CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Pyroxsulam

EC Number: Not assigned

CAS Number: 422556-08-9

Index Number: Not assigned

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CONTENTS

Part A.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Pyroxsulam***
EC number:	Not assigned
CAS number:	422556-08-9
Annex VI Index number:	None available
Degree of purity:	≥ 96.5 %
Impurities:	Confidential – not relevant to the CLH proposal

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	None
Current proposal for consideration by RAC	Skin Sens 1; H317 – May cause an allergic skin reaction Aquatic Acute 1; H400 - Very toxic to aquatic life (Acute M factor = 100) Aquatic Chronic 1; H410 - Very toxic to aquatic life with long lasting effects (Chronic M factor = 100)
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Skin Sens 1; H317 – May cause an allergic skin reaction Aquatic Acute 1; H400 - Very toxic to aquatic life (Acute M factor = 100) Aquatic Chronic 1; H410 - Very toxic to aquatic

	life with long lasting effects (Chronic M factor = 100)

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification

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	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.2.	Flammable gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.3.	Flammable aerosols	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.4.	Oxidising gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.5.	Gases under pressure	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.6.	Flammable liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.7.	Flammable solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.10.	Pyrophoric solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.13.	Oxidising liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.14.	Oxidising solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification

2.15.	Organic peroxides	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
	Acute toxicity - dermal	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
	Acute toxicity - inhalation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	Not classified	Not applicable	Not classified	Data lacking
3.4.	Skin sensitisation	**Skin Sens 1; H317 – May cause an allergic skin reaction**	**None**	**None**	
3.5.	Germ cell mutagenicity	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.6.	Carcinogenicity	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.7.	Reproductive toxicity	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.10.	Aspiration hazard	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification

4.1.	Hazardous to the aquatic environment	**Aquatic Acute 1; H400 - Very toxic to aquatic life** **Aquatic Chronic 1; H410 - Very toxic to aquatic life with long lasting effects**	Acute M factor = 100 Chronic M factor = 100)		
5.1.	Hazardous to the ozone layer	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification

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

Labelling:

Pictogram(s): GHS07, GHS09

Signal word: Warning

Hazard statements: H317: May cause an allergic skin reaction
H410 - Very toxic to aquatic life with long lasting effects

Precautionary statements: Not required, P statements are not included in Annex VI

Proposed notes assigned to an entry: None

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Pyroxsulam is a pesticide active substance approved under Directive 91/414/EEC (subsequently replaced by EU Regulation 1107/2009), for which the UK were the Rapporteur Member State (RMS). Refer to Commission Implementing Regulation (EU) No 1176/2013 of 20 November 2013. There is no entry on Annex VI of CLP and there have been no previous classification and labelling discussions for this substance. Therefore, in accordance with Article 36(2) of the CLP Regulation, pyroxsulam should now be considered for harmonised classification and labelling. As the substance does not have a current entry on Annex VI of CLP this proposal considers all physical, human health and environmental hazard classes.

At the time of submission the substance is not registered under REACH.

2.2 Short summary of the scientific justification for the CLH proposal

Pyroxsulam is a member of the triazolopyrimidine sulfonamides, a class of herbicides known to inhibit the plant enzyme acetolacate synthase (ALS). It is broadly active on annual grass and broadleaf weeds, with some activity on certain perennial weed species.

The conclusion of the EFSA peer review process (EFSA Journal 2013;11(4):3182) noted concern for skin sensitisation and carcinogenicity. However, there was no consensus between the experts regarding the latter. Classification with Aquatic Acute 1; H400 and Aquatic Acute 1; H410 were also considered appropriate.

In a standard guinea pig maximisation study, the sensitisation response was 80 % in treated animals receiving an intradermal induction of 5% pyroxsulam. Classification in Skin Sens 1: H317 – May cause an allergic skin reaction is therefore proposed. Refer to section 4.6 of this report for full details.

Large granular lymphocyte leukaemia (LGL) in Fischer 344 rats and hepatocellular adenomas and carcinomas in mice were observed. The leukaemia was not considered to be related to treatment and therefore was not considered for classification. The increased incidence of liver adenomas and carcinomas in the mouse was slightly higher than the contemporaneous and laboratory historical control in males, but the carcinomas were within the control range provided for Charles River Labs (from which the mice were sourced). In addition, these findings occurred in male mice only, which appeared to be susceptible to liver tumour formation with multiple adenomas (rather than single incidences) observed in the livers of both control and treated animals. In conclusion, it is considered that there is insufficient evidence in this study to conclude that there is a treatment-related carcinogenic effect of pyroxsulam. Refer to 4.10 of this report for full details.

Aquatic acute toxicity data on pyroxsulam are available for fish, invertebrates, algae and aquatic plants. Aquatic plants are the most acutely sensitive trophic group. The lowest $L(E)C_{50}$ value is a 7-day E_rC_{50} of 0.00388 mg/l for *Lemna minor* in the range 0.001 to ≤0.01 mg/l. On this basis pyroxsulam should be classified as Aquatic Acute 1 with an M factor of 100.

Adequate chronic toxicity data on pyroxsulam are available for fish, invertebrates, algae and aquatic plants. The lowest value is a 7-day NOE_rC for *Lemna minor* of 0.0007 mg/l. Given this is in the

range 0.0001 to ≤0.001 mg/l and the substance is considered non-rapidly degradable, pyroxsulam should be classified as Aquatic Chronic 1 with an M factor of 100.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Not currently listed.

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling

The following entries are included in the classification and labelling inventory at the time of submission

Classification		Labelling		
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Supplementary Hazard Statement Code(s)**	**Pictograms, Signal Word Code(s)**
Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H317 H400 H410	H317 H410	-	GHS07 GHS09 Wng
Skin Sens. 1B Aquatic Chronic 1	H317 H410	H317 H410	-	GHS07 GHS09 Wng
Skin Sens. 1 Aquatic Chronic 1	H317 H410	H317 H410	-	GHS07 GHS09 Wng

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Pyroxsulam is a pesticide active substance approved under Directive 91/414/EEC (subsequently replaced by EU Regulation 1107/2009), for which the UK were the Rapporteur Member State (RMS). Refer to Commission Implementing Regulation (EU) No 1176/2013 of 20 November 2013. There is no entry on Annex VI of CLP and therefore, in accordance with Article 36(2) of the CLP Regulation, pyroxsulam should now be considered for harmonised classification and labelling. All physical, human health and environmental hazard classes are considered in this report.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

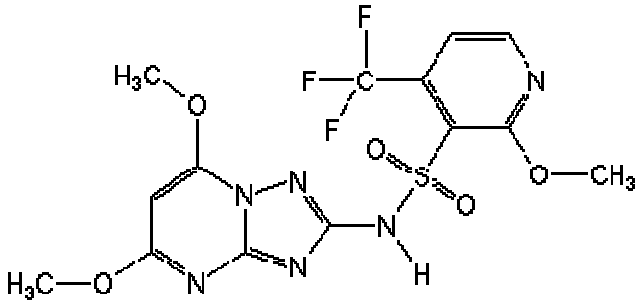
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 4: Substance identity

EC number:	Not assigned
EC name:	-
CAS number (EC inventory):	-
CAS number:	422556-08-9
CAS name:	3-Pyridinesulfonamide, *N*-(5,7-dimethoxy[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-
IUPAC name:	N-(5,7-dimethoxy[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)pyridine-3-sulfonamide
CLP Annex VI Index number:	Not applicable
Molecular formula:	$C_{14}H_{13}F_3N_6O_5S$
Molecular weight range:	434.4

Structural formula:



1.2 Composition of the substance

Table 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Pyroxsulam	≥ 96.5 g/kg		

Current Annex VI entry: None

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Confidential			

There are a number of process impurities in the substance. These have been taken into consideration and are not considered to impact on the classification proposed in this dossier. Further information on the impurities is considered to be confidential but full details are provided in the technical dossier.

