control group mean, $p < 0.01$ (Student's t-test, 2-sided)

Functional observation battery (FOB):

Clinical observations: All animals were physically normal and displayed normal behaviour prior to the start of the study. For male rats fed 350 ppm, treatment-related findings included increased activity, irregular breathing, increased breathing rate, reduced splay reflex and paw flicking. Increased breathing rate had the highest incidence, which reduced as the study progressed, the other observations were noted for 1 or 2 animals only.

Treatment-related findings (increased activity, ataxia, increased breathing rate, reduced splay reflex, upward curvature of the spine, piloerection, increased response to sound, abnormal gait and paw flicking) were observed in female rats fed 350 ppm. There was an increase in the incidence and severity as the study progressed for the ataxia, increased activity, upward curvature of the spine and reduced splay reflex.

There were no clinical observations considered to be treatment-related for males fed 150 or 50 ppm.

Two females fed 150 ppm tefluthrin had increased breathing rate in week 5, another female in week 14; and one female had upward curvature of the spine from week 9. One female fed 50 ppm had increased breathing rate at week 2 only. As the findings were transient in nature, despite continued exposure to tefluthrin, they are considered not to be toxicologically significant (see table below).

Table 87: Intergroup comparison of FOB clinical observations – selected parameters - number of animals affected (week)

	Dietary Concentration of tefluthrin (ppm)							
	Males				Females			
Observation	**0**	**50**	**150**	**350**	**0**	**50**	**150**	**350**
Increased activity - s				1 (2), 2 (5)				1 (2), 5 (5), 8 (9), 10 (14)
Irregular breathing				1 (2), 1 (5)				
Increased breathing rate				6 (2), 4 (5), 3 (9), 1 (14)		1 (2)	2 (5), 1 (14)	7 (2), 7 (5), 6 (9), 5 (14)
Reduced splay reflex - s		1 (2)		2 (14)	1(9), 2 (14)	1(5), 1 (14)	1 (5), 2(9), 1(14)	2 (5), 2 (9), 7 (14)
- m								3 (5), 3 (9), 4 (14)
Paw flicking				1(5)				1 (2)
Ataxia - s								5 (5), 4 (9), 3 (14)
- m								1 (9)

	Dietary Concentration of tefluthrin (ppm)							
	Males				Females			
Upward curvature of spine - s							1 (9), 1 (14)	1 (2), 6 (5), 8 (9), 9 (14)
-m								1 (14)
Piloerection								1 (9), 1 (14)
Increased response to sound								1 (2), 1 (5), 1 (9)
Abnormal gait								1 (2)

s = slight , m = moderate

Landing foot splay: There were no effects of treatment on landing foot splay in male rats at any dose level and in females fed 150 and 50 ppm during the study.

Landing foot splay was significantly increased in weeks 5, 9 and 14 for female rats in the 350 ppm group (see table below)

Table 88: Intergroup comparison of landing foot splay (mm)

	Dietary Concentration of tefluthrin (ppm)							
	Males				Females			
week	**0**	**50**	**150**	**350**	**0**	**50**	**150**	**350**
-1	63.9	64.3	55.2	60.4	57.2	52.8	53.8	56.4
2	86.3	84.2	83.3	76.9	65.1	67.5	67.1	75.6
5	80.7	75.5	79.1	75.8	59.4	61.6	68.0	83.9**
9	71.0	81.0	72.9	77.0	59.5	61.1	63.3	98.4**
14	81.8	74.8	75.8	73.0	65.0	61.1	66.5	85.8**

* Statistically significant difference from control group mean, $p < 0.05$ (Student's t-test, 2-sided)
** Statistically significant difference from control group mean, $p < 0.01$ (Student's t-test, 2-sided)

Time-to-tail flick: There were no effects of treatment on time-to-tail flick in either sex during the study. There was an isolated statistically significant difference in males fed 150 ppm in week 14, but in the absence of an effect at 350 ppm, this is considered to be unrelated to treatment.

Hindlimb grip strength measurements: There were no effects of treatment on hindlimb grip strength of male or female rats during the study.

In week 14, hindlimb grip strength of male rats in all groups was lower than the control group mean. However, both the group means and individual values were within the historical control data and although group means for 50 and 350 ppm achieved statistical significance, there was no dose-response and the differences are considered to be incidental to treatment with tefluthrin.

Forelimb grip strength measurements: There were no effects of treatment on forelimb grip strength in either sex at any time point. Forelimb grip strength was statistically significantly lower for male rats and higher for female rats fed 350 ppm in week 14. However, for both sexes the range of individual values were similar in control and 350 ppm groups with only one value outside concurrent control range. The mean differences were small and conflicting between the sexes and are, therefore, considered to be incidental to treatment with tefluthrin.

Motor activity measurements: There were no effects of treatment on motor activity in either sex at any time point at any dose level. Any statistical differences are sporadic, show no consistent pattern over the duration of the study and are considered to be unrelated to treatment.

Brain weights, histopathology: There were no effects on brain weights in either sex at any dose level.

Focal cell loss in the granular layer of the cerebellum was observed in a single female rat fed 350 ppm. This is an unusual lesion, which is rarely seen in control animals. All other microscopic findings in the selected nervous system tissues examined in this group were considered to be spontaneous in origin and unrelated to treatment. No treatment-related lesions in the nervous system tissues examined were seen for animals fed diets containing 50 or 150 ppm tefluthrin.

Conclusion:

Oral administration of 350 ppm (26.6 mg/kg bw/d) tefluthrin in diet for at least 90 consecutive days resulted in clinical signs, food and body weight effects and increased landing foot splay in female rats. There were no neuropathological findings with the exception of a change in brain pathology in a single female rat at this highest dose level. Male rats were much less affected at this dose level with only some clinical signs in a few animals.

Transient clinical signs in a small number of animals and decreased group mean food consumption in week 1 were the only findings noted for females fed 150 ppm; these were considered not to be toxicologically significant.

The no-observed effect level for toxicologically significant findings is considered to be 150 ppm (equivalent to 11.6 mg/kg bw/d).

4.11.1.2 Immunotoxicity

No studies submitted by the applicant.

4.11.1.3 Specific investigations: other studies

In a research study to evaluate the methodology for neurotoxicity, 2,5-hexanedione and tefluthrin showed no consistent effects on motor or sensory nerve electrophysiology or function, clinical or histopathological signs of neurotoxicity were observed in male or female rats treated chronically with near lethal doses of tefluthrin for eight weeks. Animals surviving this dosing regimen were indistinguishable from control animals in all respects.

Report:	Allen S (1988, TOX2004-2694), An Investigation into the Neurotoxicity of 2,5-Hexanedione and Tefluthrin. Central Toxicology Laboratory, UK., Syngenta Unpublished Report No. CTL/R/905 (revised), study dates 1 September 1986 to 24 October 1986 (in-life phase). (Syngenta File No. ICI933/0004)
Guidelines:	There are no suitable guidelines for research studies of this type
Deviations:	This was an investigative study with no applicable guidelines
GLP:	This report was based on carefully conducted research studies which, however, are not fully compliant with GLP standards. The report fully and accurately reflects the procedures used and the raw data generated in the above study.

Acceptability: The study is considered to be supplementary.

Materials and methods:

Tefluthrin technical; batch No. not reported; analysed purity, not reported.

Groups of 10 male and 10 female Alpk rats received oral doses of vehicle alone (corn oil), 2,5-HD (300 mg/kg) which acted as a positive control, or tefluthrin (5 mg/kg or 15 mg/kg) for 5 days per week for 8 weeks. The animals were examined and weighed regularly and neurophysiological assessments performed at weekly intervals throughout the study. On day 54 two rats from each group were anaesthetised and killed by whole body perfusion. Remaining rats were killed by over-exposure to halothane. Selected tissues were removed from each group of rats for histopathological investigation.

Findings:

General observations: On day 2 all the animals from the 15 mg/kg tefluthrin group and all the females and one male from the 5 mg/kg group were found dead. At 5 mg/kg one female was found dead on day 5 and another found dead on day 51. Toxicity at these dose levels was unexpected as in a previous study (unpublished data) no toxic signs were observed after a single dose of 15 mg/kg tefluthrin. However, the dose volume was previously 10 times greater than in this study. This, combined with the fact that the animals had been anaesthetised for tail nerve conduction velocity measurements shortly before dosing, is thought to have resulted in the increased toxicity. Six replacement females were assigned to the 5 mg/kg group on day 2.

The only clinical signs of toxicity observed in the surviving tefluthrin treated animals were in females. These were of relatively little significance (staining of the coat and/or nose) and generally occurred early in the study. No clinical signs had previously been seen in either of the two females which died on days 5 and 51.

Up until about week 3 of the study, animals treated with 5 mg/kg tefluthrin failed to gain weight at the same rate as the control animals. From week 3 onwards, body weight gain was similar in all groups.

During the first to second week of the study, transient episodes of muscle weakness were detected in tefluthrin treated animals as indicated by the pull-up test. At the end of week 1 in females and week 2 in males statistically significant increases in time taken to complete the test were recorded. From week 3 until the end of the study the values were similar to control.

There was no evidence of an effect of treatment with tefluthrin on motor nerve conduction velocity measurements (MNCV) or sensory nerve conduction velocity measurements (SNCV). Amplitude of the sensory nerve action potentials (SNAP) was reduced in week 2 in both sexes and in week 3 in males and week 6 in females, suggestive of a small, transient insult to the peripheral sensory nerves. However, as no clinical signs of toxicity were seen and the animals showed complete recovery despite continued exposure to 5 mg/kg tefluthrin, this finding was considered to have little biological significance.

The sensitivity of the methods used was confirmed from the findings in animals dosed with 2,5-HD, which induced a peripheral neuropathy which was first detected in changes in tail nerve conduction velocity. Gait abnormalities became apparent after 5 ½ weeks and muscle weakness, as indicated by the pull-up test was detected after 5-7 weeks of treatment. At termination, clear evidence of a neuropathy classified as a central-peripheral distal axonopathy was found in all rats exposed to 2,5-HD.

Gross pathology, histopathology: Due to mortalities, only four male and three female rats were available for neuropathological assessment. In the spinal cord of the three 5 mg/kg tefluthrin treated females the size of the vacuoles in the white matter appeared to be larger than in the spinal cord of the control of either sex or of the tefluthrin treated males. However, no obvious axonal degenerative changes were seen.

Conclusion:

No consistent effects on motor or sensory nerve electrophysiology or function, clinical or histopathological signs of neurotoxicity were observed in male or female rats treated chronically with near lethal doses of tefluthrin for eight weeks. Animals surviving this dosing regimen were indistinguishable from control animals in all respects.

4.11.1.4 Human information

No studies submitted by the applicant.

Medical surveillance on manufacturing site personnel

There are no specific health surveillance programmes currently being undertaken for tefluthrin workers. Tefluthrin is only produced in plants where workers are trained in the normal safety measures (helmet, gloves, mask, safety glasses and boots), which are monitored and enforced by the plant management.

Syngenta maintains a database of "adverse reactions" of incidents involving chemical exposure of workers since 1983. Searching the database has revealed three reports of adverse reactions with tefluthrin formulations (2 FORCE® 3G, 1 FORCE® 20 CS). There are 21 reports of paraesthesia (16 facial, 3 forearms and 2 eyes) occurring with the handling of tefluthrin technical material in research, manufacture and formulation. Facial paraesthesia can occur through minimal exposure to pyrethroid insecticides, and whilst it is unpleasant for the individual who experiences it, there are no long-term health effects.

Direct observations, e.g. clinical cases and poisoning incidents

Dermal exposure of spray operators to synthetic pyrethroids in the field has been reported to cause cutaneous sensations which are transient and reversible, and have not been associated with any persistent abnormalities. (Ref. Wilks M. F. Clinical Toxicology, 38(2), 103-105, 2000).

From 1994 to 1999, the agricultural toxico-vigilance network (Mutualité Sociale Agricole, Paris) recorded 44 observations which implicated tefluthrin preparations in combination with anthraquinone and oxyquinoleate seed treatment. The reported reactions and exposure modalities enhance the description of the subjective facial syndrome (dysesthesia and cutaneous irritations, accentuated by water contact, alterations of thermal perception, functional influence on smell and taste). Common underlying factors of exposure draw attention on the role of the dust as an active substance vector. (Ref. Leray I.M. et al: Vet. Human Toxicol. 43 (4), 243, 2001).

The Syngenta Emergency Toxicological Response database, in which details of human incidents associated with the use of Syngenta Agrochemicals' products are recorded, shows 19 recorded cases, 17 of which are associated with the seed treatment product 'Evict', where operators exhibited typical symptoms of paraesthesia. These paraesthesia effects are fully reversible within 24 hours and are not signs of systemic toxicity. Of the other two cases, one involved the handling of pellets, the other was handling drums of tefluthrin technical material. Both of these cases reported mild symptoms of paraesthesia.

Six cases of human exposure associated with tefluthrin were reported in the United States between January 1999 and July 2000. Four cases were asymptomatic, one reported skin effects similar to sunburn, and one complaint of nasal irritation.

Expected effects and duration of poisoning

Local Symptoms:

As with other pyrethroids, specific subjective sensations (paraesthesia) have been described in occupational use (Moretto, 1991, Chester et al., 1992). These may consist of burning, tingling or numbness, particularly in the face, upon direct skin contact with tefluthrin. The effects are fully reversible within 24 hours and are not signs of systemic toxicity.

Nose and throat irritation, sometimes associated with coughing or sneezing have been described by spray operators using similar synthetic pyrethroids. (Moretto, 1991, Chester et al., 1992).

An experimental study in humans was carried out to assess abnormal sensations in the facial skin of human volunteers (Allen, 1990). Commercially available formulations of three pyrethroids (cypermethrin, lambda-cyhalothrin and tefluthrin) were applied at various dilutions to establish concentration thresholds and dose-response (0.1 mL applied to area 3 cm x 3 cm). Concentration threshold for paraesthetic response was 0.05% w/w (equivalent to approximately 6 $\mu g/cm^2$) for both lambda-cyhalothrin and tefluthrin.

Peak mean responses were similar for these two compounds although, with tefluthrin, onset was faster and duration generally longer.

In a human study involving exposure of the facial skin of volunteers to lambda-cyalothrin atmospheres generated at 20 °C and 80 °C, paraesthesia was caused by the vapour/aerosol mixture generated at the higher temperature (Allen, 1990). It should be noted that, since tefluthrin has an appreciably higher volatility than lambda-cyhalothrin, then (by extrapolation) tefluthrin has even greater potential for causing such skin effects by vapour exposure.

Systemic Effects:

Skin absorption of tefluthrin is extremely low (approximately 0.1 % of a dose applied directly on the skin) and no systemic effects from skin absorption of tefluthrin have been described.

No reports are available, either in the scientific literature or in company records, on poisoning associated with tefluthrin. Signs and symptoms of systemic poisoning are therefore described by analogy with other pyrethroids for which information is available (He et al., 1989).

Following ingestion of pyrethroids, numbness of the lips and tongue can occur, followed by epigastric pain, nausea, vomiting and diarrhoea. Systemic effects can include dizziness, headache, fatigue, weakness, increased stomal secretion, palpitations, blurred vision, increased sweating and low grade pyrexia. In severe cases there may be loss of consciousness, coarse muscular fasciculations, convulsions, pulmonary oedema and cardiorespiratory failure (Poulos et al., 1982). There are no specific symptoms indicative of pyrethroid poisoning.

4.11.2 Summary and discussion

Neurotoxic effects in rats were also observed in an acute neurotoxicity study (NOAEL 2.5 mg/kg bw) and in a 90-d neurotoxicity study (NOAEL 11.6 mg/kg bw/d), but no signs of delayed neurotoxicity were observed in domestic hens.

No consistent effects on motor or sensory nerve electrophysiology or function, clinical or histopathological signs of neurotoxicity were observed in male and female rats treated chronically

with near lethal doses of tefluthrin for eight weeks. Animals surviving this dosing regimen were indistinguishable from control animals in all respects.

4.11.3 Comparison with criteria

Based on neurotoxic effects observed in the most sensitive species dog, classification with STOT-RE. H372 is proposed. Please refer to 4.8.