Current Annex VI entry: Not applicable

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
None				

Current Annex VI entry: Not applicable

1.2.1 Composition of test material

The batches used in the relevant studies were considered to be equivalent to the manufactured material during the review of the active substance under Dir 91/414/EEC.

1.3 Physico-chemical properties

Table 8: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated etc.,)
State of the substance at 20°C and 101,3 kPa	White crystalline solid	S. Madsen 2006a, 2006c	Visual observation 99.3%
Melting/freezing point	208.3 °C	S Madsen 2006a	OPPTS 830.7200 ASTM E967-92 99.3% GLP
Boiling point	Decomposes at 213 °C (immediately after melting) before boiling.	S Madsen 2006a	EEC Method A1/A2 99.3%
Relative density	1.618	S. Madsen, R. Kastel 2003	EEC Method A3 99.3% GLP
Vapour pressure	< 1x10-7 Pa at 20 °C	S. Madsen, R. Kastel, 2003	OECD Guideline 104 (thermogravimetic method) 99.3% GLP
Surface tension	Not surface active 62.3 mN/m at 20 °C (0.01% solution) 63 mN/m at 20 °C (1.0% solution)	S. Madsen, R. Katsel, 2003	EEC Method A5 99.3% GLP
Water solubility	At 20°C 0.0626 g/l (purified water) 0.0164 g/l pH4 3.20 g/l pH7 13.7 g/l pH9	B. Turner 2004a	EEC Method A6 99.3% GLP
Partition coefficient n-octanol/water	At 20 °C LogPow = 1.08 pH 4 buffer solution LogPow = -1.01 pH7 buffer solution LogPow = -1.60 pH 9 buffer solution	B. Turner 2004b	EEC Method A8 (shake flask) 99.3% GLP
Flash point	Not applicable substance is a solid		
Flammability	Sample ignited but failed to sustain combustion for more than 2 seconds. Experience in handling and use indicates that it is not a pyrophoric solid and does not emit flammable gas on	B. Turner 2005	EEC Method A10 98% GLP

	contact with water.		
Explosive properties	Not explosive. No evidence of ignition or explosion but slight decomposition indicated.	B Turner, 2005	EEC Method A14 98% GLP
Self-ignition temperature	No self ignition < 400 oC	B Turner 2005	EEC Method A16 98% GLP
Oxidising properties	Not oxidising. Charred but did not burn to completion	B. Turner, 2005	EEC Method A17 98% GLP
Granulometry	No data		
Stability in organic solvents and identity of relevant degradation products	No data		
Dissociation constant	At 20 ^{o}C pKa = 4.67 (deprotonation of the nitrogen at the sulphonamide location occurs at higher pH)	C. Cathie, 2004	OECD Test Guideline 112 100% GLP
Viscosity	Not applicable		

Reference should be made to the Draft Assessment Report (DAR) – Pyroxsulam - Volume 3, Annex B2: Physical and Chemical Properties – January 2012

2 MANUFACTURE AND USES

2.1 Manufacture

Pyroxsulam is manufactured outside of the EU.

2.2 Identified uses

Pyroxsulam is placed on the market within the EU as an herbicide.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 9: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
Refer to table 8			

3.1 Physico-chemical Hazards

3.1.1 Summary and discussion of Physico-Chemical Hazards

3.1.2 Comparison with criteria

In a standard flammability study (EEC Method A10), pyroxsulam ignited but failed to sustain combustion. As such, it does not meet the criteria for classification as a flammable solid. The self ignition temperature was found to be > 400 ^{o}C. Further, experience in handling and use indicates that it is not a pyrophoric solid and does not emit flammable gas on contact with water.

In a standard study (EEC Method A14), pyroxsulam did not exhibit any explosive properties. As such, it does not meet the criteria for classification as an explosive substance.

Finally, in a standard study (EEC Method A17), pyroxsulam ignited and charred, but did not burn to completion. As such, it is not classified as an oxidising solid.

3.1.3 Conclusions on classification and labelling

Not classified – conclusive but not sufficient for classification

4 HUMAN HEALTH HAZARD ASSESSMENT

References are taken from the Draft Assessment Report (DAR) – Pyroxsulam - Volume 3, Annex B6: Toxicology and Metabolism – January 2012

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

The following summary is derived from the Pesticide Assessment Report made for the review under Directive 91/414/EEC.

The toxicokinetics of pyroxsulam have been investigated in two species: rat and mouse.

In the rat study, pyroxsulam was shown to be rapidly absorbed with around 74-78 % of the dose being absorbed after administration with 10 mg/kg bw/day. The 1000 mg/kg bw/day was absorbed to a lesser extent. Of the tissues investigated, highest systemic levels occurred in the plasma, liver and kidney. Pyroxsulam was rapidly excreted in the urine and faeces (nearly 100 % of the absorbed dose within 48 h). Pyroxsulam was mostly excreted unchanged (85-90% of administered dose). The only identified metabolite was 2-desmethyl-XDE-742, which was present in both urine and faeces (at least 5 % of low dose administered). There were no differences in findings between the two labelling positions (labelled in the triazole or pyridine rings), nor between single or repeat dosing. Notably, there was no evidence for metabolic induction (no alteration in metabolism of pyroxsulam) as a result of repeat dosing with unlabelled pyroxsulam. The rapid and extensive excretion with very low levels in carcass at 38 h post dose (< 1% of administered dose) suggests there is little potential for accumulation.

In the mouse study, pyroxsulam was rapidly absorbed. After oral dosing with 10 mg/kg bw/day, about 60 % was absorbed; a lesser percentage was absorbed at 1000 mg/kg bw/day. Limited data indicate that liver concentrations of radiolabel rose to significantly higher levels in males than females. Radiolabel was cleared quickly from plasma, RBC and liver during the initial elimination phase ($t_{1/2}$ of 2-3h) and subsequently more slowly (especially from the liver) at the high dose. The slow elimination from the liver, will favour accumulation of pyroxsulam/metabolites in the liver on repeated dietary exposure. Of the limited tissues investigated at 72 h, highest systemic levels were in the liver.

Compared to male rats, at the plasma Cmax following an oral dose of 10 mg/kg bw, the concentration of radiolabel in the liver was slightly higher for male mice, but decreased to similar levels in both species at 2h and 48h. It is also notable that at 48h (only timepoint with data available) after dosing with 1000 mg/kg bw, the concentration in the liver of male rats (16.7 ug-eq./g) was slightly higher than in the male mice (8.2 ug-eq./g).

Pyroxsulam-derived radioactivity was rapidly and extensively excreted in urine and faeces (93-100 % within 24 h). Excretion was mainly in urine at 10 and 100 mg/kg bw, but mainly in faeces at 1000 mg/kg bw.

4.1.2 Human information

No information available

4.1.3 Summary and discussion on toxicokinetics

The toxicokinetics of pyroxsulam was investigated orally in rats (single and repeated administration) and mice (single dose only). Following single (rats and mice) and repeat administration (rat only), pyroxsulam was well absorbed. In rats, distribution was highest in the plasma, liver and kidney. Only a small proportion of pyroxsulam was metabolised. Excretion was via both the urine and faeces in rats and mainly via the urine in mice at the low dose and via the faeces at the high dose. There was no evidence of bioaccumulation.

4.2 Acute toxicity

Table 10: Summary table of relevant acute toxicity studies

Acute Oral		
Method	**LD_{50}**	**Observations and remarks**
OECD 423 (2001) GLP 6 female Wistar rats Single dose of 2000 mg/kg bw *Gamer and Leibold (2003a)*	> 2000 mg/kg bw	An initial dose (2000 mg/kg bw/day) was given to 3 fasted rats. As none died a further 3 rats were dosed in the same manner. No mortality or effects observed
Acute Inhalation		
Method	**LC_{50}**	**Observations and remarks**
OECD 403 (1981) GLP 5 F344 rats/sex Exposed nose only for 4 h to 5.12 mg/L (dust/aerosol) MMAD – 3.6 microns *Lowe (2007a)*	> 5.12 mg/L	There were no deaths or clinical signs of toxicity. Although most rats had lost weight by day 1 or 3 (post-exposure), all animals surpassed their pre-exposure weight by day 7 and continued to gain body weight through day 14. There were no treatment-related lesions at necropsy.
Acute Dermal		
Method	**LD_{50}**	**Observations and remarks**
OECD 402 (1987) GLP 5 Wistar rats/sex Single dose of 2000 mg/kg bw Vehicle: doubly distilled water Semi occlusive *Gamer and Leibold (2003b)*	> 2000 mg/kg bw	No mortality or adverse effects observed

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

An oral LD_{50} of > 2000 mg/kg bw/day was derived from a study conducted in rats.

4.2.1.2 Acute toxicity: inhalation

An inhalation 4 hr LC_{50} of > 5.12 mg/L was derived from a study conducted in rats.

4.2.1.3 Acute toxicity: dermal

A dermal LD_{50} of > 2000 mg/kg bw/day was derived from a study conducted in rats.

4.2.1.4 Acute toxicity: other routes

No information available

4.2.2 Human information

No information available

4.2.3 Summary and discussion of acute toxicity

See section 4.2.1

4.2.4 Comparison with criteria

Via the oral, inhalation and dermal routes, the LD_{50} values were higher than the respective guidance values (2000 mg/kg, 5 mg/l and 2000 mg/kg respectively); no classification is required.

4.2.5 Conclusions on classification and labelling

Not Classified: conclusive but not sufficient for classification

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

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

No clinical signs or changes in organs were observed in any of the acute studies (table 10).

4.3.2 Comparison with 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 are classified in STOT-SE 1 or 2. Classification is supported by evidence associating single exposure to the substance with a consistent and identifiable toxic effect.

Classification in STOT-SE 3 is reserved for transient target organ effects and is limited to substances that have narcotic effects or cause respiratory tract irritation.

Since no clinical signs or changes in organs were observed (table 10), the criteria for STOT SE are not met

4.3.3 Conclusions on classification and labelling

Not Classified: conclusive but not sufficient for classification

4.4 Irritation

4.4.1 Skin irritation

Table 11: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
OECD 404 (2002) GLP 0.5g of test substance moistened with distilled water and applied for 4 hours. 3 New Zealand rabbits Semi-Occlusive	Slight erythema (grade 1) was observed in all animals immediately and up to 1 hour after removal of the patch. No other cutaneous reactions were observed during the study. Mean scores over 24, 48 and 72 hours were 0 for erythema and oedema	Pyroxsulam showed slight transient irritation at the 1 hour time point only	Kaufmann and Leibold (2003a) and Kaufmann (2006a)

4.4.1.1 Non-human information

The skin irritation potential of pyroxsulam has been investigated in one standard guideline study in rabbits. Only slight transient irritation was observed.

4.4.1.2 Human information

No information available

4.4.1.3 Summary and discussion of skin irritation

The skin irritation potential of pyroxsulam has been investigated in one standard guideline study in rabbits. Slight transient irritation was observed at the 1 hr observation only.

4.4.1.4 Comparison with criteria

No oedema or erythema was observed over the time points relevant for classification (24, 48 and 72 hours); therefore, no classification for skin irritation is required.

4.4.1.5 Conclusions on classification and labelling

Not Classified: conclusive but not sufficient for classification

4.4.2 Eye irritation

Table 12: Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference
OECD 405 (2002) GLP 0.1 ml of test substance was applied for 1 hour. 3 New Zealand rabbits (application was a stepwise procedure starting with one animal and then two additional animals)	Slight conjunctival redness (grade 1) was observed in all animals 1 hour after application. This persisted in two animals up to 24 hours and in one animal up to 48 hours Grade 1 chemosis was observed in one animal between 1-24 hour Mean scores for each animal calculated over 24, 48 and 72 hours 0, 0 and 0 for corneal opacity and iris lesions 0.7, 0.3, 0.3 for redness of the conjunctiva 0, 0 and 0.3 for chemosis	Injected scleral vessels in a circumscribed area were noted in one animal after 24 hours	Kaufmann and Leibold (2003b) and Kaufmann (2006b)

4.4.2.1 Non-human information

The eye irritation potential of pyroxsulam has been investigated in a standard guideline study. No effects on the cornea or iris were noted. Effects on the conjunctivae were limited to mild erythema and oedema.

4.4.2.2 Human information

No information available

4.4.2.3 Summary and discussion of eye irritation

The eye irritation potential of pyroxsulam has been investigated in a standard guideline study. No effects on the cornea or iris were noted. Effects on the conjunctivae were limited to erythema and mild oedema.

4.4.2.4 Comparison with criteria

No effects in the iris or cornea were noted. The mean scores for each animal calculated over 24, 48 and 72 hours for erythema and oedema of the conjunctivae were less than the guidance value of 2. No classification is required.