4.11.4 Conclusions on classification and labelling

Please refer to 4.8.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 89: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Aqueous hydrolysis at pH 5, 7 and 9	hydrolyse only slowly at pH 5, 7 and 9	--	Steward; Leahey (1986, Rep .No. RJ0512B)
Photodegradation in sterile water at pH 7	DT_{50} > 31 d	--	Amos (1987, Rep No.RJ0562B)
Biodegradation in water/sediment systems	DT_{50} = 60 – 146 d (whole system) DT_{50} = 203 - 204 d (sediment)	--	Muttzall; Vonk (1990, Rep. No. R89/382A)
Biodegradation in water/sediment systems	DT_{50} = 51 – 58 d (whole system) DT_{50} = 57-59 d (sediment)	--	Dean (1995. Rep. No. ISN 321/9504441)

5.1.1 Stability

Hydrolytic degradation:

Author: Steward J., Leahey, J.P. (1986)
Title: 'Tefluthrin: Hydrolysis at pH5, 7 and 9 in sterile aqueous solutions'. ICI Plant Protection Division, Jealott's Hill Research Station
Date: Study date: 08.08.1986. Dates of experimental work: December 1985 to June 1986
Doc ID: Report No. RJ0512B, Syngenta File No. ICI993/0470) unpublished report
Guideline: Not stated in report
Deviations: Not Applicable
GLP: Yes: This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.
Validity: Acceptable

Materials and Methods:
The hydrolysis of tefluthrin was studied using both [U-^{14}C]-phenyl-tefluthrin (Batch ref. 83-J7, specific activity 4.68 kBq/µg, radiochemical purity 97 %) and [1-^{14}C]-cyclopropyl-tefluthrin (Batch ref. 85-J7, specific activity 5.08 kBq/µg, radiochemical purity 98 %) in sterile aqueous buffer solutions at pH 5, 7 and 9 maintained at 25 ^{o}C. Tefluthrin was added as an acetonitrile solution at 2 µg/mL to water to give an initial concentration of 2 x 10^{-2} mg active substance/litre, the limit of tefluthrin solubility in water at 20 ^{o}C. Aliquots were analysed for tefluthrin and radiolabelled degradates at 0 and 30 days after application for pH values of 5 and 7 and after 0, 3, 7, 15 and 30 days for pH 9. There were increasing amounts of radiolabel adsorbed to the glass vials as the study progressed and this unextracted material was not analysed. The solutions were assayed by passage through Bond-Elut columns to adsorb radioactive fractions from the water, and the material in the aqueous phase that was not retained was not analysed. Thus, recoveries and hence amounts analysed by chromatography varied between 42.6 % (pH 9, 7 DAT, phenyl label - single replicate) to 105.4 % (pH 9, 0 DAT, phenyl label - single replicate).

Findings:
At pH 5 or pH 7 up to the 30-day timepoint tefluthrin was stable to hydrolysis. At pH 9 analysis of the individual extracts showed that hydrolysis products, Compound Ia and Compound II, were found at average levels of 34.6 % and 21.4 % respectively 30 days after application.

Recovery of radioactivity was not always high and it is assumed that, similar to other pyrethroids, residues bound to glass are likely to be predominantly parent tefluthrin. Table 90 contains details of the analyses of organic extracts for tefluthrin and its degradates.

Table 90: Analysis of organic fractions of aqueous hydrolysis of tefluthrin at pH 9

% Radioactivity in organic fraction of extracts					
Incubation time (days)	**Replicate**	**[1-^{14}C]- Cyclopropyl label**			
		Recovery[1]	**Tefluthrin**	**Compound Ia**	**Remainder[2]**
0	1	85.7	96.4	ND	3.7
	2	94.6	95.5	ND	4.5
3	1	91.9	93.9	5.2	0.9
	2	87.2	92.4	5.9	1.7
7	1	48.0	81.7	16.1	2.3
	2	83.4	91.4	7.1	1.5
15	1	81.2	81.8	17.6	0.7
	2	82.2	75.4	21.0	3.6
30	1	89.3	66.6	32.9	0.6
	2	65.3	60.2	36.3	3.6
[U-^{14}C]-Phenyl label					
		Recovery[1]	**Tefluthrin**	**Compound II**	**Remainder[2]**
0	1	105.4	97.1	ND	2.9
	2	ND	ND	ND	ND
3	1	86.3	94.2	2.8	3.0
	2	82.4	95.0	2.5	2.6
7	1	81.6	91.4	4.4	4.2
	2	42.6	87.7	8.3	4.1
15	1	69.4	83.8	11.9	4.3
	2	50.0	85.3	10.4	4.4
30	1	49.4	75.2	21.3	3.6
	2	95.1	75.6	21.4	3.0

[1] - Percentage of total applied radioactivity in the fraction analysed
[2] - Radioactivity not associated with discrete bands on the chromatograms

Conclusions:
Tefluthrin will hydrolyse only slowly in water under normal environmental conditions.
The study is acceptable. The results of the study are plausible.

Photochemical degradation:

Author: Brodsky J. (2000)
Title: 'Determination of the Direct Phototransformation of tefluthrin in Water'. CAU GmbH, Germany for Covance Laboratories Ltd.
Date: Study date: 20.6.2000.
Dates of experimental work: May 2000-June 2000.
Doc ID: Report No.38/276, Syngenta File No. ICI993/0476
unpublished report

Guideline:	UBA Draft Test Guideline - Phototransformation of Chemicals in Water, Part A, Direct Phototransformation, December 1992
Deviations:	No
GLP:	Yes (certified laboratory)
Validity:	Acceptable

Materials and Methods:
The UV spectrum of tefluthrin (Lot No. ASJ10025-01S, Purity 98.1 % w/w) was measured in methanol and the molar extinction coefficients at wavelengths of 290 nm and 295 nm were calculated in order to determine whether a quantum yield study should be carried out on tefluthrin in accordance with the guidelines.

Findings:
The experimentally determined molar extinction coefficients for tefluthrin were 5.0 and 2.6 at 290 nm and 295 nm respectively.

Conclusions:
The measured extinction coefficients were below the level required to make a quantum yield study necessary under the guidelines.
The study is acceptable. The results are plausible.

Author:	Amos R. et al. (1987)
Title:	'Tefluthrin: Photodegradation in sterile water at pH 7'. ICI Plant Protection Division, Jealott's Hill Research Station
Date:	Date of study: 03.03.1987. Dates of experimental work: January 1986 –January1987
Doc ID:	Report No. RJ0562B, Syngenta File No. ICI993/0472 unpublished report
Guidelines:	Not stated in report
Deviations:	Not Applicable.
GLP:	Yes. This study was performed prior to the GLP Certification of Laboratories but was conducted according to the principles and practices of Good Laboratory Practice. A Quality Assurance Statement is included in the report.
Validity:	Acceptable

The photolysis of both [1-^{14}C]-cyclopropyl-tefluthrin and [U-^{14}C]-phenyl-tefluthrin was studied at 25 ^{o}C ± 1 ^{o}C in aqueous solutions at pH 7 *(Amos R and Leahey JP, 1987)*.

Materials and Methods:
Samples of both labels were applied at the solubility limit of tefluthrin – 20 µg/L. At nominal irradiation periods equivalent to 0, 7, 15, 22 and 31 days of Florida summer sunlight - Latitude ~30 ^{o}N - samples were taken for analysis. Aqueous buffers, treated with [1-^{14}C]-cyclopropyl-tefluthrin (Batch ref. 85-J7, specific activity 2.13 GBq/mmol, radiochemical purity 98.6 %) and [U-^{14}C]-phenyl-tefluthrin (Batch ref. 83-J9, specific activity 2.08 GBq/mmol, radiochemical purity 97.9 %), were maintained in the dark at 25 ^{o}C ± 1 ^{o}C. Polyurethane foam bungs were used to trap any volatiles. The solutions were assayed by passage through Bond-Elut columns to adsorb radioactive fractions from the water. The vessels were extracted with acetonitrile to remove adsorbed material from glass and similarly the polyurethane foam and the silicone tubing used were

extracted with methanol to remove any residues. These extracts were analysed for tefluthrin and its degradates by TLC. Recoveries of radioactivity ranged from 92.0 % to 105.5 %.

Findings:
The percentage of parent compound and degradates recovered at each sampling interval are tabulated in Table 91 to Table 97. The figures are presented as total recovery, vial fractions and volatile fractions for each label.

Table 91: Distribution of radioactivity in both the vial and volatile fractions for the aqueous photolysis of tefluthrin

% Distribution of applied radioactivity						
	Cyclopropyl label			Phenyl label		
Irradiation period (days)	**Vial**	**Volatile**	**Total recovery**	**Vial**	**Volatile**	**Total recovery**
0	104.4	NA	104.4	104.3	NA	104.3
7	28.1	68.4	96.5	96.1	2.7	98.8
7	58.3	36.7	94.0	44.2	54.0	98.2
15	63.5	34.2	97.7	36.9	61.0	97.9
15	62.9	42.6	105.5	51.4	40.6	92.0
22	79.2	22.2	101.4	50.5	52.8	103.3
22	33.8	70.5	104.3	25.0	71.7	96.7
31	58.5	52.6	111.1	50.0	43.5	93.5
31	56.8	40.7	97.5	44.2	57.7	101.9
31 (Dark Control)	104.4	NA	104.4	97.5	NA	97.5

NA - not assayed

Table 92: Composition of radioactive components from the aqueous photolysis of [1-^{14}C]-Cyclopropyl-tefluthrin

Irradiation period (equivalent Florida Summer Sunshine)	**% radioactivity recovered**			
	tefluthrin	**Trans-tefluthrin**	**Unknowns[1]**	**Remainder[2]**
0 days	97.7	1.4	ND	ND
7 days 3hrs	70.4	17.5	2.4	3.0
15 days 11hrs	65.8	22.9	3.5	0.4
15 days 8hrs	76.2	22.4	5.3	1.7
22 days 23hrs	51.3	31.3	4.6	3.0
22 days 21hrs	63.6	26.3	3.7	1.3
31 days 3hrs	59.7	37.2	3.3	2.9
31 days 2hrs	60.9	21.2	5.0	3.5
Dark Control (day 31)	93.6	1.2	ND	0.1

ND =Not detected in samples at this time interval
1 baseline material on TLC
2 Diffuse regions of radioactivity, which do not contain discrete components.

Table 93: Composition of radioactive components from aqueous photolysis of [U-^{14}C]-Phenyl-tefluthrin

Irradiation period (equivalent Florida summer sunshine)	% radioactivity recovered			
	Tefluthrin	Trans-tefluthrin	Unknowns[1]	Remainder[2]
0 day	100.0	1.1	ND	ND
7 days 3hrs	81.5	7.9	1.7	3.0
7 days 4hrs	79.4	12.2	1.7	ND
15 days 8hrs	70.2	16.9	3.5	0.9
15 days 8hrs	67.0	16.7	2.6	2.1
22 days 16hrs	66.5	21.8	1.9	2.3
22 days 16hrs	72.2	21.3	3.2	ND
31 days 2hrs	60.0	29.1	3.3	1.3
31 days 3hrs	62.8	23.3	4.1	0.6
Dark control (day 31)	94.6	1.0	ND	ND

ND = Not detected in samples at this time interval
1 baseline material on TLC
2 Diffuse regions of radioactivity, which do not contain discrete components.

Table 94: Composition of radioactive components from the vials of the aqueous photolysis of [1-^{14}C]-Cyclopropyl-tefluthrin

Irradiation period (equivalent Florida summer sunshine)	% radioactivity recovered			
	Tefluthrin	Trans-tefluthrin	Unknowns[1]	Remainder[2]
0 day	92.9	1.3	ND	5.8
7 days 4hrs	75.5	15.2	4.4	7.0
7 days 3hrs	71.0	21.7	1.8	5.5
15 days 11hrs	70.9	24.6	2.1	2.4
15 days 8hrs	70.3	22.9	3.5	3.3
22 days 23hrs	54.7	35.4	4.0	5.9
22 days 21hrs	50.4	40.8	3.4	5.5
31 days 3hrs	53.6	41.4	2.3	2.8
31 days 2hrs	68.0	24.1	3.5	4.8
Dark control (day 31)	93.4	1.2	ND	5.4

ND = Not detected in samples at this time interval
1 baseline material on TLC
2 Diffuse regions of radioactivity, which do not contain discrete components.

Table 95: Composition of radioactive components from the vials of the aqueous photolysis of [U-^{14}C]-Phenyl-tefluthrin

Irradiation period (equivalent Florida summer sunshine)	% radioactivity recovered			
	Tefluthrin	Trans-tefluthrin	Unknowns[1]	Remainder[2]
0 day	94.2	1.0	ND	4.8
7 days 3hrs	85.6	8.3	1.8	4.4
7 days 4hrs	81.6	11.9	1.4	5.1
15 days 8hrs	71.3	20.5	4.3	4.0
15 days 8hrs	75.1	17.9	1.8	5.3
22 days 16hrs	64.7	26.1	1.7	7.5
22 days 16hrs	64.6	26.0	3.5	6.0
31 days 2hrs	58.2	34.5	3.4	4.0
31 days 3hrs	59.1	27.8	7.6	5.5
Dark control (day 31)	93.8	1.0	ND	5.3

ND = Not detected in samples at this time interval
1 baseline material on TLC
2 Diffuse regions of radioactivity, which do not contain discrete components.

Table 96: Composition of radioactive components in the volatile fraction of the aqueous photolysis of [1-^{14}C]-Cyclopropyl-tefluthrin

Irradiation period (equivalent Florida summer sunshine)	% radioactivity recovered			
	Tefluthrin	Trans-tefluthrin	Unknowns[1]	Remainder[2]
7 days 3hrs	78.6	13.3	3.7	4.4
15 days 11hrs	67.5	23.8	6.4	3.1
15 days 8hrs	72.6	18.0	7.2	2.2
22 days 23hrs	58.0	28.5	8.5	5.0
22 days 21hrs	71.8	21.2	3.8	2.7
31 days 3hrs	63.6	29.2	4.4	2.8
31 days 2hrs	65.2	21.7	8.2	4.9

ND = Not detected in samples at this time interval
[1] baseline material on TLC
[2] Diffuse regions of radioactivity, which do not contain discrete components.

Table 97: Composition of radioactive components found in the volatile fraction of the aqueous photolysis of [U-^{14}C]-Phenyl-tefluthrin

Irradiation period (equivalent Florida summer sunshine)	% radioactivity recovered			
	Tefluthrin	Trans-tefluthrin	Unknowns[1]	Remainder[2]
7 days 4hrs	80.1	12.7	2.2	5.0
15 days 8hrs	75.6	16.4	3.3	4.7
15 days 8hrs	71.6	18.9	4.2	5.3
22 days 15hrs	73.8	19.9	2.1	4.2
22 days 16hrs	74.6	19.3	3.0	3.2
31 days 2hrs	66.3	24.6	3.5	5.6
31 days 3hrs	70.8	22.3	2.0	5.0

ND = Not detected in samples at this time interval
[1] baseline material on TLC
[2] Diffuse regions of radioactivity, which do not contain discrete components.

There are no major photodegradates other than trans-tefluthrin, which is formed in amounts of between 21.2 % and 37.2 % after 31 days irradiation. There is a significant amount of volatile loss during the experiment (between 40.7 % and 57.7 % of applied radioactivity after 31 days). The ratio of cis-tefluthrin to its trans-isomer in both the volatile and solution fractions declines with time; varying from a maximum of 8.4:1 (phenyl label, solution fraction) after 7 days to a minimum of 2.1:1 (cyclopropyl label, solution fraction) after 31 days.

Conclusions:
At a temperature of 25 ^{o}C in pure water tefluthrin degraded in light to give its trans-isomer with a DT_{50} greater than 31 days.
The study is acceptable. The results are plausible.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

5.1.2.2 Screening tests

No ready biodegradability study for tefluthrin has been carried out.

5.1.2.3 Simulation tests

Biodegradation in water/sediment systems:

Study 1

Author: Muttzall P.I., Vonk, J.K. (1990)
Title: 'Biodegradation of tefluthrin in a static water/sediment system'. Netherlands Organisation for Applied Scientific Research
Date: Study date: 17.01.1990.
Dates of experimental work: May 1989 – August 1989
Doc ID: Report No R89/382A, Syngenta File No. ICI993/0474
unpublished report

Guideline: Dutch Regulations for Biocides G. 2.1 Biodegradability in Water ≅ SETAC - Europe (1995): Assessing Environmental Fate and Ecotoxicity of Pesticides. Section 1.8.2 Aerobic Aquatic Degradation. The study was performed prior to the above guidelines but has been checked for compliance with the above.

Deviations: Yes - Recovery of radioactivity varied between 73 % and 92 % of that applied. This deviation is considered not to compromise the scientific validity of the study.