4.4.2.5 Conclusions on classification and labelling

Not Classified: conclusive but not sufficient for classification

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

This endpoint was not investigated directly; however, no signs of respiratory irritation were observed in the acute inhalation study (see section 4.2).

4.4.3.2 Human information

No information available

4.4.3.3 Summary and discussion of respiratory tract irritation

This endpoint was not investigated directly; however, no signs of respiratory irritation were observed in the acute inhalation study (see section 4.2).

4.4.3.4 Comparison with criteria

No signs of respiratory tract irritation were observed.

4.4.3.5 Conclusions on classification and labelling

Not Classified: Data lacking

4.5 Corrosivity

Table 13: Summary table of relevant corrosivity studies

Method	Results	Remarks	Reference
Refer to table 11			

4.5.1 Non-human information

Pyroxsulam is not irritating to skin (see section 4.4)

4.5.2 Human information

No information available

4.5.3 Summary and discussion of corrosivity

Pyroxsulam is not irritating to skin (see section 4.4)

4.5.4 Comparison with criteria

No signs of corrosivity were observed in an *in vivo* skin irritation study.

4.5.5 Conclusions on classification and labelling

Not Classified: conclusive but not sufficient for classification

4.6 Sensitisation

4.6.1 Skin sensitisation

Table 14: Summary table of relevant skin sensitisation studies

Species/Method	Doses	No. sensitised/total no.	Result	Reference
OECD 406 (1992) GLP Guinea-pig/Dunkin-Hartley 10 control animals 20 test animals Intradermal induction performed on day 0 and epicutaneous induction on day 7. Challenge was 14 days after the epicutaneous induction.	Induction: Intradermal: 5 % pyroxsulam in 1 % CMC (carboxymethylcellulose) sodium solution in water Topical: 50 % pyroxsulam in 1 % CMC-solution in water Challenge: 25 % pyroxsulam in 1 % CMC-solution water Erythema and/or swelling observed following intradermal and topical induction.	Test: 24 h: 16/20 48 h: 15/20 Negative Control: 0/10 at 24 and 48 h Positive control: alpha-hexylcinnamaldehyde, techn. 85% showed test system was able to detect sensitizing compounds	Positive	Gamer and Leibold (2004)

4.6.1.1 Non-human information

The skin sensitisation potential has been investigated in a standard maximisation study. Positive responses were observed in 16/20 animals at 24 hours and 15/20 animals at 48 hours compared to 0/10 in the control.

4.6.1.2 Human information

No information is available.

4.6.1.3 Summary and discussion of skin sensitisation

The skin sensitisation potential has been investigated in a standard maximisation study. Positive responses were observed in 16/20 animals (80%) at 24 hours and 15/20 (75%) animals at 48 hours compared to 0/10 in the control.

4.6.1.4 Comparison with criteria

A substance is classified in Category 1A where

a) there is a ≥ 30% response in animals receiving an intradermal induction dose of ≤ 0.1% or

b) there is ≥ 60% response in animals receiving an intradermal induction dose of > 0.1% and ≤ 1% in a GPMT.

A substance is classified in Category 1B where

a) there is a ≥ 30% to <60% response in animals receiving an intradermal induction dose of > 0.1% and ≤ 1% or

b) there is a ≥ 30% response in animals receiving an intradermal induction dose of > 1% in a GPMT;

where there is no information to suggest that classification in Category 1A should be considered,

The sensitisation response in the available Guinea-Pig maximisation study with pyroxsulam was 80%, with an intradermal induction of 5%. Whilst this meets the criteria for classification in Category 1B, it should be noted that a relatively high response (80%) was observed with an induction dose of 5% and no data are available from standard studies at lower induction concentrations. As such it could be that classification in Category 1A can not be excluded and a simple argument for classification in Category 1 can be made.

4.6.1.5 Conclusions on classification and labelling

Skin Sens 1; H317 May cause an allergic skin reaction

4.6.2 Respiratory sensitisation

Table 15: Summary table of relevant respiratory sensitisation studies

Method	Results	Remarks	Reference
Not applicable			

4.6.2.1 Non-human information

No data are available.

4.6.2.2 Human information

No data are available.

4.6.2.3 Summary and discussion of respiratory sensitisation

No data are available.

4.6.2.4 Comparison with criteria

No data are available.

4.6.2.5 Conclusions on classification and labelling

Not classified: Data lacking.

4.7 Repeated dose toxicity

Information on repeated dose toxicity is available from short-term dietary studies in rats, mice and dogs. A short-term dermal study in rats is also available.

Table 16: Summary table of relevant repeated dose toxicity studies

Method	Dose Levels	Observations and Remarks	Reference
Rat 28-day study Dietary OECD 407 (1995) GLP 5 F344 **rats**/sex/dose	0, 10, 100, 500 or 1000 mg/kg bw/day Actual doses received were in excess: 0, 11.8, 120, 583 and 1165 mg/kg bw/day in males 0, 11.6, 112, 563 and 1140 mg/kg bw/day in females Dose level relevant for classification (determined from the guidance value for 90-day rat study) - 300 mg/kg bw/d	1000 mg/kg bw/day Perineal urine soling of 1 female, 4% ↓ bodyweight gain (both sexes), ↓ serum ALT in females (not statistically significantly) 500 mg/kg bw/day Perineal urine soiling of 2 females 100 and 10 mg/kg bw/day No treatment related effects observed NOAEL of 1000 mg/kg bw/day in both sexes	Stebbins and Day (2001)

Method	Dose Levels	Observations and Remarks	Reference
Rat 90-day study Dietary OECD 408 (1998) Main treatment group: 10 F344 rats/sex/dose 28-day recovery group: 10 F344 rats/sex/dose	0, 10, 100 or 1000 mg/kg bw/day Dose level relevant for classification (guidance value for 90-day rat study) - 100 mg/kg bw/d	1000 mg/kg bw/day 3 males and 15 females showed perineal urine soiling 6/15% ↓ bodyweight gain in males/females 9% ↑ relative liver weight in males 4% ↓ serum ALT 37% ↑ serum cholesterol in males 20% ↑ in urine volume (ml) and ↓ protein (mg/dL) 100 mg/kg bw/day 4% ↓ bodyweight gain in females 10 mg/kg bw/day No treatment related effects observed Recovery group: effects had completely recovered or showed signs of recovery during the 28-day recovery period NOAEL of 100 mg/kg bw/day based on reduced bodyweight at 1000 mg/kg bw/day	Stebbins, Dryzga, Brooks, Thomas (2003)
Mouse 90-day study Dietary OECD 407 (1998) GLP 10 CD-1 mice/sex/dose	0, 10, 100, 1000 mg/kg bw/day Dose level relevant for classification (determined from the guidance value for 90-day rat study) - 100 mg/kg bw/d	1000 mg/kg bw/day 25% ↑ in male and female bodyweight ↑ food consumption in males 22/ 30% ↑ serum cholesterol in males/females (but within the historical control range) 18.3/ 8 % ↑ absolute liver weight in males/females, 12.3/5% ↑ relative liver weight in males/females 100 and 10 mg/kg bw/day No treatment related effects observed The NOAEL for males is 100 mg/kg bw/day based on increased liver weight at 1000 mg/kg bw/day The NOAEL for females is 1000 mg/kg bw/day	Johnson, Brooks, Drygza (2003)