GLP: Yes (certified laboratory)

Validity: Acceptable

Material and methods:

[1-^{14}C]-cyclopropyl-tefluthrin (Batch ref. 89-J1, specific activity 1.56 GBq/mmol, radiochemical purity 99 %) and [U-^{14}C]-phenyl-tefluthrin (Batch ref. 89-J2, specific activity 2.293 GBq/mmol, radiochemical purity 98 %) were applied at a rate of 0.25 mg/L and 0.20 mg/L respectively to two water-sediment systems. The physico-chemical characteristics of the systems are given in Table 98 and Table 99. The natural water and sediment were combined in biometer flasks to give a sediment to water ratio of 1:10 (w/v) for the Kromme Rijn and TNO Zuidpolder systems. Each flask contained a total volume of water of 200 mL and a depth of sediment of 2 cm. The prepared systems were pre-incubated for 13 days before treatment with the test substance. The oxygen content of the waters was adjusted by aeration before application to around 8 mg/L. The systems were treated with tefluthrin by addition of 10 µL of a solution in DMSO and were incubated at a temperature of 20 °C in a light-dark regime under conditions that allowed $^{14}CO_2$ and any other volatilised radioactivity to be trapped. Samples of both water and sediment were taken for analysis at 0, 7, 14, 28, 42, 56, 70 and 84 days after application. The sediment was extracted using acetonitrile followed by methanol. The water was acidified and then extracted with either dichloromethane ([1-^{14}C]-cyclopropyl-tefluthrin) or ethyl acetate ([U-^{14}C]-phenyl-tefluthrin). Composition of the extracts was determined by TLC. Bound residues were determined by combustion analysis.

Table 98: Physico-chemical characteristics of the sediments

Sediment property	Kromme Rijn	TNO Zuidpolder
% Sand#	47.8	34.7
% Silt#	28.7	36.3
% Clay#	20.4	29.0
% Organic matter	5.5	8.4
pH	7.3	7.4
% $CaCO_3$	7.7	4.0
Soil classification (ADAS Soil Triangle)	clay loam	clay loam

- normalised from reported data which took Organic Matter and $CaCO_3$ into account

Table 99: Physico-chemical characteristics of the waters

Water properties	Kromme Rijn	TNO Zuidpolder
Dissolved oxygen before application (mg/L)	2.6	4.9
Dissolved oxygen after 12 weeks (mg/L)	8.5	8.0
pH (at application)	8.2	8.8
pH after 12 weeks	9.1	9.3

Findings:

The percentages of parent compound and degradates recovered at each sampling interval are summarised in Table 100 to Table 103. The mass balances for all of the water-sediment systems at all sampling intervals were in the range 73 % to 92 % of applied radioactivity.

Table 100: Distribution of radioactivity in Kromme Rijn water-sediment systems - [1-^{14}C]-Cyclopropyl-tefluthrin

Distribution of radioactivity (% applied)								
Phase	**Days incubation**							
	0	**7**	**14**	**28**	**42**	**56**	**70**	**84**
$^{14}CO_2$	na	nd	nd	2.0	2.5	3.0	3.5	3.0
Water	34.5	7.5	8.5	12.5	16.5	17.0	16.5	18.0
Extractable	48.5	73.5	69.0	65.5	63.0	58.0	56.0	55.5
Unextracted	0.5	2.0	2.0	3.5	6.0	6.5	8.0	10.5
Total recovered	83.5	83.0	79.5	83.5	88.0	84.5	84.0	87.0
Present on holders	0	13.0	10.0	3.0	2.0	1.0	nd	nd
Overall total	83.5	96.0	89.5	86.5	90.0	85.5	84.0	87.0

Average of two replicates
nd = not detected
na = not analysed

Table 101: Distribution of radioactivity in Kromme Rijn water-sediment Systems - [U-^{14}C]-Phenyl-tefluthrin

Distribution of radioactivity (% applied)								
Phase	**Days incubation**							
	0	**7**	**14**	**28**	**42**	**56**	**70**	**84**
$^{14}CO_2$	na	nd	nd	nd	nd	1.0	1.0	1.0
Water	29.0	8.5	10.5	13.5	18.0	17.0	21.0	22.5
Extractable	60.0	71.5	68.5	65.0	67.0	63.5	54.5	54.5
Unextracted	1.0	1.5	2.5	3.5	4.0	5.5	7.0	8.5
Total recovered	90.0	81.5	81.5	82.0	89.0	87.0	83.5	86.5
Present on holders	nd	13.0	10.0	3.0	2.0	1.0	nd	nd
Overall total	90.0	94.5	91.5	85.0	91.0	88.0	83.5	86.5

Average of two replicates
nd = not detected
na = not analysed

Table 102: Distribution of radioactivity in TNO Zuidpolder water-sediment systems - [1-^{14}C]-Cyclopropyl-tefluthrin

Distribution of radioactivity (% applied)								
Phase	**Days incubation**							
	0	**7**	**14**	**28**	**42**	**56**	**70**	**84**
$^{14}CO_2$	na	0.5	1.0	4.0	4.5	5.0	6.0	6.0
Water	38.0	17.0	13.0	20.0	23.0	28.5	29.0	29.5
Extractable	43.0	59.0	60.0	55.0	50.5	45.0	44.0	38.0
Unextracted	0.5	3.0	4.5	7.0	8.5	10.0	11.0	13.0
Total recovered	81.5	79.5	88.5	86.0	86.5	88.5	90.0	86.5
Present on holders	nd	13.0	10.0	3.0	2.0	nd	nd	nd
Overall total	81.5	92.5	98.5	89.0	88.5	88.5	90.0	86.5

Average of two replicates
nd = not detected
na = not analysed

Table 103: Distribution of radioactivity in TNO Zuidpolder water-sediment systems - [U-^{14}C]-Phenyl-tefluthrin

Distribution of radioactivity (% applied)								
Phase	**Days incubation**							
	0	**7**	**14**	**28**	**42**	**56**	**70**	**84**
$^{14}CO_2$	na	nd	nd	nd	nd	1.0	1.0	1.5
Water	26.0	17.5	21.0	31.5	30.0	39.5	33.5	41.0
Extractable	59.0	59.0	61.5	55.5	52.5	42.5	44.5	40.0
Unextracted	0.5	2.5	3.5	4.0	5.0	6.5	9.0	10.0
Total recovered	85.5	79.0	86.0	91.0	87.5	89.5	88.0	92.5
Present on holders	nd	13.0	10.5	3.0	2.0	1.0	nd	nd
Overall total	85.5	92.0	96.5	94.0	89.5	90.5	88.0	92.5

Average of two replicates
nd = not detected
na = not analysed

Table 104: Average amounts of radioactivity in Kromme Rijn water-sediment system - [1-^{14}C]-Cyclopropyl-tefluthrin

Distribution of radioactivity (% applied)								
Component	**Phase**	**Days incubation**						
		0	**7**	**14**	**28**	**42**	**56**	**84**
Tefluthrin	Sediment	47	na	66	58	52	52	49
	Water	26	3	2	1	nd	nd	nd
	Total	73	-	68	59	52	52	49
Compound Ia	Sediment	na	na	1	3	8	3	4
	Water	1	1	2	4	10	10	11
	Total	1	-	3	7	18	13	15
Baseline	Sediment	1	na	2	3	3	2	2
	Water	1	2	4	5	5	5	5
	Total	2	-	6	8	8	7	8

nd = not detected
na = not analysed

Table 105: Average amounts of radioactivity in TNO Zuidpolder water-sediment system - [1-^{14}C]-Cyclopropyl-tefluthrin

Distribution of radioactivity (% applied)								
Component	**Phase**	**Days incubation**						
		0	**7**	**14**	**28**	**42**	**56**	**84**
Tefluthrin	Sediment	42	55	50	45	45	33	28
	Water	29	1	2	1	1	nd	nd
	Total	71	56	52	46	46	33	28
Compound Ia	Sediment	na	3	2	5	4	6	7
	Water	na	2	3	9	13	18	22
	Total	-	5	5	14	17	24	29
Baseline	Sediment	1	3	2	5	2	5	3
	Water	2	5	6	7	6	6	6
	Total	3	8	8	12	8	11	9

nd = not detected
na = not analysed

Table 106: Average amounts of radioactivity in Kromme Rijn water-sediment system - [U-^{14}C]-Phenyl-tefluthrin

Distribution of radioactivity (% applied)								
Component	**Phase**	**Days incubation**						
		0	**7**	**14**	**28**	**42**	**56**	**84**
Tefluthrin	Sediment	56	70	66	61	60	60	52
	Water	23	4	3	1	1	nd	nd
	Total	79	74	69	62	61	60	52
Compound II	Sediment	na	1	1	2	2	2	1
	Water	na	1	nd	nd	nd	nd	nd
	Total	-	2	1	2	2	2	1
Baseline[1]	Sediment	1	1	2	2	4	2	1
	Water	6	4	6	11	18	16	23
	Total	7	5	8	13	22	18	24

[1] - Baseline material contains a number of compounds in a band from RF 0-0.15 a major component being Compound IV being 20 % of applied radioactivity after 84 days
nd = not detected
na = not analysed

Table 107: Average amounts of radioactivity in TNO Zuidpolder water-sediment system - [U-^{14}C]-Phenyl-tefluthrin

Distribution of radioactivity (% applied)								
Component	**Phase**	**Days incubation**						
		0	**7**	**14**	**28**	**42**	**56**	**84**
Tefluthrin	Sediment	50	54	49	45	47	37	37
	Water	21	3	2	1	1	nd	nd
	Total	71	57	51	46	48	37	37
Compound II	Sediment	na	3	3	3	2	2	1
	Water	1	3	1	1	nd	nd	1
	Total	-	6	4	4	2	2	2
Baseline[1]	Sediment	1	3	2	7	4	3	2
	Water	2	10	17	27	30	39	39
	Total	3	13	19	34	34	42	41

[1] - Baseline material contains a number of compounds in a band from RF 0-0.15 a major component being Compound IV being 34 % of applied radioactivity after 84 days
nd = not detected
na = not analysed

Tefluthrin rapidly dissipated from the aqueous phase by adsorption to sediment. Radioactivity generally declined in the aqueous phase immediately after application due to the rapid adsorption of tefluthrin to the sediment. Between 21 % and 29 % of applied tefluthrin was found in the water phase immediately after application but by 1 week after application this level had fallen to between 1 % and 4 %. Levels of degradates in the water phase increased with time so that between 18 % and 41 % of applied radioactivity was present after 12 weeks (Table 104 to Table 107).

Levels of tefluthrin adsorbed to sediment after 12 weeks were 49 % to 52 % for Kromme Rijn and 28 % to 37 % for TNO Zuidpolder for the cyclopropyl and phenyl labels respectively.
Dissipation of parent tefluthrin was generally faster in the TNO - Zuidpolder system than for Kromme-Rijn. Compound Ia and Compound II, the products of hydrolysis of tefluthrin, were identified as degradates in both systems. Of the TLC baseline material (as analysed only at the final timepoint) Compound IV was found to be the major degradate in the water phase; being present at 20 % in the Kromme-Rijn and 34 % in the TNO-Zuidpolder systems respectively. Compound Ia was found at increasing levels up to 12 weeks after treatment - 15 % in Kromme Rijn and 29 % in

TNO Zuidpolder, predominantly in the water phase. Compound II was found at lower levels peaking at 2 % in Kromme Rijn and 6 % in TNO Zuidpolder and was generally found at higher levels in the sediment rather than the water. Other degradates were present: Compounds III and V were found at a combined level of 3 % but all others were below 1 % each in either system.

Some volatilisation of tefluthrin itself was seen with the holders of the vessels being contaminated with up to 13 % radiolabel 1 week after application and declining thereafter. There was little mineralisation during this test with a maximum of 3 % $^{14}CO_2$ detected 12 weeks after application.

ModelManager v1.1 (ModelKinetix, UK) was used to calculate the DT_{50} values for tefluthrin in the water-sediment system and the sediment compartment. In the case of the sediment compartment, the analysis ignored the zero timepoint because the initial rapid redistribution of tefluthrin from the water compartment to the sediment was incomplete at the time of sampling. The degradation of tefluthrin from the Kromme Rijn water-sediment system was slower than that from the TNO Zuidpolder system. The values obtained are given in Table 108.

Table 108: Calculated tefluthrin DT_{50} Values

Water-Sediment System	Compartment	Simple Exponential Model	First Order Multi-Compartment Model
Kromme Rijn	Sediment*	203	#
	Water-Sediment	146	#
TNO Zuidpolder	Sediment*	204	#
	Water-Sediment	60	#

^ - calculated from the [1-^{14}C]-Cyclopropyl label values only as [U-^{14}C]-Phenyl gave clearly unrealistic values
# - no numerical solution possible
* - modelled after elimination of the zero timepoint to discount for rapid redistribution from water to sediment immediately following application

Study 2

Author: Dean G.M. (1995)
Title: ^{14}C-tefluthrin: Degradability and Fate in a Water-Sediment under Aerobic, Anaerobic and Sterile Conditions.
Huntingdon Research Centre Ltd.
Date: Study date: 19.10.1995.
Dates of experimental work: August 1993 – December 1994
Doc ID: Report No ISN 321/950441, Syngenta File No. ICI993/0475
unpublished report
Guideline: Trade Memorandum T-1-255, Environmental Chemistry and Fate Guidelines for Registration of Pesticides in Canada, Section 6.1 C.2, July 1987
Deviations: Yes. Organic matter at 20.3 % exceeds the amount of 12.9 % stated in the guidelines. This deviation is considered not to compromise the scientific validity of the study.
GLP: Yes (certified laboratory)
Validity: Acceptable

Material and methods:

[U-^{14}C]-phenyl-tefluthrin (batch number 93-J21, specific activity 2.05 GBq/mmol, radiochemical purity 98 %) and [1-^{14}C]-cyclopropane-tefluthrin (batch number 89-J1, specific activity 1.56 GBq/mmol, radiochemical purity 97.5 %) were applied at a rate equivalent to a direct overspray of approximately 450 g tefluthrin/ha to a single water sediment system. The physico-chemical characteristics of the system are given in Table 109 and Table 110. The natural water and sediment were combined to give a ratio of sediment to water between 1:2.4 and 1:3 (v/v). The depth of the sediment was between 2 and 2.5 cm and that of the water 6cm above the surface of the sediment in cylindrical glass vessels in a flow through system. The prepared systems were preincubated for between 21 and 35 days before treatment with the test substance. Sterile water-sediment systems were also prepared to distinguish between microbial and chemical degradation processes in the test system. The systems were incubated at temperatures of 20 °C ± 2 °C and 5 ^{o}C ± 2 ^{o}C in the dark under conditions that allowed $^{14}CO_2$ and any other volatilised radioactivity to be trapped. Both aerobic and anaerobic conditions were used. Depending on the incubation regime samples were taken for analysis at intervals between 0 and up to 360 days after application. The sediment was extracted using acetonitrile at ambient temperature followed by acetonitrile-water under reflux conditions and the extracts analysed by TLC. Water samples were analysed directly using TLC. The foam bungs used to trap volatiles were extracted with acetone and the extracts analysed by TLC.

Table 109: Physico-chemical characteristics of the sediment

Sediment property	Old basing
% Sand	45.5
% Silt	37
% Clay	17.6
% Organic matter	20.3
pH	7.6
Cation exchange capacity (meq/100g)	46.5
Microbial biomass at zero time (microgC/g)	239-1017
Soil classification	loam (USDA)

Table 110: Physico-chemical characteristics of the water

Water properties	Old basing
Dissolved oxygen at surface % saturation (at collection)	100 %
pH (at collection)	7.6
Total organic carbon mg C/L	25.8
Total hardness mmol/L of alkaline earth ions	3

Findings:

The percentages of parent compound and degradates recovered at each sampling interval are summarised in Table 111 to Table 112. The mass balances for all of the water-sediment systems at all sampling intervals were in the range 86.2 to 110 % of applied radioactivity.

Table 111: Distribution of radioactivity in old basing water-sediment systems – [U-^{14}C]-Phenyl-tefluthrin under aerobic conditions at 20 °C

Degradates detected	Phase	Distribution of radioactivity (% applied)									
		Days incubation									
		0	3	7	14	30	59	120	180	270	360
$^{14}CO_2$		ND	ND	0.7	1.3	4.6	15.3	32.3	43.0	50.6	53.4
Tefluthrin	water	12.4	ND	< 0.1	< 0.1	< 0.1	< 0.1	ND	ND	ND	ND
	sediment	82.8	90.5	81.1	76.2	65.4	49.6	17.6	10.3	5.0	2.7
	volatile	ND	1.5	2.3	4.0	6.2	11.2	13.4	20.0	14.7	15.4
Compound V	water	< 0.4	ND	1.7	1.5	1.1	0.6	ND	ND	ND	ND
	sediment	< 0.8	1.5	3.3	4.4	4.1	2.4	0.9	0.4	0.1	0.1
Compound III	water	< 0.8	ND	0.3	0.7	0.1	0.1	ND	ND	ND	ND
Compound M2	sediment	< 0.8	2.5	2.3	1.4	1.1	0.9	0.4	0.3	0.1	0.1
Compound IV	water	ND	ND	3.9	7.0	6.3	3.6	ND	ND	ND	ND
Compound M3	water	ND	ND	0.3	0.6	< 0.1	< 0.1	ND	ND	ND	ND
Others[1]	water	0.8	3.6	0.3	0.2	0.2	0.2	1.7	0.9	0.7	0.3
	sediment	2.2	2.1	2.5	2.7	1.6	1.5	1.8	1.3	1.1	1.0
	volatile	ND	0.1	0.1	0.1	0.3	0.3	1.0	1.1	0.5	0.2
Unextracted		0.3	0.6	1.6	2.4	3.3	11.8	22.0	20.3	28.6	15.9
Total		101.3	102.4	100.5	102.6	94.5	97.7	91.1	97.5	101.4	89.1

[1] Radioactivity not specifically identified with any particular component and no component exceeding 4 %
ND = not determined
Data for compounds averaged from two chromatography systems wherever possible, otherwise taken from a single value

Table 112: Distribution of radioactivity in old basing water-sediment systems - [1-^{14}C]-Cyclopropyl-tefluthrin under aerobic conditions at 20 °C

Degradates detected	Phase	Distribution of radioactivity (% applied)									
		Incubation period, days									
		0	3	7	14	30	59	120	180	270	360
$^{14}CO_2$		ND	1.8	3.0	4.6	15.6	25.3	48.6	48.3	62.2	66.8
Tefluthrin	water	9.6	ND	<0.1	< 0.1	< 0.1	< 0.1	ND	ND	ND	ND
	sediment	81.6	81.6	77.9	67.1	51.4	40.4	17.6	10.3	3.2	0.9
	volatile	ND	1.9	2.1	5.4	4.9	11.1	8.9	12.4	14.1	14.7
Compound M6	water	< 0.9	ND	1.2	2.4	1.7	1.5	ND	ND	ND	ND
	sediment	< 0.8	0.9	< 0.9	< 0.7	1.0	0.7	<0.2	0.2	0.1	0.2
Compound V	water	ND	ND	2.3	1.6	1.9	0.9	ND	ND	ND	ND
	sediment	< 0.8	1.6	3.9	4.1	6.6	2.5	1.4	0.5	< 0.1	0.1
Compound M2	sediment	< 0.8	2.7	2.4	1.2	1.2	0.4	0.3	0.2	< 0.1	< 0.1
Compound M1	water	0.2	ND	0.2	0.5	0.8	1.0	ND	ND	ND	ND
Others[1]	water	0.5	2.5	0.6	0.7	0.8	0.9	1.7	0.8	0.4	0.2
	sediment	1.6	1.9	1.8	< 1.4	< 1.3	1.7	1.4	0.8	0.4	0.4
	volatile	ND	0.1	0.2	0.4	0.3	0.8	1.5	3.0	0.9	1.2
Unextracted		0.2	0.9	1.8	2.3	3.3	6.5	9.8	9.7	10.6	7.8
Total		97.0	95.9	98.3	92.5	90.9	93.8	91.4	86.2	92.1	92.4

[1] Radioactivity not specifically identified with no individual compound exceeding 3 %
Data for compounds averaged from two chromatography systems wherever possible, otherwise taken from a single value
ND = not done

Table 113: Distribution of radioactivity in old basing water-sediment systems – [U-^{14}C]-Phenyl-tefluthrin under aerobic conditions at 5 °C

Degradates detected	Phase	Distribution of radioactivity (% applied)						
		Incubation period, days						
		0	7	14	30	60	180	360
$^{14}CO_2$		ND	< 0.1	< 0.1	< 0.1	0.2	1.0	4.1
Tefluthrin	water	12.3	ND	ND	ND	0.1	0.1	< 0.3
	sediment	87.3	90.6	90.1	87.7	85.1	67.5	50.3
	volatile	ND	1.1	1.0	0.4	2.1	5.9	7.3
Compound V	water	0.2	ND	ND	ND	0.9	1.3	2.1
	sediment	< 0.9	< 0.9	< 0.9	2.7	2.1	3.7	5.1
Compound III	water	0.7	ND	ND	ND	0.4	0.4	0.3
Compound IV	water	< 0.1	ND	ND	ND	5.6	8.9	22.6
Compound M2	sediment	< 0.9	1.0	1.7	1.8	1.1	1.1	0.7
Compound M3	water	0.2	ND	ND	ND	0.2	0.3	0.9
Others[1]	water	0.7	2.9	3.4	4.4	0.7	0.7	0.4
	sediment	< 1.8	2.0	2.0	2.0	2.0	2.1	1.8
	volatile	ND	0.1	0.2	0.2	0.2	0.1	0.1
Unextracted		0.2	0.3	1.0	0.7	0.9	1.9	4.8
Total		105.3	99.0	100.4	100.0	101.6	95.0	100.8

[1] Radioactivity not specifically identified and with no individual compound exceeding 4 %
ND = not done
Data for compounds averaged from two chromatography systems wherever possible, otherwise taken from a single value

Table 114: Distribution of radioactivity in old basing water-sediment systems – [U-^{14}C]-Phenyl-tefluthrin under anaerobic conditions at 20 °C

Degradates detected	Phase	Distribution of radioactivity (% applied)						
		Incubation period, days						
		0	7	14	30	60	181	360
$^{14}CO_2$		ND	0.4	0.9	1.0	2.5	12.7	21.5
Tefluthrin	water	5.1	ND	ND	ND	0.1	0.2	0.2
	sediment	90.6	102.0	99.5	NR	85.7	58.8	36.6
	volatile	ND	ND	ND	ND	ND	7.7	9.0
Compound V	water	0.3	ND	ND	ND	2.5	1.2	2.7
	sediment	< 0.9	< 1.0	< 1.0	NR	2.5	7.9	6.4
Compound M6	water	2.2	ND	ND	ND	2.1	0.5	3.2
	sediment	< 0.9	< 1.0	< 1.0	NR	0.9	1.3	1.1
Compound M1	water	1.2	ND	ND	ND	0.4	0.4	3.2
Compound M2	sediment	< 0.9	< 1.0	1.4	NR	1.1	1.1	0.8
Compound M5	water	1.8	ND	ND	ND	1.2	3.0	6.0
Others[1]	water	0.5	3.6	2.9	3.9	< 0.7	< 0.2	< 0.4
	sediment	< 2.1	< 2.4	< 2.0	NR	< 2.3	< 1.4	1.0
	volatile	ND	0.2	1.2	1.3	2.4	0.4	0.9
Unextracted		0.3	0.4	0.8	0.6	1.1	3.4	5.7
Total		106.8	112.0	110.7	NR	105.4	100.2	98.7

[1] Radioactivity not specifically identified, with no individual compound exceeding 4 %
Data for compounds averaged from two chromatography systems wherever possible, otherwise taken from a single value
ND= not done

Table 115: Distribution of radioactivity in old basing water-sediment systems - [1-^{14}C]-Cyclopropyl-tefluthrin under anaerobic conditions at 20 °C

Degradates detected	Phase	Distribution of radioactivity (% applied)									
		Incubation period, days									
		0	3	7	14	30	59	120	180	270	360
Tefluthrin	water	66.6	28.7	9.6	ND	ND	ND	ND	ND	ND	ND
	sediment	23.3	42.3	46.5	40.1	36.1	42.9	36.2	37.2	29.0	34.1
	volatile	ND	19.4	31.7	44.8	58.1	46.6	48.9	49.7	54.9	49.5
Compound M6	water	2.0	1.1	1.2	ND	ND	ND	ND	ND	ND	ND
	sediment	<0.2	<0.4	<0.5	0.4	0.4	0.6	0.6	1.0	0.8	1.1
Others[1]	water	1.5	0.5	0.4	4.8	1.8	2.0	2.3	3.1	3.5	4.6
	sediment	0.2	<0.4	0.5	<0.4	0.5	0.9	0.5	0.8	<0.3	0.5
	volatile	ND	0.2	0.3	0.7	<0.6	<0.5	0.5	<0.5	<0.5	<0.5
Unextracted		<0.1	0.1	0.2	0.1	0.2	0.3	0.3	0.4	0.5	0.4
Total		93.9	93.1	90.9	91.3	97.7	93.8	89.3	92.7	89.5	90.7

[1] Radioactivity not specifically identified, with no individual compound exceeding 4 %

Data for compounds averaged from two chromatography systems wherever possible, otherwise taken from a single value

ND = not done

Table 116: Distribution of radioactivity in old basing water-sediment systems – [U-^{14}C]-Phenyl-tefluthrin under anaerobic conditions at 5 °C

Degradates detected	Phase	Distribution of radioactivity (% applied)						
		Incubation period, days						
		0	7	14	30	60	181	360
Tefluthrin	water	71.9	57.5	25.8	ND	ND	ND	ND
	sediment	23.8	16.4	39.5	NR	37.4	32.3	27.7
	volatile	ND	17.9	27.4	55.7	57.3	67.9	68.4
Compound M2	water	3.3	1.2	0.5	ND	ND	ND	ND
Compound V	water	2.8	1.9	3.7	ND	ND	ND	ND
Compound III	water	<0.8	3.4	1.9	ND	ND	ND	ND
Others[1]	water	2.1	1.9	1.0	4.8	3.4	1.3	1.0
	sediment	0.7	0.8	2.3	NR	0.7	0.7	1.2
	volatile	ND	0.2	0.4	0.6	0.7	1.8	1.8
Unextracted		<0.1	<0.1	0.1	0.1	0.1	0.1	0.2
Total		105.5	101.3	102.6	NR	99.6	104.1	100.3

[1] Radioactivity not specifically identified, with no individual compound exceeding 4 %

Data for compounds averaged from two chromatography systems wherever possible, otherwise taken from a single value

ND = not done

NR = no result due to experimental error

Table 117: Distribution of radioactivity in old basing water-sediment systems - [1-^{14}C]-Cyclopropyl-tefluthrin under anaerobic conditions at 5 °C

Degradates detected	Phase	Distribution of radioactivity (% applied)						
		Incubation period, days						
		0	7	14	30	60	181	360
Tefluthrin	water	70.1	33.5	12.8	ND	ND	ND	ND
	sediment	18.1	44.3	40.2	NR	41.0	34.6	26.8
	volatile	ND	5.7	42.2	59.7	59.1	70.1	67.1
Compound M6	water	5.1	4.9	4.2	ND	ND	ND	ND
	sediment	<0.2	<0.4	0.7	NR	<0.4	0.4	0.4
Others[1]	water	6.8	4.8	2.7	3.6	4.6	2.2	1.9
	sediment	0.6	0.6	3.4	NR	0.4	<0.4	0.6
	volatile	ND	0.2	0.5	0.8	0.9	2.1	2.7
Unextracted		<0.1	0.1	0.2	0.2	0.2	0.2	0.2
Total		101.0	94.5	106.9	NR	106.6	110.0	99.7

[1] Radioactivity not specifically identified, with no individual compound exceeding 4 %

Table 118: Mean quantities of [1-^{14}C]-cyclopropyl-tefluthrin in sterile, aerobic old basing water-sediment system at 20 °C as percentage of applied

Time after application (days)	Sediment extract	Water	Total in sediment and water	Volatile tefluthrin	Total tefluthrin
0	83.3	9.1	92.4	NS	92.4
7	93.6	NA	93.6	3.7	97.3
30	87.1	NA	87.1	4.3	91.4
60	83.3	NA	83.3	11.4	94.7
122	59.7	NA	59.7	32.2	90.9

NS = No Sample
NA = Between 2.5-5.2 % applied radioactivity
Data for compounds averaged from two chromatography systems wherever possible, otherwise taken from a single value

At 20 °C no major degradation products (>10 %) were found in either the aerobic, anaerobic or sterile water-sediment systems. Loss of tefluthrin from the water phase was rapid with an average of only 11 % being found at 0 DAT in the aerobic studies (no assessment of the aerobic units was made between 0 and 7 DAT); losses were by dissipation to sediment and by volatile loss. Volatility of tefluthrin was significant with levels of up to 20 % (180DAT) seen under aerobic conditions and 60.5 % (59 DAT) under anaerobic conditions.

The most abundant degradate, Compound V [4-carboxy-2,3,5,6-tetrafluorobenzyl cis-3-(Z-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate], reached a peak total of 8.5 % (6.6 % in the sediment) 30 DAT under aerobic conditions. Residues of Compound IV [2,3,5,6-tetrafluoro-1.4-benzenedicarboxylic acid] were found at maximum levels of 7 % (in water under aerobic conditions 14 DAT declining thereafter). Unidentified metabolites M2 and M3 (in aerobic systems) and M6 (anaerobic) were found, nowhere exceeding 2.7 % of applied radioactivity. Mineralisation was significant under aerobic conditions reaching 48.6 % 120DAT for cyclopropyl label and 32.3 % for phenyl label.

Under anaerobic conditions there was, as expected, no significant mineralisation. Under sterile conditions tefluthrin was not significantly degraded up to the last time point four months after application.

At the lower temperature of 5 °C and under aerobic conditions, dissipation of tefluthrin from the water to the sediment was less rapid and volatile losses were much reduced. Mineralisation was also much reduced with very significant differences between the two labels: CO_2 formation after 360 days was 21.5 % for the [1-^{14}C]-cyclopropyl-tefluthrin but only 4.1 % from the [U-^{14}C]-phenyl-tefluthrin. Levels of Compound IV reached 22.6 % by 360 DAT, whereas Compound V peaked reached maximum levels of 7.9 % in sediment 181 DAT and 2.7 % in water 360 DAT.

At this temperature but under anaerobic conditions tefluthrin dissipated from the water phase with an average of 19.3 % remaining 14DAT. Levels in the sediment peaked at an average of 39.9 % 14 DAT and levels in the volatile phase levelled at around 69 % 181 DAT. The only identifiable metabolite Compound V reached a level of 3.5 % 14DAT and the largest level of a single unknown metabolite was 6.8 % at 0 DAT.

The DT_{50} and DT_{90} for tefluthrin in the total water-sediment systems and the sediment compartment separately, were determined using ModelManager v1.1 (ModelKinetix, UK) applying Simple Exponential (SE) and First Order Multi-Compartment (FOMC) models. The rate of dissipation from the water column was rapid and was not calculated owing to insufficient early data points. Loss to the vapour phase was excluded. Tefluthrin dissipated rapidly from surface water in natural water-sediment systems incubated in the dark at 20 °C. The rapid initial loss from the surface waters was probably due mainly to binding to the sediment and is consistent with the strongly adsorptive properties of tefluthrin. The DT_{50} and DT_{90} values for the sediment alone and sediment-water system are summarised in Table 119.

Table 119: Tefluthrin - DT_{50} and DT_{90} values for degradation in a water-sediment system and in the sediment fraction at 20 °C

	[1-^{14}C]-Cyclopropyl label		^{14}C-Phenyl label	
	DT_{50}	**DT_{90}**	**DT_{50}**	**DT_{90}**
Water-sediment	58 days	190 days	51 days	185 days
Sediment only	57 days	189 days	59 days	195 days

Conclusions:
In Study 1, tefluthrin dissipates rapidly from the water phase in water-sediment systems and binds predominantly to the sediment from which it is released on conversion to more polar metabolites or degradates. The DT_{50} values of tefluthrin in the total system and in the sediment compartment alone were 60-146 days and 203-204 days respectively. This is entirely consistent with the high K_{OC} values seen for this compound and in line with observations for other pyrethroids. Two degradates are observed: The major metabolite Compound Ia was found at levels up to 22 % in water and 7 % in sediment and Compound II 3 % in water and 3 % in sediment.

In Study 2, tefluthrin also initially dissipated rapidly from surface water in natural water-sediment systems due to binding to the sediment. There was significant loss of tefluthrin to the vapour phase. Under aerobic conditions levels of Compound V reached a peak of 6.6 % in the sediment (no major metabolite, no sequential measures > 5 %) and Compound IV was found at a maximum of 7 % in water (major metabolite, 2 sequential measures above 5 %). There was extensive mineralisation under aerobic conditions at the higher temperature. The DT_{50} for tefluthrin in this water sediment system was 51-58 days and in the sediment alone it was 57-59 days. Dissipation from water was < 1 day under aerobic conditions and somewhere between 1 and 2 days under anaerobic conditions.