Method	Dose Levels	Observations and Remarks	Reference
Dog 28-day study Dietary US EPA QPPTS 870.3700 GLP (except for histological processing and examination) 2 Beagle dogs/sex/dose Minimal quantitative detail is included due to low animal number	0, 0.3, 1 and 3% in the diet Equivalent to 0, 85, 421, 868 mg/kg bw/day in males and 0, 169, 333 and 1004 mg/kg bw/day in females Dose level relevant for classification (determined from the guidance value for 90-day rat study) - 300 mg/kg bw/d	3% dose level Slight ↓ bodyweight in males and females 79% and 37% ↑ serum cholesterol in each female dog ↑ absolute and relative liver weight in males 1% dose level ↑ absolute and relative liver weight in males 0.3% dose level No treatment related effects observed No NOAEL derived due to small group sizes	Merriman (2002)
Dog 90-day study Dietary OECD 409 (1998) GLP 4 Beagle dog/sex/dose	0, 0.03, 0.3 and 3% Equivalent to 0, 11, 91 and 884 mg/kg bw/day in males and 0, 10, 99 and 1142 mg/kg bw/day in females Dose level relevant for classification (determined from the guidance value for 90-day rat study) - 100 mg/kg bw/d	3% dose level ↓bodyweight in both sexes, 34/31% ↓ bodyweight gain in males/females (female reduction mainly due to one female who didn't gain any weight over period), slightly ↓ food consumption in males from week 3 27% ↑serum cholesterol in females (within historical control range), 23% ↑alkaline phosphatase levels in females (mainly due to an increase in one female) 11% ↑ in relative liver weight in males, 28% ↑ in absolute liver weight in females and 32% ↑ in relative liver weight in females. Slight panlobular hepatocellular hypertrophy in female livers 0.3 and 0.03% doses levels No treatment related effects noted A NOAEL of 0.3% (99 and 99 mg/kg bw/day in males and females, respectively) based on reduced bodyweight gain in males and effects in the liver in females	Stebbins and Baker (2003)
Dog 1 year study Beagle dogs OECD 452 (1981) GLP Four/sex/dose	0, 0.05, 0.3 and 2% 0, 13, 93 and 630 mg/kg bw/day in males and 0, 17, 89 and 589 mg/kg bw/day	2% dose level ↓ 9-11% decrease in red blood cell parameters in females. NB, the RBC parameters in the high dose group were slightly lower than controls at the start of the study 42/100% ↑ serum cholesterol in males/females. For males, the 12-month high dose value (reported here) exceeded the historical control, whereas none of the	Stebbins and Dryzga (2004)

Method	Dose Levels	Observations and Remarks	Reference
	in females Dose level relevant for classification (determined from the guidance value for 90-day rat study) – c.a. 25 mg/kg bw/d	individual values exceeded the range of values seen in the concurrent controls 145/38% ↑ alkaline phosphatase in males and females 23/ 20% ↑ absolute liver weight in males/females, 20/ 23% ↑ relative liver weight in males/females 0.3 and 0.05% dose levels No treatment related effects A NOAEL of 0.3% (93 mg/kg bw/day in males and 89 mg/kg bw/day in females) was derived based on increased liver weight	
14-day dermal study No guideline – range finding study GLP (but no QA)	0, 1000 mg/kg bw/day	1000 mg/kg bw/day No treatment related findings observed A NOAEL of 1000 mg/kg bw/day	Kaspers (2004)

NB: The values for NOAEL and LOAEL are provided for information only: they have already been agreed at a PRAPER expert meeting. ↓= decrease compared to control. ↑/↓ = increased/decreased compared to control.

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Sub-acute toxicity

Information on sub-acute toxicity is available from a 28-day study in rats and a 28-day and a 90-day study in dogs.

There were no adverse effects observed below the relevant guidance values for classification (300 mg/kg bw/day) in any study. At dose levels above the cut-off (~1000 mg/kg bw/day) effects included reduction in bodyweight and slight changes in clinical chemistry parameters (ALT and ↑ serum cholesterol)[1]. In both dog studies, liver weights were also increased, and were accompanied by associated histopathological changes in the 90-day study.

Sub-chronic toxicity

Information on sub-chronic toxicity comes from a 90-day study in rats, a 90-day study in mice and a one-year study in dogs.

There were no adverse effects observed below the relevant guidance values for classification (100 mg/kg bw/day). At dose levels above the guidance values (> 589 mg/kg bw/day) effects including

[1] In a number of rat studies, perineal urine staining was observed. This effect was not considered adverse and is not discussed further.

reductions in bodyweight (rats and dogs only), slight, non-adverse, changes in clinical chemistry (↑ alkaline phosphatase and ↑ serum cholesterol) and increased liver weights were observed in all species unless specified.

Chronic toxicity

Information on chronic toxicity comes from a study in rats and a study in mice (see section 4.10).

In both studies, effects were only noted at the limit dose (1000 mg/kg bw/day) and were comparable to those observed in the other studies (bodyweight, liver effects, and clinical chemistry changes). The only exception to this was an increase in kidney weight (relative and absolute) observed in mice.

4.7.1.2 Repeated dose toxicity: inhalation

No information available.

4.7.1.3 Repeated dose toxicity: dermal

Limited information on sub-acute toxicity is available from a 14-day study in rats. In this study no effects were observed at the limit dose. No classification is warranted.

4.7.1.4 Repeated dose toxicity: other routes

No information available.

4.7.1.5 Human information

No information available.

4.7.1.6 Other relevant information

Not applicable

4.7.1.7 Summary and discussion of repeated dose toxicity

See sections 4.7.1.1 and 4.7.1.3

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

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

Information on pyroxsulam is available from oral studies in rats, mice and dogs. There is also information available from a dermal study in rats.

The rat data show that there are no serious adverse effects of pyroxsulam below the guidance values (300 mg/kg bw/day in a 90-day study in rats) for classification, with effects occurring only at higher dose levels (reduced bodyweight and liver effects). The mouse and dog data confirm pyroxsulam is of low toxicity. The main adverse effects were reduced bodyweight (dog) and effects on the liver (both dogs and mice).

The results of a 14-day dermal range-finding study showed no effects up to the limit dose.

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

The available information indicates that classification for repeated dose toxicity is not warranted as no significant adverse effects were observed below the guidance values for classification.