Both studies have deficiencies e.g. low recoveries. However, the results are plausible and it is not expected that additional tests will lead to a better classification.

5.1.3 Summary and discussion of degradation

No studies on ready biodegradability according to OECD 301 and on inherent biodegradability were submitted. However, these studies are not deemed to be necessary, since higher tiered studies, namely simulation tests for the relevant environmental compartments 'water/sediment', are available.

In water/sediment systems it was shown that tefluthrin was not rapidly degradable with DT_{50} values of 51 – 146 days (whole system) and DT_{50} values of 57 – 204 days (sediment).

Tefluthrin is hydrolytically stable under acidic and neutral conditions. Aquatic photolysis is not considered to be an important transformation route for tefluthrin in the environment with DT_{50} of > 31 days.

The results of the test on the biodegradation of Fluopyram in the water/sediment system and abiotic degradation show that tefluthrin is considered not rapidly degradable (a degradation > 70 % within 28 days) for purposes of classification and labelling.

5.2 Environmental distribution

Not relevant for this dossier.

5.3 Aquatic Bioaccumulation

Table 120: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
OECD 305	$BCF_{steady\ statc}$ = 1400 (whole fish, parent)	Not lipid normalized	Hamer; Farelly; French; Hill (1987, Rep.No. RJ0521B)

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

The log $K_{o/w}$ of tefluthrin is 6.4 at 20 °C. So there is an indication for bioaccumulation potential of tefluthrin. A bioconcentration study on fish is triggered.

5.3.1.2 Measured bioaccumulation data

Report: Hamer MJ, Farrelly E, French D, Hill IR (1987) Tefluthrin: Accumulation in bluegill sunfish in a flow-through system. ICI Agrochemicals, Jealott's Hill Research Station, Jealott's Hill, United Kingdom, unpublished report No. RJ0521B (Syngenta file No. ICI993/0552).
Guidelines: OECD Guideline 305E
Deviations: None
GLP: Yes
Validity: Acceptable

Material and methods

Test substance: ^{14}C-methylene (more typically known as ^{14}C-benzyl) labelled tefluthrin; reference 83-19; measured radiochemical purity 93.4 %; specific activity 2.08 G Bq/mmol^{-1}.

Bluegill sunfish (*Lepomis macrochirus*) were exposed to maintained concentrations of ^{14}C-methylene labelled tefluthrin (nominally 0.01 µg/L) in two fresh-water flow-through systems (*ca.* 250 mL/minute throughout). System I (containing fish weighing 1.5 g) was used to monitor accumulation and elimination of total ^{14}C-residues and System II (containing fish weighing *ca.* 40 g) was used for extraction and characterisation of accumulated residues at the end of the exposure and depuration periods. Controls with a nominal acetone concentration of 0.01 % were maintained under identical conditions to the treated systems. Samples of water from both Systems I and II were analysed at regular intervals for total ^{14}C-residues and characterisation of these residues.

At each sampling date in Test System I, fish were removed from the tank and their lengths and weights recorded before analysis. For the depuration phase, remaining fish were transferred to untreated aquaria for a further 65 days. On the final days of exposure and depuration (Days 33 and 98 respectively), fish were removed from Test System II for characterisation of the radioactivity.

Findings

Throughout the study, dissolved oxygen levels were in the range 7.0 - 9.4 mg/L and the temperature was in the range 17.0 - 19.0 °C.

During the exposure phase, the mean measured concentrations of ^{14}C-residues as tefluthrin equivalents in the water were 0.0115 and 0.0103 µg/L (115 and 103 % of nominal) in Systems I and II, respectively. The majority of the radioactivity (> 52 % in Test System I and > 66 % in test System II) co-chromatographed with tefluthrin. In addition to this there was one metabolite found to represent 13 – 26 % and 6 – 18 % of the total radioactivity in Test System I and II, respectively.

The radioactive residues measured in the fish at the various sampling intervals during the exposure and depuration phases are presented in Table 121 and Table 122 below.

Table 121: ^{14}C-tefluthrin: Residues in bluegill sunfish during the exposure phase of the bioconcentration study

Exposure (days)	Mean water concentration day 0 to sampling date (µg tefluthrin/L)	Mean concentration in tissues (µg tefluthrin equivalents/kg wet weight)			Bioconcentration factor (BCF)		
		Muscle	Viscera	Whole fish	Muscle	Viscera	Whole fish
System I							
1	0.0062	1.0	19	3.1	158	3081	503
3	0.0061	2.2	28	6.2	362	4656	1013
7	0.0085	3.6	65	11.6	424	7659	1365
10	0.0102	5.6	70	12.3	553	6912	1206
14	0.0105	5.5	85	14.5	527	8114	1381
21	0.0105	6.6	95	16.0	624	9057	1524
28	0.0111	6.0	84	15.8	543	7532	1423
31	0.0117	8.8	149	24.0	750	12761	2051
33	0.0115	6.8	90	17.5	595	7783	1522
System II							
33	0.0095	65.2	14.9	10.3	893	6330	1467

After 14 days of the test exposure period the concentration of tefluthrin in the fish in System I plateaued and the BCF in the whole fish, muscle and viscera were calculated as approximately 1400, 550 and 8000, respectively. In System II the BCF in the whole fish, muscle and viscera were calculated as approximately 1500, 900 and 6300, respectively.

Table 122: ^{14}C-tefluthrin: Residues in bluegill sunfish during the depuration phase of the bioconcentration study

Study day	Depu-ration day	Mean concentration in tissues (µg tefluthrin equivalents/kg wet weight)			Concentration in tissues as % of day 33 exposure value		
		Muscle	Viscera	Whole Fish	Muscle	Viscera	Whole Fish
System I							
34	1	4.9	68	15.8	72	76	90
36	3	4.0	39	10.9	62	44	62
40	7	4.7	46	10.5	68	51	60
47	14	4.3	46	8.0	63	51	47
61	28	2.8	26	5.7	41	29	32
89	56	1.7	22	3.2	25	25	18
98	65	1.1	6	2.4	16	6	14
System II							
98		1.5	11.0	2.7	16	17	18

In System I, during the depuration phase, 50 % of the accumulated residues were eliminated from the whole fish, muscle and viscera within approximately 14, 21 and 3 days, respectively. By the end of the 65-day depuration period, 86, 84 and 94 % of the accumulated residues had been eliminated from the whole fish, muscle and viscera respectively. As with the exposure phase, the results for the fish from System II were similar to those from System I, with 82, 84 and 83 % of the accumulated residues being eliminated from the whole fish, muscle and viscera in the 65 day depuration period. The majority of the residues in the fish remained as the parent compound.

Conclusion
Bioconcentration factors of tefluthrin in whole fish, muscle and viscera were approximately 1400, 550 and 8000 respectively. At the end of the 65-day depuration period, 86, 84 and 94 % of the accumulated residues had been eliminated from the whole fish, muscle and viscera, respectively.

5.3.2 Summary and discussion of aquatic bioaccumulation

Tefluthrin has a log $K_{o/w}$ of 6.4 (20°C). The experimentally derived steady state BCF of 1400 L/Kg ww for tefluthrin related to parent and whole fish is above the trigger of 100 (criterion for bioaccumulation potential conform Directive 67/548/EEC) for not rapidly degradable substances and is also above the trigger of 500 (criterion for bioaccumulation potential conform Regulation EC 1272/2008) for not rapidly degradable substances.

5.4 Aquatic toxicity

Table 123: Summary of relevant information on aquatic toxicity

Group, specie	**Time-scale (Test type)**	**Endpoint**	**Toxicity (mg a.s./L)**	**Reference**
Fish				
Oncorhynchus mykiss	96 h (flow through)	Mortality, LC_{50}	0.00006 mm	Hill (1985; Rep.No. BL/B/2410
Lepomis macrochirus	96 h (static)	Mortality, LC_{50}	0.00013mm	Hill (1985; Rep.No. BL/B/2411
Pimephales promelas	28 d (flow through) ELS	Length and weight / larval survival, NOEC	0.0000096 mm	Tapp, Maddock, Harland (1988; Rep.No. BL/B/3037)
Pimephales promelas	345 d (flow through) FLC	Survival of F1, NOEC	0.00000397 mm	Tapp, Maddock, Gillings, Stanley, Riddle (1990; Rep.No. BL/3737/B)
Aquatic invertebrates				
Daphnia magna	48 h (static)	Immobility, EC_{50}	0.000064mm	Farrelly, Hamer (1993; Rep.No. RJ1213B)
Daphnia magna	48 h (static)	Immobility, EC_{50}	0.00007mm	Farrelly, Hamer, Hill (1984; Rep.No. RJ0377B)
Mysidopsis bahia	96 h (flow trough)	Mortality, EC_{50}	0.000053 mm	Thompson (1986; Rep.No. BL/B/2967)
D. magna	21 d (flow trough)	Offspring production, parental body length, NOEC	0.00000792 mm	Farrelly, Hamer, Hill (1989; Rep.No. RJ0769B)
Algae and aquatic plants				
Pseudokirchneriella subcapitata	96 h (static)	Biomass, E_bC_{50} Growth rate E_rC_{50} NOEC	> 1.05 mm > 1.05 mm 0.51 mm	Thompson (1986; Rep.No. BL/B/2798)
Other aquatic organism				
Chironomus riparius	48 h (static, spiked water)	Immobility, EC_{50}	0.0025 mm	Benyon, Wyeth (2006; Rep.No. T013668-05-REG 2032840)
Chironomus riparius	28 d (static, spiked sediment)	Emergence, NOEC	0.47 mg/kg im	Pfeifle, Wyeth, Dark (2005; rep. No. RJ3676B)

mm…mean measured

im...initial measured

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Study 1

Report: Hill RW (1985)
PP993: Determination of acute toxicity to bluegill sunfish (*Lepomis macrochirus*).
Brixham Environmental Laboratory, Brixham, United Kingdom, unpublished report No. BL/B/2411 (Syngenta file No. ICI993/0524).
Guidelines: US EPA FIFRA Subdivision E, 72-1 ≅ OECD 203
Deviations: None
GLP: Yes
Validity: Acceptable

Material and methods
Test substance: Tefluthrin (PP993); batch no. P14; analysed purity 90.4 % w/w.
Groups of 20 bluegill sunfish (*Lepomis macrochirus*) were exposed to concentrations of tefluthrin in a freshwater flow-through test system for 96 hours at 22 ± 1 ^{o}C. The nominal tefluthrin concentrations were 0.040, 0.071, 0.126, 0.227, 0.403, and 0.706 µg/L. A freshwater control and solvent control (containing 10 mg acetone/L) were also included in the study. Actual concentrations of tefluthrin were determined daily by chemical analysis. Records of mortality and symptoms of toxicity were made at 24, 48, 72 and 96 hours, and at other times during the study.

Findings
Mean measured tefluthrin concentrations ranged from 35.4 % - 50.7 % of the nominal values; therefore the results reported are based on the mean measured concentrations.

Table 124: Tefluthrin: Acute effects on Bluegill sunfish

Mean measured concentration	**Cumulative percentage mortality**			
(µg tefluthrin/L)	**24 h**	**48 h**	**72 h**	**96 h**
Dilution water control	0	0	0	0
Acetone control (10 mg/L)	0	0	0	0
0.016	0	0	0	0
0.036	0	0	0	0
0.047	0	0	0	0
0.091	0	0	0	0
0.18	5	70	90	100
0.25	95	100	100	100
LC_{50} (µg tefluthrin/L)	0.21	0.16	0.14	0.13
(95 % confidence interval)	(0.16 – 0.29)	(0.13 – 0.18)	(0.12 – 0.16)	(0.091 – 0.18)[a]

[a] 98 % confidence limits.

The general symptoms of toxicity observed in this study were loss of equilibrium, quiescence, darkening in colour, erratic swimming and rapid respiration.

Conclusion
Based on mean measured concentrations, the 96-hour LC_{50} value for tefluthrin to bluegill sunfish was 0.13 µg tefluthrin/L.

Study 2

Report: Hill RW (1985)
PP993: Determination of acute toxicity to rainbow trout (*Salmo gairdneri*). Brixham Environmental Laboratory, Brixham, United Kingdom, unpublished report No. BL/B/2410 (Syngenta file No. ICI993/0526).

Guidelines: US EPA FIFRA Subdivision E, 72-1 ≅ OECD 203

Deviations: None

GLP: Yes

Validity: Acceptable

Material and methods

Test substance: Tefluthrin (PP993); batch no. P14; analysed purity 90.4 % w/w.

Groups of 20 rainbow trout (*Oncorhynchus mykiss* formerly *Salmo gairdneri*) were exposed to concentrations of tefluthrin in a freshwater flow-through test system for 96 hours at 12 ± 1 °C. The nominal tefluthrin concentrations were 0.071, 0.126, 0.227, 0.403, 0.706, and 0.945 µg/L. A freshwater control and solvent control (containing 10 mg acetone/L) were also included in the study. Actual concentrations of tefluthrin were determined daily by chemical analysis. Records of mortality and symptoms of toxicity were made at 24, 48, 72 and 96 hours, and at other times during the study.

Findings

Mean measured tefluthrin concentrations ranged from 33.8 - 49.7 % of the nominal values; the results reported are based on the mean measured concentrations.

Table 125: Tefluthrin: Acute effects on rainbow trout

Mean measured concentration	**Cumulative percentage mortality**			
(µg tefluthrin/L)	**24 h**	**48 h**	**72 h**	**96 h**
Dilution water control	0	0	0	0
Acetone control (10 mg/L)	0	0	0	0
0.024	0	5	5	5
0.048	0	0	0	10
0.098	0	45	100	100
0.15	55	100	100	100
0.25	100	100	100	100
0.47	100	100	100	100
LC_{50} (µg tefluthrin/L)	0.15	0.09	0.06	0.06
(95 % confidence interval)	(0.134 – 0.166)	(0.041 – 0.192)	(0.028 – 0.145)	(0.038 – 0.094)

The general symptoms of toxicity observed in this study were loss of equilibrium, hyperactivity and rapid respiration.

Conclusion

The 96-hour LC_{50} value for tefluthrin to rainbow trout was 0.06 µg tefluthrin/L, based on mean measured concentrations.

5.4.1.2 Long-term toxicity to fish

Study 1

Report: Tapp JF, Maddock BG, Harland BJ (1988)
Tefluthrin: Determination of chronic toxicity to fathead minnow

(*Pimephales promelas)* embryos and larvae.
Brixham Environmental Laboratory, Brixham, United Kingdom, unpublished report No. BL/B/3037 (Syngenta file No. ICI993/0549).

Guidelines: US EPA FIFRA, sub-division E, Guideline 72-4 ≅ OECD 210
Deviations: None
GLP: Yes
Validity: Acceptable

Material and methods

Test substance: Tefluthrin technical (PP993); batch P22; analysed purity 94.4 - 95.0 % w/w (two analyses).

Newly fertilised fathead minnow (*Pimephales promelas*) eggs were exposed to maintained concentrations of tefluthrin in a freshwater flow-through test system at 25 ± 1 ^{o}C, with exposure continuing for 28 days post-hatch.

The nominal concentrations were 0.08, 0.04, 0.02, 0.01 and 0.005 µg tefluthrin/L. A dechlorinated dilution water control and solvent control (containing 100 µL triethylene glycol/L) were also included in the study. Actual test concentrations were measured regularly throughout the study using gas liquid chromatography (GLC).

The test exposure was initiated by placing two incubation cups, each containing 20 eggs, into each duplicate tank (giving a total of 40 eggs per duplicate and 80 eggs per concentration). The numbers of live and dead eggs were recorded daily and dead eggs and fry were discarded. When the hatch was complete the number of live, deformed and dead fish in each duplicate tank was recorded. The percentage hatch was then calculated. The "hatch day" was determined to be that day on which the greatest number of fry was released into the progeny tanks (exposure day 4).

The fry were fed regularly on a variety of foods including Pruteen®, brine shrimp larvae (*Artemia*) and Promin®. Daily observations of fry mortality, behaviour and appearance were made and any abnormal effects recorded. The test was terminated at 28 days post-hatch and the surviving fry were counted and individually weighed and measured.

Findings

Actual tefluthrin concentrations measured ranged from 46 % to 72 % of nominal values; therefore the results reported are based on the mean measured concentrations. The results are summarised in Table 126 below.