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

Not Classified: conclusive but not sufficient for classification

4.9 Germ cell mutagenicity (Mutagenicity)

Table 17: Summary table of relevant in vitro and in vivo mutagenicity studies

In Vitro Data			
Method	**Organism/strain**	**Concentrations tested**	**Result**
Ames OECD 471 (1997) GLP Engelhardt and Leibold (2003)	*Salmonella strains* TA 1535, TA 100, TA 1537 and TA 98 *E.Coli* WP2 urvA	0-5000 µg/plate with and without S9 Vehicle dimethylformamide	Negative Precipitation was observed at 2500 µg/plate and above Depending on strain, a bacteriotoxic effect was observed between 750-5000 µg/plate Positive controls responded as expected
In vitro cytogenetic study OECD 473 (1997) GLP Schisler (2006)	Rat lymphocytes	0-200 µg/plate (top dose determined by solubility in the vehicle [DMSO], not cytotoxicity)	Negative No cytotoxicity or precipitation was observed No evidence of polyploidy Positive controls responded as expected
Mammalian cell gene mutation assay OECD 476 GLP Schisler and Grundy (2006)	Chinese hamster ovary (CHO) cells	0-200 µg/plate (top dose determined by solubility in the vehicle DMSO not cytotoxicity)	Negative No cytotoxicity or precipitation was observed Positive controls responded as expected
In vivo Data			
Method	**Organism/strain**	**Concentrations tested**	**Result**
Bone marrow micronucleus assay OECD 474 (1997) GLP Oral gavage (administered once on two consecutive days) Sacrificed 24 h after second dose Spencer and	CD-1 Mice 6 males/dose	0, 500, 1000 and 2000 mg/kg bw/day in 0.5% w/v methylcellulose	Negative No clinical signs or effects on bodyweight were observed No change in the % PCE values observed between treated and controls The positive control responded as expected

In Vitro Data			
Method	**Organism/strain**	**Concentrations tested**	**Result**
Grundy (2004)			
Unscheduled DNA Synthesis (UDS) Assay OECD 486 (1997) GLP Sacrificed 12-14h or 2-4 h after dosing Oral gavage Beevers (2006)	CD-1 mice 6 males/dose Hepatocytes from 3 animals/dose treated with [^{3}H] thymidine for 4 h	0, 1000 and 2000 mg/kg bw/day in 0.5% w/v methylcellulose	Negative No clinical signs of toxicity were observed The positive controls responded as expected

4.9.1 Non-human information

4.9.1.1 In vitro data

The genotoxicity of pyroxsulam has been investigated in an Ames test, an *in vitro* cytogenetics study and an *in vitro* mammalian cell gene mutation study. Positive controls were included in all assays and showed the expected responses. The result of all assays was negative.

4.9.1.2 In vivo data

The genotoxicity of pyroxsulam has been investigated *in vivo* in a mouse micronucleus study and an unscheduled DNA synthesis (UDS) study in mouse livers. The results of both studies were negative. No deaths or cytotoxicity was observed in either study. This is not considered to be a problem as toxicokinetic studies have shown pyroxsulam to be well distributed. In addition, with regards the UDS study, the liver has been identified as the target organ for this substance.

4.9.2 Human information

No information available

4.9.3 Other relevant information

Not applicable

4.9.4 Summary and discussion of mutagenicity

Data indicate pyroxsulam is not mutagenic *in vitro* or *in vivo*.

4.9.5 Comparison with criteria

Data indicate pyroxsulam is not mutagenic *in vitro* or *in vivo* and classification as a germ cell mutagen is not warranted.

4.9.6 Conclusions on classification and labelling

Not Classified: conclusive but not sufficient for classification

4.10 Carcinogenicity

Table 18: Summary table of relevant carcinogenicity studies

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Two year chronic toxicity/carcinogenicity and chronic neurotoxicity study OECD 453 (1981) GLP Oral (dietary) 65 Fischer 344 rats/sex/dose 10 rats/sex/dose were necropsied at 1 year (chronic toxicity group). Of these, 5/rats/sex were shared with the group below In addition to the 5 rats above, a further 5 rats/sex/dose were necropsied at 1 year (chronic neurotoxicity group) 50 rats/sex/dose were fed diets up to two years and necropsied (oncogenicity group) Stebbins and Brooks (2005) and Stebbins and Brooks (2008) – revised report	0, 10, 100 and 1000 mg/kg bw/day	***Non-neoplastic effects*** *Mortality* No substance related effect on survival of female rats (2 year mortality was 20-24%). In males, mortality was slightly higher during the last 5 weeks of the study at 100 (44% at termination) and 1000 (52% at termination) mg/kg bw/day compared to the control (34%). *Clinical signs of toxicity* Incidence of perineal urine soiling was increased in both sexes of the 100 and 1000 mg/kg bw/day treatment groups. *Bodyweight* There were no effects observed in males. Female body weight gain of the 1000 mg/kg bw/day dose group was 8-10% ↓ over the two years. *Feed consumption* No effect in males Food consumption in females was statistically lower than controls between days 8 to 84. *Haematology* Minimally lower mean red blood cell counts in both sexes at 1000 mg/kg bw/day. Statistically significant at 6 months only and did not progress throughout the study. *Clinical Chemistry* Males at 1000 mg/kg bw/day had 36-38% ↓ ALT levels at 6 and 12 months and a 22-33% ↑ serum cholesterol at 3, 6 and 12 months *Urinalysis* 23/33% ↑ urine volume in males/females at 24 months in the 1000 mg/kg bw/day *Organ weights* 4.1/6.1% ↑ absolute liver weight in males/females and 8.8/10.9% ↑ relative liver weight in males/females of the 1000 mg/kg bw/day group *Gross pathology* No treatment related findings observed *Histopathology* ↓ incidence and/or severity of basophilic foci of altered hepatocytes in females given 1000 mg/kg bw/day (12 and 24 months) and in males given 1000 mg/kg bw/day (24 months) Slight ↑ erosion/ulceration of the glandular stomach and of diffuse hyperplasia of the non-glandular stomach in males of 1000 mg/kg bw/day (NB. Disparity between these findings and those of gross pathology where no increase in these