Table 126: Tefluthrin: Effects on fathead minnow embryos and larvae

Mean measured concentration (µg tefluthrin/L)	% Hatch	% Mean larval survival*	Mean larval length (mm)	Mean larval weight (mg)
Dilution water control	92.6	74.1	17.7	80.6
Solvent control	95.0	83.8	17.4	83.0
0.0035	95.0	91.3	17.6	80.2
0.0063	98.7	82.3	17.3	78.8
0.0096	95.0	81.3	17.5	80.9
0.019	97.5	1.3[+]	19.0 [a+]	109.8 [a+]
0.039	93.8	- [b]	- [b]	- [b]

[*] From initial number of embryos.
[+] Significantly different from control (P = 0.05).
[a] Values are derived from a single surviving larvae.
[b] No larvae surviving.

The 28-day no observed effect concentration (NOEC) based on larval survival, length and weight was 0.0096 µg tefluthrin/L (mean measured concentration).

Conclusion
The 28-day NOEC value for tefluthrin technical to fathead minnow based on larval survival, length and weight was 0.0096 µg tefluthrin/L, based on mean measured concentrations.

Study 2

Report:	Tapp JF, Maddock BG, Gillings E, Stanley RD, Riddle AM (1990) Tefluthrin (Force, ICIA0993): Determination of chronic toxicity to fathead minnow (*Pimephales promelas)* full lifecycle. Brixham Environmental Laboratory, Brixham, United Kingdom, unpublished report No. BL3737/B (Syngenta file No. ICI993/0550).
Guidelines:	US EPA FIFRA, sub-division E, Guideline 72-5
Deviations:	None
GLP:	Yes
Validity:	Acceptable

Material and methods

Test substance: ^{14}C-tefluthrin; sample reference S399; radiochemical purity 99 %; specific activity 2.100 GBq/mmol.

Newly fertilised fathead minnow (*Pimephales promelas*) eggs were exposed to maintained concentrations of tefluthrin in a freshwater flow-through test system at 25 ± 1 ^{o}C, with exposure continuing for 300 days through a complete life-cycle.

The nominal concentrations were 0.0015, 0.003, 0.006, 0.012 and 0.024 µg tefluthrin/L. A dechlorinated dilution water control and solvent control (containing 1.375 µl triethylene glycol/L) were also included in the study. Actual test concentrations were measured regularly throughout the study using liquid scintillation counting (LSC).

Test exposure was initiated by placing two batches of two incubation cups, each containing 25 eggs, into duplicate spawning (adult) tanks (each 42.5 L working capacity) for each treatment (giving a total of 100 eggs per duplicate and 200 eggs per treatment). The numbers of live and dead eggs were recorded daily and dead eggs and dead larvae were discarded. When the hatch was complete, the number of live, deformed and dead fish in each tank was recorded. The percentage hatch was then calculated. Twenty-five larvae, selected at random from each of the two batches in each spawning tank (two tanks per treatment) were then released into progeny tanks (9 L working capacity; one tank per egg batch). The "hatch day" was determined to be that day on which the greatest number of fish larvae hatched, this was exposure day 4. Daily observations of fish larvae mortality, behaviour and appearance were made and any abnormal effects recorded. On exposure days 32 and 60 (post-hatch days 28 and 56 respectively) all surviving fish were photographed to allow the standard length (snout to base of tail) to be determined. The fish were transferred to their respective spawning tanks (adult tanks) on exposure day 60 (post-hatch day 56).

On exposure day 155 each spawning tank was divided into four equal sized breeding compartments. On the same day the fish were individually examined and were randomly paired (1 male and 1 female per breeding compartment). One spawning tile was also introduced into each chamber. These were checked daily and any eggs present were collected for quantification and observation under a microscope. For each duplicate tank, hatchability and early life stage studies were

performed (for the F_1 generation) using spawnings of 50 or more eggs. In these studies, the eggs were checked daily and any dead eggs were noted and discarded. When the hatch was complete, the F_1 generation fish larvae from the hatchability trials were discarded, but those for the early life stage studies were transferred to the corresponding progeny tanks.

The F_1 generation early life stage tests terminated on post-hatch day 56 and measurements of individual fish larvae weight and length were recorded. The fish larvae from all the early life stage studies from each replicate tank were frozen after measurement and stored for subsequent residue analysis.

The adult fish exposure was terminated on exposure day 300. Each fish was sexed, weighed and measured. All fish were then frozen and stored for residue analysis. The last day of the early life stage studies was terminated on day 345.

Findings

LSC analysis of test solutions

The results of the LSC analysis are shown in Table 127 below.

Table 127: Tefluthrin: Mean measured concentrations over the test period of the full lifecycle study with fathead minnow (day –5 to day 322)

Nominal concentration (µg/L)	Mean measured concentration (µg/L)	Number of samples	Mean measured concentration as % of nominal
Dilution water control	-	-	-
Solvent control	-	-	-
0.0015	0.00101	223	67
0.003	0.00200	250	67
0.006	0.00397	239	66
0.012	0.00802	238	67
0.024	0.0171	196	71

Pooling of replicate data

There were no significant inter-replicate differences (at $P = 0.05$) in the F_0 hatch, survival and length data. However, there was a significant difference ($P < 0.001$) in survival of F_1 generation larvae in the top concentration in which they were produced (nominally 0.012 µg tefluthrin/L). Furthermore, the larvae in the B replicate of the solvent control were significantly bigger (length and weight) than the fish in the other solvent control and those in both the dechlorinated water control replicates. Despite these differences it was still deemed acceptable for the purposes of subsequent analysis to pool the replicates of each concentration.

F_0 and F_1 generation survival

The LC_{50} values determined for the F_0 and F_1 generations during the study are summarised in Table 128 below.

Table 128: Tefluthrin: LC_{50} values determined in the fathead minnow full lifecycle study

Generation	Time	LC_{50} value (µg/L) based on mean measured concentrations	95 % confidence limits
F_0	7 days post-hatch	0.0134	0.0127 - 0.0143
	14 days post-hatch	0.0132	0.0125 - 0.0141
	21 days post-hatch	0.0132	0.0125 - 0.014.1
	28 days post-hatch	0.0126	0.0118 - 0.0135
	42 days post-hatch	0.0126	0.0118 - 0.0135
	56 days post-hatch	0.0126	0.0118 - 0.0135
	300 days (exposure)	0.0103	0.0082 - 0.0141
F_1	56 days post-hatch	> 0.00802	-

The lowest observed effect concentrations (LOECs) and no observed effect concentrations (NOECs) determined in this chronic lifecycle toxicity study are summarised in Table 129 below.

Table 129: Tefluthrin: LOEC and NOEC values determined for various parameters during the fathead minnow full lifecycle study

Generation	Days	Parameter	LOEC (µg/L)		NOEC (µg/L)	
			Nominal	Mean measured	Nominal	Mean measured
F_0	4	Hatch	>0.024	>0.0171	≥0.024	>0.0171
	28	Survival	0.024	0.0171	0.012	0.00802
	56	Survival	0.024	0.0171	0.012	0.00802
	28	Length	>0.024 [a]	>0.0171 [a]	≥0.024 [a]	>0.0171 [a]
	56	Length	>0.024	>0.0171	≥0.024	≥0.0171
	150-300	Survival	0.024	0.0171	0.012	0.00802
	300	Length (females)	>0.024	>0.0171	≥0.024	≥0.0171
	300	Length (males)	>0.024	>0.0171	≥0.024	≥0.0171
	300	Weight (females)	>0.024	>0.0171	≥0.024	≥0.0171
	300	Weight (males)	>0.024	>0.0171	≥0.024	≥0.0171
	165-300	Egg Production	0.024	0.0171	0.012	0.00802
F_1	3-5	Hatch	>0.012	>0.00802	≥0.012	≥0.00802
	56	Survival	0.012	0.00802	0.006	0.00397
	56	Length	>0.012	>0.00802	≥0.012	≥0.00802
	56	Weight	>0.012	>0.00802	≥0.012	≥0.00802
		Overall	0.012	0.00802	0.006	0.00397

[a] Significant increases in length or weight relative to the controls were recorded in lower concentrations.

The overall NOEC and LOEC values were 0.00397 and 0.00802 µg tefluthrin/L respectively, based on mean measured concentrations. The critical parameter was survival of F_1 generation larvae to 56 days post-hatch. There was however no significant effect (at P = 0.05) on survival to 56 days post-hatch of F_0 generation larvae at 0.00802 µg tefluthrin/L.

Conclusion

Newly fertilised fathead minnow (*Pimephales promelas*) eggs exposed to maintained concentrations of tefluthrin in a freshwater flow-through test system through-out a complete life-cycle, resulted in a NOEC value of 0.00397 µg tefluthrin/L, based on mean measured concentrations.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Study 1

Report:	Farrelly E, Hamer MJ, Hill IR (1984) PP993: Toxicity to first instar *Daphnia magna.* ICI Agrochemicals, Jealott's Hill Research Station, Jealott's Hill, United Kingdom, unpublished report No. RJ0377B (Syngenta file No. ICI993/0557).
Guidelines:	US EPA-660/3-75-009 ≅ OECD 202
Deviations:	None
GLP:	Yes
Validity:	Acceptable

Material and methods

Test substance: ^{14}C-benzyl labelled tefluthrin; reference D3129-140; specific activity 1.98 GBq/mmol; measured radiochemical purity 98.3 %.

First instar (< 24 hours old) *Daphnia magna* were exposed to ^{14}C-tefluthrin in a static test system for 48 hours at 20 ± 1 °C in two separate, consecutive test runs. The nominal test concentrations were 0.0625, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 µg tefluthrin/L. The control group was maintained in dilution water containing 0.01 % acetone. Four replicate groups were set up for each concentration, with each containing 10 *Daphnia*. Three of the replicate groups were used for *Daphnia* assessments and the fourth was used for the analysis of tefluthrin at 24 hours. Liquid scintillation analysis was used to measure the concentration of tefluthrin in samples obtained at zero time, 24 hours and 48 hours. At zero time, 24 hours (in test 1 only) and 48 hours, 100 mL samples were taken from representative treatments (from the prepared concentrations at zero time; from the 'fourth' replicate vessel at 24 hours; and from the bulked contents of the three replicates assessed at 48 hours) and extracted into hexane and analysed using TLC for characterisation of extracted activity. The numbers of *Daphnia* affected (immobilised or showing only minor movements) were recorded after 3, 9, 24 and 48 hours.

Findings

Total radioactivity in the water at zero time was approximately 80 % of nominal. The measured concentration declined to approximately 30 % and 20 % of nominal after 24 and 48 hours, respectively. This decrease may have been due to adsorption of tefluthrin onto the walls of the test vessels, as has been commonly observed with other pyrethroids. The majority (> 78 %) of the radioactivity in the water was extracted into hexane. However, losses ranging from 10 – 80 % occurred during the sample preparation for quantification of tefluthrin by TLC. No defined individual radio-components other than ^{14}C-tefluthrin (which accounted for 60 – 100 % of the radioactivity applied to the TLC plate) were detected. Results were based on the mean measured concentrations as determined by liquid scintillation.

Table 130: Tefluthrin: Effects on first instar *Daphnia magna*

Nominal concentration (µg tefluthrin/L)	Mean measured concentration 0-48 hours [a] (µg/L)	No. affected at 48 hours (30 *Daphnia* per concentration)	48-hour EC_{50} [b] (with 95% confidence limits) (µg/L)
Test 1			
Control	-	0	0.07 (0.05-0.10)
0.0625	0.02	4	
0.125	0.05	11	
0.25	0.09	20	
0.5	0.18	23	
1.0	0.42	28	
2.0	0.85	28	
4.0	1.9	30	
8.0	4.3	30	
Test 2			
Control	-	0	0.08 (0.06-0.09)
0.0625	0.02	2	
0.125	0.04	6	
0.25	0.09	20	
0.5	0.21	26	
1.0	0.43	30	
2.0	0.82	29	
4.0	1.8	30	
8.0	3.9	30	
			Mean 0.07

[a] The control samples were used as the background readings. The limit of determination was calculated to be 0.3 dps (degradations per second) above a mean background of 0.7 dps, which is equivalent to 0.006 µg/L.

[b] Based on mean measured concentrations.

Conclusion

The 48-hour EC_{50} value (mean of two tests) of tefluthrin to *Daphnia magna* was 0.07 µg tefluthrin/L, based on mean measured concentrations in a static test system.

Study 2

Report: Farrelly E, Hamer MJ (1993) Tefluthrin: Acute toxicity to first instar *Daphnia magna*. Zeneca Agrochemicals, Bracknell, Berkshire, United Kingdom, unpublished report No. RJ1213B (Syngenta file No. ICI993/0566).

Guidelines: EPA-540/9-85-005; OECD Guideline (1981) *Daphnia* sp. 14 day reproduction test (including an acute immobilisation test)

Deviations: None

GLP: Yes

Validity: Acceptable

Material and methods

Testsubstance: Tefluthrin analytical standard; batch no. 993/01/016; analysed purity 99.1 %.

First instar *Daphnia magna*, less than 24 hours old at the start of the test, were exposed to concentrations of tefluthrin for 48 hours in a static test system at approximately 20 °C, with a 16 hour daily photoperiod at approximately 700 lux. The test concentrations were: control, 0.037, 0.111, 0.333, 1.00 and 3.00 µg/L. Twenty *Daphnia* were used per treatment, held together in a test solution volume of 20 L. Toxicity was assessed after 48 hours.

Findings
The measured concentrations of tefluthrin ranged from 62 – 107 % at 0 hours and 40 – 70 % at 48 hours, with means in the range 53 – 77 %; results presented are based on mean measured values. The results are shown in Table 131.

Table 131: Tefluthrin: Effects on first instar *Daphnia magna*

Nominal concentration (µg tefluthrin/L)	Mean measured concentration (µg tefluthrin/L)	Number affected at 48 hours (20 *Daphnia* per concentration)
Control	< 0.01	0
0.037	0.024	2
0.111	0.086	12
0.333	0.195	20
1.00	0.532	20
3.00	2.02	20

The 48-hour EC_{50} value was calculated to be 0.064 µg/L (95 % confidence limits not stated), based on mean measured concentrations.

Conclusion
The 48-hour EC_{50} value for tefluthrin on *Daphnia magna* was 0.064 µg/L, based on mean measured concentrations in a static test system.

Study 3

Report: Thompson RS (1986)
Tefluthrin: Determination of acute toxicity to mysid shrimps (*Mysidopsis bahia*).
Brixham Environmental Laboratory, Brixham, United Kingdom, unpublished report No. BL/B/2967 (Syngenta file No. ICI993/0559).
Guidelines: ASTM E729-80 (1980).
Deviations: None
GLP: Yes
Validity: Acceptable

Material and methods
Test substance: ^{14}C-tefluthrin; batch 86-J13; radiochemical purity 98.5 %; specific activity 2.1 GBq/mmol.
Marine mysid shrimps (*Mysidopsis bahia*), 4 - 5 days old at the start of the test, were exposed to concentrations of ^{14}C-tefluthrin for 96 hours in a seawater flow-through test system at 25 ± 1 °C, with a 14 hour daily photoperiod. The test concentrations were: control, solvent control, 0.010, 0.018, 0.032, 0.056 and 0.1 µg/L. Twenty mysids were used per treatment, distributed to give 5 mysids in each of 4 retention chambers within each 14 L test vessel. Toxicity was assessed after 24, 48, 72 and 96 hours.

Findings
The mean measured concentrations of tefluthrin ranged from 50 to 75 % of nominal; results presented are based on mean measured values.

Table 132: Tefluthrin: Acute effects on mysid shrimps

Nominal concentration (µg tefluthrin/L)	Mean measured concentration (µg tefluthrin/L)	Percentage mortality at 96 hours (20 mysids per concentration)
Control	-	0
Solvent control	-	0
0.010	0.007	0
0.018	0.009	0
0.032	0.024	0
0.056	0.038	15
0.1	0.073	85

The 96-hour EC_{50} value was calculated to be 0.053 µg/L (95 % confidence intervals 0.046 to 0.063), based on mean measured concentrations.

Conclusion
The 96-hour EC_{50} value for tefluthrin on the mysid shrimp *Mysidopsis bahia* was 0.053 µg/L, based on mean measured concentrations in a seawater flow-through system.

5.4.2.2 Long-term toxicity to aquatic invertebrates

Report: Farrelly E, Hamer MJ, Hill IR (1989)
PP993: Tefluthrin: *Daphnia magna* life-cycle study using a flow-through system.
ICI Agrochemicals, Jealott's Hill Research Station, Jealott's Hill, United Kingdom., unpublished report No. RJ0769B (Syngenta file No. ICI993/0572).
Guidelines: US EPA Standard Evaluation Procedure (1986) US EPA 540/9-86-141 ≅ OECD 202
Deviations: None
GLP: Yes
Validity: Acceptable

Material and methods
Test substance: ^{14}C-phenyl labelled tefluthrin; reference 89-J2; radiochemical purity ≥ 95 %; specific activity 2.293 GBq/mmol.

The chronic toxicity of tefluthrin to *Daphnia magna* (< 24 hours old) was determined in a 21-day study conducted at 20 ± 2 °C. *Daphnia* were exposed in a flow-through system using ^{14}C-radiolabelled tefluthrin to facilitate analysis. The test concentrations were nominally 0.00128, 0.0032, 0.008, 0.02 and 0.050 µg tefluthrin/L, plus a solvent control and a reconstituted water control. Ten vessels were prepared at each test concentration. The test vessels used were 400 mL glass beakers with capacity of 200 mL to an overflow (guarded by a retaining mesh). The test chemical was dosed in triethylene glycol (TEG) at approximately 100 µL/day into the dilution water flow. Radiolabelled material was used to allow rapid reading of the levels of chemical to ensure flow rates were correct. The solvent control was also dosed with TEG at approximately 100 µL/day.

At the start of the study, seven replicates (A-G) at each concentration were allocated a single first instar *Daphnia* (to produce data on growth and reproduction) and the remaining 3 vessels (H-J) received five first instar *Daphnia* (for F_0 generation survival data only). Assessments of survival,

growth and reproduction were made three times per week throughout the study. On assessment days, the *Daphnia* originally introduced in all chambers A-J were assessed as alive or dead. In vessels A-G any young produced were removed by sieving and counted prior to being discarded. Any young produced in chambers H-J were removed from the vessels and discarded without being counted. On day 21 the length of the surviving adult females from chambers A-G was measured.

The total ^{14}C-radiolabelled tefluthrin equivalents were determined 3 times a week at each concentration by extraction into hexane and analysed by liquid scintillation counting (LSC). Once a week, samples were taken from three replicate test chambers at the highest, middle and lowest concentrations. On study days 0, 7, 14 and 21, samples were taken from representative test concentrations for characterisation of the radioactivity by thin layer chromatography using 2 solvent systems (hexane:diethyl ether (10:1) and methanol:water:acetic acid (7:2:1).

Findings

The nominal concentrations are based on a flow rate of 100 µL TEG/day from the syringes. Mean measured concentrations ranged from 35 % to 47 % of nominal values. All results are therefore based on mean measured concentrations. Results from the characterisation of the radioactivity in the water revealed that at all sample times ≥ 34 % of the radioactivity applied to the plate co-chromatographed with tefluthrin.

The effects of tefluthrin on reproduction and growth are summarised in Table 133.

Table 133: Tefluthrin: Effects on *Daphnia magna* reproduction and growth

Nominal concentration (µg tefluthrin/L)	Mean (days 0-21) measured concentration (µg tefluthrin/L)	F_0 mortality in chambers H-J (N = 15)	Total young per chamber	Young per female reproductive day	*Daphnia* length at day 21 (mm)
Control	-	2	55.1[a]	4.60[a]	4.47
Solvent Control	-	2	68.1	5.68	4.41
0.00128	0.00045	1	67.9	5.65	4.39
0.0032	0.00142	2	69.9	5.82	4.40
0.008	0.00292	1	66.7	5.56	4.40
0.02	0.00792	2	65.9	5.49	4.41
0.05	0.0236	14	3.3[+*b]	0.47[+*b]	- [c]

[+] Significantly different from control (P = 0.01).
[*] Significantly different from the solvent control (P = 0.01).
[a] Values are based on all 7 chambers. However, the adult *Daphnia* in chamber F died on day 5.
[b] Values are based on all 7 chambers. However, the adult *Daphnia* in chambers D and G died on days 5 a and 7 respectively.
[c] No *Daphnia* alive.

The 21-day LC_{50} (based on survival data from test vessels H-J) was 0.0144 µg tefluthrin/L (95 % confidence intervals of 0.0029 - 0.0198 µg/L). The no observed effect concentration based on *Daphnia* reproduction and *Daphnia* length (data generated from chambers A-G) was 0.00792 µg/L.

Conclusion

The *Daphnia magna* 21-day LC_{50} value was 0.0144 µg tefluthrin/L and the NOEC value for reproductive effects was 0.00792 µg tefluthrin/L, based on mean measured concentrations in a flow-through system.

5.4.3 Algae and aquatic plants

Report: Thompson RS, Smyth DV (1986)
PP993: Determination of toxicity to the green alga *Selenastrum capricornutum*.
Brixham Environmental Laboratory, Brixham, United Kingdom, unpublished report No. BL/B/2798 (Syngenta file No. ICI993/0576).
Guidelines: OECD 201
Deviations: None
GLP: Yes
Validity: Acceptable

Material and methods

Test substance**:** Tefluthrin technical (PP993); reference code RS/144/C; analysed purity 93.0 %.
Pseudokirchneriella subcapitata (formerly *Selenastrum capricornutum*) was inoculated at 1.0×10^4 cells/mL and cultured in concentrations of tefluthrin technical in an aqueous culture medium for 96 hours at 24.1 - 24.2 °C. Six replicate cultures of the solvent control (0.1 mL acetone/L) and triplicate cultures of the control (culture medium only) and each test concentration were used. The nominal concentrations of the test solutions were 0.18, 0.32, 0.56, 1.0 and 1.8 mg tefluthrin/L. Actual concentrations of tefluthrin were determined at 0 and 96 hours (from test vessels incubated without algae). Algal cell numbers were determined with a Coulter counter at 24, 48, 72 and 96 hours.

Findings
The mean measured tefluthrin concentrations at the start of the study ranged from 89 % - 122 % of the nominal values; after 96 hours the measured concentrations ranged from 2 – 28 % of nominal. Results were based on mean measured concentrations.
The results are summarised in Table 134.

Table 134: Tefluthrin: Effects on *Pseudokirchneriella subcapitata*

Nominal concentration (mg tefluthrin/L)	Mean measured concentration (mg tefluthrin/L)	Mean area under growth curve	Mean growth rate
Control	-	386.2	1.492
Solvent control	-	412.0	1.513
0.18	0.11	353.7 ** [a]	1.467 ** [a]
0.32	0.17	368.1 * [a]	1.472 ** [a]
0.56	0.28	351.6 ** [a]	1.472 ** [a]
1.0	0.51	275.2 ** [b]	1.399 ** [b]
1.8	1.05	329.0 ** [b]	1.447 ** [c]

* Significant difference from control (at P = 0.05); [a] significant difference from solvent control only; [b] significant difference from both controls.
** Significant difference from control (at P = 0.01); [a] significant difference from solvent control only; [b] significant difference from both controls.
[c] Significant difference from solvent control at P = 0.01 and from control at P = 0.05.

At the maximum tefluthrin concentration tested, the area under the growth curve was reduced by 20 % compared with the solvent control. Therefore the 96-hour E_bC_{50} value based on mean measured concentrations was > 1.05 mg tefluthrin/L. Significant reductions (at P = 0.05) in growth curve areas were obtained at all test concentrations compared with the solvent control. However,

compared with the dilution water control, significant reductions were obtained only at a mean measured concentration of ≥ 0.51 mg tefluthrin/L. Reductions in growth curve area may have been due to the physical effects of undissolved test substance, since all the concentrations tested were in excess of the solubility of the material. There was no clear concentration-related response in the growth reductions.
The growth rate at the maximum concentration tested was reduced by 4 % compared with the solvent control. Therefore the E_rC_{50}, based on mean measured concentrations, was > 1.05 mg tefluthrin/L. The significant differences in growth rate identified were similar to those described for areas under the growth curve.

Conclusion
The 96-hour E_bC_{50} and E_rC_{50} values for tefluthrin to *Pseudokirchneriella subcapiatata* (formerly *Selenastrum capricornutum*) were both > 1.05 mg/L, based on mean measured concentrations.

5.4.4 Other aquatic organisms (including sediment)

Study 1

Author:	Benyon K., Wyeth K.
Title:	Tefluthrin technical: Acute toxicity to *Chironomus riparius* under static conditions
Date:	25.04.2006
Doc ID:	report no.: T013668-05-REG 2032840, SYN ICI993/0980 BVL registration number: 1864767
Guidelines:	OECD 202
GLP:	Yes
Validity:	Acceptable

The acute toxicity of tefluthrin technical to *Chironomus riparius* was determined. The organisms were exposed to nominal concentrations of 8, 4, 2, 1, 0.5, 0.25 µg tefluthrin/L, together with a dilution

Materials and Methods
Test Material: Tefluthrin technical, off-white solid, lot/batch P25, purity: 91.9 % w/w, stable for the test conditions and period of use in the study, reanalysis March 2006

Test concentrations:
Dilution water control, solvent control (acetone) and nominal formulation concentrations of 0.25. 0.5, 1.0, 2.0, 4.0, 8.0 µg tefluthrin/L, positive control acetone

The concentrations of tefluthrin in the test solutions were measured at 0 and 48 hours using gas chromatography with mass spectroscopy detection in chemical ionisation mode (GC/MSD CI).

Species:
Chironomus riparius, continuous laboratory cultures, originally from Brixham Environmental Laboratory, Brixham, Devon, TQ5 8BA, UK.

Static exposure regime, two replicates each containing 5 organisms, 10 chironomids per test concentration. Fine fish food extract (Tetramin™), containing 3563 mg total organic carbon /L; 200°µL per vessel at 0 and 24 hours.

Test temperature 19.4 to 19.7 °C in the test vessels, pH range 7.46 to 7.90, dissolved oxygen: 85 to 100 % air saturation value, total hardness of dilution water 258 mg/L $CaCO_3$, lighting: 16 hours fluorescent light and 8 hours dark with 30 minute dawn and dusk transition periods. 606-740 lux. Length of test: 48 hours.

The test was performed in 250 mL glass beakers, covered with watch glasses, filled with 100 mL of test medium. The chironomids were randomly distributed among the test vessels at test initiation.

A stock solution with a nominal concentration of 160 mg/L was prepared by dissolving 32.29 mg of the test item completely in 200 mL of acetone. A series of stock solutions were then prepared by serial dilution (with acetone) of the first stock. To prepare the test solutions, 25 µL of the relevant stock solution was spiked into 500 mL of dilution water. All test solutions were clear and colourless.

The immobility of the chironomids was determined by visual observations after 24 and 48 hours of exposure. Those organisms not able to swim within 15 seconds after applying a gentle stimulus were considered to be immobile. At the start and end of the test, pH dissolved oxygen and water temperature were determined in each test concentration and the control. The temperature within the room was monitored in a vessel filled with deionised water, throughout the exposure period, by means of a data logger.

Results

Measured concentrations at the start of the test ranged from 76 to 121 % of the nominal values. At the end of the test, measured concentrations ranged between 8 and 22 % of the nominal values. The results are based on mean measured concentrations. The limit of quantification (LOQ) in this study was 0.01 µg tefluthrin/L.

The numbers of *C. riparius* immobilised after 24 and 48 hours are given in Table 135.

Table 135: Effects of tefluthrin technical on *Chironomus riparius* in an acute static test

Mean measured conc.	Chironomids immobilised after 24 h (out of 10 tested)		Chironomids immobilised after 48 h (out of 10 tested)	
(µg as/L)	No.	%	No.	%
0	0	0	0	0
0 (solvent control)	0	0	1	10
0.176	0	0	0	0
0.322	0	0	0	0
0.565	0	0	0	0
1.17	1	10	2	2
2.35	1	10	4	40
3.83	0	0	8	80
LC_{50} 24 h	>3.83			
LC_{50} 48 h	2.5 (1.7-3.9)			

Conclusions

The 48-hour EC_{50} of tefluthrin technical to *Chironomus riparius* was 2.5 µg as/L based on mean measured concentrations of test item.

Study 2

Author:	Pfeifle, V., Wyeth, K., Dark, R.
Title:	Tefluthrin technical: Effects on the development of sediment-dwelling larvae of *Chironomus riparius* in a water-sediment system
Date:	2005
Doc ID:	report no.: RJ3676B, SYN ICI993/0868 BVL registration number: 1864768
Guidelines:	OECD 218
GLP:	Yes
Validity:	Acceptable, with restrictions

The effects of ASF611C (tefluthrin technical) on the development of *Chironomus riparius* was determined. This study was run with nominal concentrations of 0.15, 0.3, 0.6, 1.2 and 2.4 mg ASF611C/kg dry weight of sediment together with a dilution water and solvent control.

Materials and Methods

Test material: ASF611C (tefluthrin technical), off-white solid, lot/batch P25, purity 91.9 % w/w, stable for the test conditions and period of use, reanalysis March 2006

Test concentrations:
Dilution water control, solvent control and nominal concentrations of 0.15, 0.3, 0.6, 1.2 and 2.4 mg tefluthrin/kg dry weight of sediment. Vehicle and/or positive control was acetone

Initial measured concentrations were 0.12, 0.23, 0.47, 1.0 and 2.0 mg tefluthrin/kg dry weight of sediment.

Species: *Chironomus riparius*, fed with Tetramin suspension (0.5-1.0 mg per larvae per day), in-house culture, originally from Brixham Environmental Laboratory, Brixam, Devon, TQ5 8BA, UK

Test temperature 18-22 °C, temperature-controlled incubator with a temperature range 19.9 to 21.1 °C, pH range of overlying water 7.74 to 8.37, dissolved oxygen of overlying water 74.4 to 109.4 % air saturation values, total hardness: 241 and 251 mg $CaCO_3$/L for the two medium batches used at the start of the test. 227 mg $CaCO_3$/L for the control and 225 mg $CaCO_3$/L for the highest test concentration at the end of the test. Photoperiod 16 hours fluorescent light and 8 hours dark with 30 minute dawn and dusk transition periods.

Artificial Sediment:
4.5 % sphagnum peat (air dried and finely ground), 20 % kaolin clay (kaolinite content >30 %), 75.5 % industrial sand (>50 % of the particles between 50 and 200 µm), Calcium carbonate (to adjust the pH). The organic carbon content of the final sediment mixture was 2.3 % (determined by wet oxidation), sediment moisture content 41 %

Length of test: 28 days

A stock solution was prepared by dissolving 121.23 mg of tefluthrin technical in 25 mL acetone (nominal concentration of 4800 mg/L). Aliquots of this solution were diluted with acetone to make application solutions for the test vessels with concentrations of 2400, 1200, 600 and 300 mg/L.

First instar larvae of *Chironomus riparius* were exposed for 28 days to the test item tefluthrin technical in glass jars (500 mL, 7.5 cm in diameter) covered with parafilm filled with 50 g dry weight of sediment and 250 mL of test medium. The test vessels were spiked three days before the larvae were introduced by adding 25 µL of the application solutions to the water column to give

nominal concentrations of 0.15, 0.3, 0.6, 1.2 and 2.4 mg tefluthrin technical/kg dry weight of sediment. The test vessels were then shaken and placed on a rolling mill for two hours to ensure the even distribution of test material throughout the water and sediment. The test vessels were then left to stand for three days and aerated four hours before larvae were introduced. Eighty chironomid larvae per test concentration were used with four replicates of twenty larvae in each. The larvae were randomly distributed amongst the test vessels. Throughout the test the larvae were fed between 0.5 and 1.0 mg Tetramin fish food suspension per larvae per day. From day one the vessels were gently aerated through a glass Pasteur pipette fixed above the sediment layer.

The concentrations of tefluthrin technical were determined by analysing the overlying water and sediment by GC-MSD using one additional replicate per treatment at day 0 and using one replicate from the biological phase of the test at test termination.

From day 10 of the test, a daily count of emerged midges was made and their sex was recorded. Once emerged, the adults were discarded. Visible pupae that failed to emerge were counted and recorded. Any signs of chemical effect on the larvae, pupae or emerged midges were recorded. The emergence ratio and development rate were calculated from the total number of emerged male and female adults and from the time of emergence.

At the start and at the end of the test and on a weekly basis the pH and dissolved oxygen were measured in each test vessel and water temperature was recorded continuously by means of a data logger. The hardness was measured of the medium batches used at the start of the test and of the overlying water in the control and the highest test concentration at the end of the test.