<table>
<tr><th>Method</th><th>Dose levels</th><th>Observations and remarks
(effects of major toxicological significance)</th></tr>
<tr><td></td><td></td><td>types of effect were observed).
<u>Neoplastic effects (key findings only)</u>
Leukemia, large granular lymphocyte (LGL), malignant, primary
<table>
<tr><td>Dose (mg/kg bw/day)</td><td>0</td><td>10</td><td>100</td><td>1000</td><td>Historical control</td></tr>
<tr><td>Male</td><td>20/50</td><td>21/50</td><td>28/50 (56 %)</td><td>29/50 (58 %)</td><td>Contemporaneous controls (2002-2005)
11/50, 18/50, 19/55, 17/50, 12/50
<u>(Older controls: 1992-1999</u>
9/50, 20/50)</td></tr>
<tr><td>female</td><td>12/50</td><td>6/50</td><td>8/50</td><td>11/50</td><td>Contemporaneous controls (2002-2005)
6/50, 9/50, 8/55, 12/50, 11/50
<u>(Older controls: 1992-1999</u>
14/50, 8/50, 14/50)</td></tr>
</table>
Other neoplastic findings have been summarized in the text below.
A NOAEL of 1000 mg/kg bw/day was derived for carcinogenicity. A NOAEL of 100 mg/kg bw/day was derived for non-neoplastic effects.</td></tr>
<tr><td>Eighteen month Dietary oncogenicity study
OECD 451 (1981)
GLP
Oral (dietary)
50 CD 1 mice/dose/sex
Johnson, Dryzga and Yano (2005)</td><td>0, 10, 100 or 1000 mg/kg bw/day</td><td><u>Non-neoplastic effects:</u>
Mortality
No substance related mortality. Mortality rates at the end of the study in control, 10, 100 and 1000 mg/kg bw/day were, respectively;
22, 20, 20 and 24% (males)
22, 28, 20 and 20% (females)
Clinical signs
There were no substance-related clinical signs
Bodyweight
There were treatment-related effects on bodyweight gain
Food consumption
Slight increases in food consumption were noted in males at 100 and 1000 mg/kg bw/day
Organ weights
25/32% ↑ absolute/relative liver weight of males at 1000 mg/kg bw/day</td></tr>
</table>

<table>
<tr><th>Method</th><th>Dose levels</th><th>Observations and remarks
(effects of major toxicological significance)</th></tr>
<tr><td></td><td></td><td>
10/12% ↓ absolute kidney weight and 6/10% ↓ relative kidney weights at 1000 mg/kg bw/day
Gross necropsy
The number of male mice with one or more liver nodules was slightly ↑ at 1000 mg/kg bw/day
Histopathology
↑ incidence of foci of altered hepatocytes observed in males at 1000 mg/kg bw/day (12 mice compared to 2 in the controls)

<u>Neoplastic effects:</u>
<table>
<tr><th>Dose</th><th>0</th><th>10</th><th>100</th><th>1000</th><th>Historical control</th></tr>
<tr><td colspan="6">Male mice</td></tr>
<tr><td>No of male mice with hepatocellular adenomas</td><td>5/50
(10%)</td><td>13/50
(26%)</td><td>9/50
(18%)</td><td>14/50
(28%)</td><td>a) 4-18%/ (2/50-9/50)
a2) 8-24% (4/50-12/50)
b) 1.4-20%</td></tr>
<tr><td>No of male mice with hepatocellular carcinomas</td><td>1/50
(2%)</td><td>0/50
(0%)</td><td>2/50
(4%)</td><td>4/50
(8%)</td><td>a) 0- 4% (0/50 – 2/50)
a2) 0-4% (0/50-2/50)
b) 1.6-15%</td></tr>
</table>

NOAEL could not be derived.
</td></tr>
</table>

a) Dow: studies necropsied Dec-2001- May 2001 (50 males/control), plus one study completed May 2007 and Notifier confirmed there were no multiple hepatocellular tumours in 50 male control mice).
a2) Dow: information from studies conducted between 2007 and 2012.
b) HCD in the Crl:CD1 mouse published by Charles River Labs (published paper M Gilkins and C. Clifford, March 2010): 13 studies initiated between 2002 – 2006. Includes studies of 78-104 weeks in duration (50-110 animals/study). An incidence of hepatocellular carcinoma of 6/60(10%) and 9/60 (15%) was observed in two 78 week studies. .

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

Information is available from a carcinogenicity study in rats and mice.

Rats

In the rat study, neoplastic changes were observed in the haematopoietic/lymphoid system, liver, thyroid, and adrenals. These are discussed individually below:

Haematopoietic/lymphoid system

Males receiving 100 (28/50) or 1000 (29/50) mg/kg bw/day had slightly higher incidence of large granular lymphocyte (LGL Fischer rat) leukaemia[2] than in the controls (20/50). These increases were not statistically significant and there was no evidence for an early onset of LGL leukaemia in rats exposed to pyroxsulam (Stebbings and Brooks, 2008).

Historical control information

The incidence in the top two dose groups in males was outside the historical control range of dietary or oral gavage toxicity studies performed in this laboratory both contemporaneously (studies initiated: 2002-2005) and in the past (studies initiated: 1992-1995). However, the control incidence was also higher or equal to that of the historical controls too.

The incidence did fall within the NTP pre-1995 historical control range (32-74%), and was just outside the NTP post-1995 historical control range (30 to 54% based on 5 dietary studies). These historical control ranges suggest this type of tumour has a high spontaneous rate in Fischer rats. In addition, it is possible the diet may also influence tumour incidence with a higher top range observed with the pre-1995 diet (which was similar to the diet used in this study) than with the post-1995 diet (lower protein and higher fibre). However, on its own this assertion is not conclusive and since the incidence in the top two treatment groups was higher than both the concurrent controls and laboratory historical control data the tumours cannot be dismissed on this basis alone.

Dose response considerations

The incidence of LGL leukaemia in the 100 and 1000 mg/kg bw/day dose groups was similar. This was somewhat surprising given that the high dose group was ten times that of the mid dose group. Failure to see a dose-related increase in tumour incidence raises doubt that the tumours are treatment related.

Information from the repeated dose studies on the target organs

No substance-related increase in white blood cell count or substance-related changes in differential white blood count in male rats was observed. Nor was there any histological evidence that lymphoid tissues/organs were a target organ for pyroxsulam.

[2] Other names for this type of leukaemia include: mononuclear cell leukaemia; Fischer rat leukaemia and monocytic leukaemia.

Conclusion

Overall, an increase in the incidence of LGL leukaemia was observed at the top two doses in one sex (males). However, since, the control values were at the top of the historical control range; this is a relatively common tumour in Fischer rats; the increase was not statistically significant, the incidence was similar at both mid and high dose even though there was a 10-fold difference in dose level; and there was no evidence from repeated dose studies of effects in relevant organs (e.g. white blood cells, spleen liver, lungs, thymus, lymph glands), the increase in tumour incidence is not considered treatment related.

Additional tumour types in rat not summarised in the table:

Liver

A slight increase in the incidence of hepatocellular adenomas was observed in males treated with 1000 mg/kg bw/day (1/50, 3/50, 3/50 and 4/50 in controls to high dose). This increase was within the historical control ranges for dietary or oral gavage toxicity studies performed contemporaneously in this laboratory (Historical control range: 1-6 hepatocellular adenomas) and therefore was not considered treatment related. No increase was noted in females.

Thyroid

A slight increase in the incidence of parafollicular cell adenomas was observed in females treated with 1000 mg/kg bw/day (2/50, 2/10, 2/12 and 7/49 in controls to high dose). This increase was within the historical control range for dietary or oral gavage toxicity studies performed contemporaneously in this laboratory (Historical control range: 2-9 parafollicular cell adenomas) and therefore was not considered treatment related. No increase was noted in males.