Results

Measured concentrations in the sediment at the start of the test (day 0) ranged from 84-92 % of the nominal values. At the end of the test (day 28) 78-88 % of the nominal values were found in the sediment. Measured concentrations at the start of the test in the overlying water ranged from 0.1-0.2 % of the nominal applied. At the end of the test in the overlying water 0.03-0.1 % of the nominal applied was measured. Results are reported based on initial measured concentrations in the sediment.

Table 136: Effects of tefluthrin technical on the reproduction of *Chironomus riparius*

Parameter	Enpoint	Value
		(mg tefluthrin/dry weight sediment)
Emergence ratio	NOEC	0.47
Development rate females	NOEC	1.0
Development rate males, females pooled	NOEC	0.47
Overall 28 day	NOEC	0.47

Conclusions

A critical point in the study is the larvae feeding with 0.5 - 1.0 mg Tetramin fish food suspension per larvae per day. Tefluthrin is strongly sorbed to the sediment and a feeding with uncontaminated food reduced the exposition of the animals. Nevertheless, based on initial measured concentrations of tefluthrin, the overall 28 day NOEC for emergence ratio and development rate can be considered 0.47 mg/kg of dry weight of sediment.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

Tefluthrin produces acute $L(E)C_{50}$ values in concentrations > 0.00001 < 0.0001 mg/L for fish, crustaceans and > 1 mg/L for algae, and produces chronic NOEC values in concentrations > 0.000001 < 0.00001 mg/L for fish and crustaceans and > 0.1 < 1 mg/L for algae.

The results of the test on the biodegradation of tefluthrin in the water/sediment system and abiotic degradation show that tefluthrin is considered not rapidly degradable (a degradation > 70 % within 28 days) for purposes of classification and labelling.

Tefluthrin has a log $K_{o/w}$ of 6.4 (20°C). The experimentally derived steady state BCF of 1400 L/Kg ww for tefluthrin related to parent and whole fish is above the trigger of 100 (criterion for bioaccumulation potential conform Directive 67/548/EEC) for not rapidly degradable substances and is also above the trigger of 500 (criterion for bioaccumulation potential conform Regulation EC 1272/2008) for not rapidly degradable substances.

CLP- Acute aquatic hazards

According to the criteria of the CLP Regulation, a substance is classified for aquatic acute toxicity if in an aquatic acute toxicity study, an $L(E)C_{50}$ of ≤ 1 mg/l is obtained for any of the three trophic levels fish, invertebrates and algae/aquatic plants.

The lowest $L(E)C_{50}$ obtained for tefluthrin are > 1.05, 0.000053 and 0.00006 mg/L in algae, invertebrates and fish, respectively. Tefluthrin therefore fulfils the criteria for classification as Aquatic Acute Cat. 1.

An M-factor of 10000 for acute toxicity is proposed based on $L(E)C_{50}$ values of 0.000053 and 0.00006 mg/L in invertebrates and fish, respectively. ($0.00001 < L(E)C_{50} \leq 0.0001$ mg/L)

CLP - Aquatic chronic hazards

According to the criteria of the 2nd ATP to the CLP Regulation, when NOEC values are available for all trophic levels, a substance is classified for aquatic chronic hazards if a NOEC or EC_{10} of ≤ 1 mg/L is obtained in a long-term aquatic toxicity study. The assignment of a hazard category depends on the NOEC value and whether the substance is rapidly degradable or not.

Tefluthrin is considered not rapidly degradable (see section 5.1.3). NOEC values for tefluthrin are available for all trophic levels. The lowest NOEC is 0.00000397 mg/L obtained for fish and 0.00000792 mg/L for invertebrates. Tefluthrin therefore fulfils criteria for classification as Aquatic Chronic Cat.1.

An M-factor of 10000 for chronic toxicity is proposed based on the NOEC value of 0.00000397 mg/L in fish and 0.00000792 mg/L invertebrates, respectively. ($0.000001 < NOEC \leq 0.00001$ mg/L)

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Tefluthrin fulfils the criteria for classification as Aquatic Acute 1 with an M-factor of 10000.

Tefluthrin fulfils the criteria for classification as Aquatic Chronic 1 with an M-factor of 10000.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

The DS proposed to classify the substance as Aquatic Acute 1 (H400) with an M-factor of 10 000 and Aquatic Chronic 1 (H410) with an M-factor of 10 000. The classification was based on the substance being not rapidly degradable, potential for bioaccumulation and very high toxicity in aquatic organisms. The lowest acute toxicity value was a 96 hour EC_{50} of 0.000053 mg/l for an invertebrate *Mysidopsis bahia* and the lowest chronic toxicity value was a 345 day NOEC of 0.00000397 mg/l for fish *Pimephales promelas*.

Degradation

Terflutrin hydrolysed slowly in water under environmental conditions. In a study using both [U-^{14}C]-phenyl-tefluthrin and [1-^{14}C]-cyclopropyl tefluthrin in sterile aqueous buffer solutions at pH 25 °C the substance was stable to hydrolysis at pH 5 and pH 7 throughout the 30 day test duration. At pH 9 hydrolysis products Compound 1a and Compound II were found at average levels of 34.6 % (([1-^{14}C]-cyclopropyl label) and 21.4 % ([U-^{14}C]-phenyl label) respectively after 30 days. Recovery of radioactivity was not always high assumably due to predominantly tefluthrin residues bound to glass.

In a photodegradation study following GLP terfluthin degraded with a DT_{50} > 31 days. The photolysis of both [U-^{14}C]-phenyl-tefluthrin and [1-^{14}C]-cyclopropyl tefluthrin was studied at 25° ± 1°C in aqueous solutions at pH7. Recoveries of radioactivity ranged from 92.0 to 105.5 %. There were no major photodegradation products other than trans-tefluthrin which is formed in amounts of between 21.2 and 37.2 % after 31 days irraditation. There were a significant amount, between 40.7 and 57.7 of applied radioactivity after 31 days, of volatile loss during the experiment.

There was no ready biodegradability test available.

Two water-sediment tests were available. The first water/sediment test was carried out according to a SETAC Guideline and GLP. Both [U-^{14}C]-phenyl-tefluthrin and [1-^{14}C]-cyclopropyl tefluthrin were applied to two water-sediment systems, Kromme Rijn and TNO Zuidpolder. The systems were incubated at 20 °C. Samples of both water and sediment were taken for analysis at 0, 7, 14, 28, 42, 56, 70 and 84 days after application. Recovery of radioactivity varied between 73 to 92 % of applied radioactivity (AR). This deviation from the test guideline is not considered to compromise the validity of the test. Tefluthrin rapidly dissipated from the aqueous phase by adsorption to sediment. Levels of degradation products in the water phase increased with time so that between 18 and 41 % of AR was present after 12 weeks. Compound 1a and Compound II were identified as degradation products in both systems. Compound IV was found to be the major degradation product in the water phase in both systems. Compound Ia was found at increasing levels up to 12 weeks after treatment predominantly in the water phase. Compound II was found at lower levels and was generally found at higher levels in the sediment rather than water. Other degradates for example Compounds III and V were present in small amounts. Mineralisation in both systems was little with the maximum of 6 % of $^{14}CO_2$ detected 12 weeks after application. The DT_{50}s calculated with ModelManager v1.1 are the following:

Table 1. Teflutrin DT_{50} values in two water-sediment systems

Water-Sediment System	Compartment	Simple Exponential Model
Kromme Rijn	Sediment	203
	Water-Sediment	146
TNO Zuidpolder	Sediment	204
	Water-Sediment	60

In the second water-sediment test performed according to the Canadian Trade Memorandum T-1-255 Guideline and GLP both [U-^{14}C]-phenyl-tefluthrin and [1-^{14}C]-cyclopropyl tefluthrin

were applied to a water-sediment system. The systems were incubated at temperatures 20°C ± 2°C and 5°C ± 2°C. Both aerobic and anaerobic conditions were used. Organic matter content in the the sediment 20.3% exceeds the amount of 12.9% stated in the guideline which is, however, considered not to compromise the validity of the study. At 20 °C no major degradation products (>10 %) were found. Loss of teflutrin from the water phase to sediment and by volatile loss was rapid with the average of only 11% being found at 0 day after treatment (DAT) in the aerobic studies. Volatility was significant with level up to 20% (180 DAT) under aerobic conditions. The most abundant degradatation product, i.e. Compound V, reached a peak total of 8.5% in water and 6.6% in the sediment 30 DAT in aerobic conditions. Other degradation products in aerobic systems were Compound IV and unidentified metabolites M2 and M3. Mineralisation was significant under aerobic conditions reaching 48.6% 120 DAT for cyclopropyl label and 32.3 % for phenyl label. At the lower temperature of 5°C under aerobic conditions, dissipation of tefluthrin from the water to the sediment was less rapid and volatile losses were much reduced. Mineralisation was also much reduced: 21.5% for cyclopropyl label and only 4.1% for phenyl label. Levels of Compound IV reached 22.6% by 360 DAT whereas Compound V reached maximum levels of 7.9% in sediment and 2.7% in water 360 DAT.

Table 2. Teflutrin DT_{50} and DT_{90} values in a water-sediment system at 20 °C

	[1-^{14}C]-cyclopropyl label		**[U-^{14}C]-phenyl label**	
	DT50	**DT90**	**DT50**	**DT90**
Water-sediment	58 days	190 days	51 days	185 days
Sediment only	57 days	189 days	59 days	195 days

The DS concluded that tefluthrin is not rapidly degradable based on the information above.

Bioaccumulation

In the bioaccumulation study where bluegill sunfish (*Lepomis macrochirus*) were exposed to ^{14}C-methylene labelled tefluthrin (OECD TG 305E and GLP), a steady state BCF of 1400 L/kg ww (whole fish based on tefluthrin parent compound) was measured. Lipid normalization was not applied and no information on the lipid content of the test fish was included in the CLH Report. The measured log P_{ow} was 6.4 (20 °C). Thus tefluthrin can be considered as potentially bioaccumulative.

Aquatic toxicity

There were acute toxicity data available from two fish studies, two *Daphnia magna* studies, one *Mysidopsis bahia* study, one algae study and one *Chironomus* study. Chronic toxicity data was available from two fish studies, one *Daphnia magna* study, one algae study and one sediment *Chironomus* study.

Table 3. The lowest aquatic toxicity values for tefluthrin

Substance and purity	**Species**	**Test Guideline**	**Endpoint**	**Toxicity value (mg/L)**	**Conditions**
Tefluthrin 90.4 % w/w	Oncorhynchus mykiss	US EPA FIFRA Subdivision E, 72-1; OECD 203; GLP	96h LC50	0.00006	flow through, mm (33.8-49.7% of nominal)
Teflutrin 90.4 % w/w	Lepomis macrochirus	US EPA FIFRA Subdivision E, 72-1; OECD 203; GLP	96h LC50	0.00013	static, mm (35.4-50.7% of nominal)
Tefluthrin 94.4-95.0 % w/w	Pimephales promelas	US EPA FIFRA Subdivision E, 72-4; OECD 210; GLP	28d NOEC (length and weight, larval survival)	0.0000096	flow through, mm (46-72% of nominal)

^{14}C-tefluthrin 99%	**Pimephales promelas**	**US EPA FIFRA Subdivision E, 72-5, GLP**	**345 d NOEC (survival of F1 generation larvae 56 days post hatch)**	**0.00000397**	**full lifecycle test, flow through, mm (66-71% of nominal)**
Tefluthrin 99.1%	Daphnia magna	EPA-540/9-85-005, OECD Daphnia 14 day study, GLP	48h EC50 (immobility)	0.000064	static, mm (53-77% of the nominal)
^{14}C labelled terfluthrin 98.3%	Daphnia magna	US EPA -660/3-75-009, OECD 202, GLP	48h EC50 (immobility)	0.00007	static, mm (at the start ~80% and at the end ~20% of the nominal)
^{14}C-tefluthrin 98.5%	**Mysidopsis bahia**	**ASTM E729-80, GLP**	**96h EC50 (mortality)**	**0.000053**	**marine, flow through, mm (50-75% of nominal)**
^{14}-C-phenyl labelled tefluthrin, ≥95%	Daphnia magna	US EPA 540/9-86-141; OECD 202/Part II (1984), GLP	21d NOEC (offspring production, parental body length)	0.00000792	flow through, mm (35-47% of nominal)
Tefluthrin 93.0%	Pseudokirchneriella subcapitata	OECD 201, GLP	96h ErC50 96h NOEC	>1.05 0.51	static, mm (at the start 89-122% and at the end 2-28% of nominal)
Tefluthrin 91.9%	Chironomus riparius	OECD 202, GLP	48h EC50 (immobility)	0.0025	static, spiked water, mm (at the start 76-121% and at the end 8-22%)

mm = mean measured

The lowest acute toxicity value is for *Mysidopsis bahia* from a study carried out according to an ASTM Guideline and GLP. The nominal concentrations were 0.000010, 0.000018, 0.000032, 0.000056 and 0.0001 mg/L. Mean measured concentrations were 50 to 75 % of the nominal namely 0.000007, 0.000009, 0.000024, 0.000038 and 0.000073 mg/L. The 96-hour EC50 value for tefluthrin on the mysid shrimp *Mysidopsis bahia* was 0.000053 mg/L based on mean measured concentration. Two acute *Daphnia* study EC_{50}s were also in the range of 0.00001 mg/L < EC_{50} ≤ 0.0001 mg/L.

The lowest chronic toxicity value comes from a full lifecycle study with fathead minnow (*Pimephales promelas*) performed according to US EPA Guideline and GLP. The nominal concentration were 0.0000015, 0.000003, 0.000006, 0.000012 and 0.000024 mg/L. Actual test concentrations were measured regularly throughout the study. Mean measured concentration over the test period were 0.00000101, 0.00000200, 0.00000397, 0.00000802 and 0.0000171 mg/L that is from 66 to 71 % of the nominal. The overall NOEC value was 0.00000397 mg/L based on mean measured concentrations.The critical parameter was

survival of F_1 generation larvae to 56 days post-hatch. Newly fertilised fathead minnow eggs exposed to maintained concentrations of tefluthrin in a freshwater flow-through test system through-out a complete life-cycle, resulted in a NOEC value of 0.00000397 mg tefluthin/L, based on mean measured concentrations. There was, however, no significant effect on survival to 56 days post-hatch of F_0 generation larvae at 0.00000802 mg/L. The NOEC values from a 28 day *Pimephales promelas* study and a 21 day *Daphnia* study were in the same range namely 0.000001 < NOEC ≤ 0.00001 mg/L.

The 96 hour ErC_{50} value for algae was > 1.05 mg/L and the NOEC value 0.51mg/l based on mean measured concentrations. The concentrations tested (0.18, 0.32, 0.56, 1.8 mg/L as nominal) were all in excess of the solubility of the substance and undissolved substance might have caused physical effects. The mean measured concentrations at the start of the study ranged from 89-122 % of nominal; after 96 hours the measured concentrations ranged from 2 to 28 % of nominal. There was no clear concentration-related response in the growth reductions.

Comments received during public consultation

Three MSCAa agreed with the proposed classification. One MSCA asked for a short summary on the environmental distribution of the substance which was not included in the response to comments table.

Assessment and comparison with the classification criteria

The substance is not rapidly degradable. The substance was stable to hydrolysis at pH 5 and pH 7 for 30 days. At pH 9 hydrolysis products Compound Ia and Compound II were found at average levels of 34.6 and 21.4 % respectively. There is no biodegradability test available. The DT_{50} values from the two available aerobic water/sediment tests in water-sediment system were in the range of 51 to 146 days.

Comparison to the classification criteria BCF ≥ 500 and log K_{ow} ≥ 4 shows that the substance is potentially bioaccumulative based on a fish BCF of 1400 and log K_{ow} of 6.4.

The lowest acute toxicity value is an EC50 of 0.000053 mg/l for invertebrate *Mysidopsis bahia* which in the range 0.00001 mg/L < $L(E)C_{50}$ ≤ 0.0001 mg/L resulting Aquatic Acute 1 classification with an M-factor of 10 000.

There is adequate chronic toxicity data available for all three trophic levels. The lowest chronic toxicity value is a NOEC of 0.00000397 mg/l for the fish *Pimephales promelas* which is in the range 0.000001 mg/L < NOEC ≤ 0.00001 mg/L. As tefluthrin is not rapidly degradable the resulting classification is Aquatic Chronic 1 with an M-factor of 10 000.

6 OTHER INFORMATION

none

7 REFERENCES

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Codes of owner
SYL: Syngenta Limited
SYD SYD Syngenta Agro GmbH (D-Maintal)

8 ANNEXES

confidential Annex