Adrenals

There was a slight increase in the incidence of benign pheochromocytoma in males at 1000 mg/kg bw/day (4/50, 2/20, 2/24 and 9/50 in the controls to high dose). This increase was slightly higher than the historical control range (historical control range: 3-7), but there was no increased incidence observed in females and no increase in the incidence of the malignant form of the tumour. It should also be noted the incidence for control males in a study terminated in 2007 (within two years of this study) was 7/50, which is close to the incidence observed in the high dose males of this study. Hence, overall the incidence of benign pheochromocytoma is not considered treatment related.

Overall, in rats there were no neoplastic findings considered relevant to human health.

Mice

In the CD-1 mouse study, an increase in hepatocellular adenoma incidence was observed in males at all doses compared to the controls. There was also an increase in the incidence of carcinomas observed in top dose males.

The increased incidence in hepatocellular adenomas in males was not statistically significant nor dose-related, but did slightly exceed the laboratory historical control (2-9; Dec 2001-May 2004 and 4-12; 2007-2012) in both the low dose (13/50 - 26%) and high dose (14/50 – 28%) males, but not the mid dose group (9/50 – 18%). The incidence also slightly exceeded the historical control range in the Charles River historical control database (1.4-20%; from studies initiated between 2002 and 2006). The study also showed that many of the affected males had multiple hepatic tumours. Multiple tumours are relatively rare in this strain of mouse; however, as they were also noted in control animals they are not considered treatment related, but do suggest these animals were

particularly susceptible to developing liver tumours. No increase in the incidence of adenomas in female mice was observed in this study (hepatocellular incidence of adenomas: 3 (control), 1 (low dose), 0 (mid dose), 1 (high dose)).

A slight increase in the incidence of hepatocellular carcinoma was noted at the limit dose in males (4/50 (8%) compared to 1/50 (2%) in the contemporary control). No carcinomas were noted in females. The increase in male carcinoma incidence at the top dose was higher than either of the laboratory historical control ranges (0/50 - 2/50 (0-4%)), but was within the historical control range available for Charles River Labs where the incidence of hepatocellular hypertrophy from 13 studies conducted between 2002 and 2006 ranged from 0-15% (including an incidence of 6/60(10%) and 9/60(15%) in two 78 week studies). See tables 18a and 18b for further information on historical controls.

Table 18a. In-House Historical Control Values: Primary Hepatocellular Neoplasms in Male CD-1 Mice from 18-Month Dietary Oncogenicity Studies

	Study						
Organ/Observation	A	B	C	D	E	F	G
Necropsy Date:	12/2001	05/2003	12/2003	04-05/2004	9/2006	12/2009	9-10/2011
Final Report:	2002	2003	2005	2004	2007	2010	2012
Liver (number examined)	50	50	50	50	50	50	50
Number of animals with one or more adenoma	8	2	5	8	9	12	4
Number of animals with one or more carcinomas	3	1	0	1	1	2	0
Total Mice with Adenoma and/or Carcinoma	10	3	5	9	10	13	4

Table 18b. HCD data from Charles River (published March 2010, with 13 studies initiated between 2002 and 2006): Incidence of hepatocellular adenomas and carcinomas

	1	2	**3**	**4**	**5**	**6**	**7**	**8**	9	10	11	12	**13**	***Range***
Date	2002	2003	**2003**	2003	**2004**	2004	2004	2004	2005	2005	2005	2005	2006	
No. on study	110	50	**60**	60	**60**	60	50	60	75	60	70	50	60	
No. surviving to termination	NA	NA	**41**	48	**46**	42	40	51	49	16	18	16	49	
% Survival	NA	NA	**68.3**	80.0	**76.67**	70.0	80.0	85.0	65.3	26.67	25.71	32.0	81.67	
Study Duration (weeks)	104	104	**78**	78	**78**	78	78	78	96	104	104	104	78	
Hepatocellular Adenoma	5	10	**5**	4	**12**	6	3	5	10	1	1	4	5	***1-12 (20%)***
Hepatocellular Carcinoma	5	2	**6**	1	**9**	1	1	3	2	1			1	***1-9 (15%)***

4.10.1.2 Carcinogenicity: inhalation

No information available

4.10.1.3 Carcinogenicity: dermal

No information available

4.10.2 Human information

No information available

4.10.3 Other relevant information

Not applicable.

4.10.4 Summary and discussion of carcinogenicity

The carcinogenicity of pyroxsulam has been investigated in rats (Fischer 344) and mice (CD-1).

No treatment-related carcinogenic effects were observed in rats.

In the mouse, the incidence of liver adenomas and carcinomas was slightly higher than the contemporaneous and laboratory historical control in males, but the carcinomas were within the control range provided for Charles River Labs. In addition, whilst the incidence of adenomas was increased at the low and top dose groups, it was within the laboratory historical control range in the mid dose group. Further, these findings occurred in male mice only, which appeared to be susceptible to liver tumour formation with multiple adenomas (rather than single incidences) observed in the livers of both control and treated animals. In conclusion, it is considered that there is insufficient evidence in this study to conclude a treatment-related carcinogenic effect of pyroxsulam.

4.10.5 Comparison with criteria

As there is insufficient evidence for a carcinogenic effect in rats and mice, and there are no other concerns about the potential carcinogenicity of pyroxsulam, no classification is proposed.

4.10.6 Conclusions on classification and labelling

Not classified – conclusive but not sufficient for classification

4.11 Toxicity for reproduction

4.11.1 Effects on fertility

Table 19: Summary table of relevant reproductive toxicity studies - Fertility

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Two-generation study OECD 416 (2001) – deviation: no functional investigation of pups and no examination of reproductive tissues of weanlings GLP Oral(dietary) 27 Sprague-Dawley rats/ sex/dose Carney, Zablotny, Stebbins (2005)	Males P1 generation – 0, 106, 321 and 1078 mg/kg bw/day P2-generation – 112, 344 and 1138 mg/kg bw/day Females P1 generation – 104, 311, 1043 mg/kg bw/day P2 generation – 104, 316 and 1049 mg/kg bw/day	Parental toxicity Parental toxicity was limited to a very low incidence of perineal staining in the 300 mg/kg bw/day and 1000 mg/kg bw/day dose groups – this effect was not considered adverse. Erosion of the stomach was observed in P1 females treated with 300 mg/kg bw/day and 3 at 1000 mg/kg bw/day. The extent of the finding was very slight. The effects were not considered treatment related as not observed in the P2 animals. Reproductive toxicity No effects of treatment on mating, conception, fertility or gestation indices, post-implantation loss, time to mating, or gestation length in either generation Offspring effects 1000 mg/kg bw/day A small non-statistically significant decrease in pup weight in F1 males and females on day 21 (circa. 1 g) and F1 and F2 males on day 22 (circa 2-3g). When the individual pup weights considered, the difference did not appear biologically significant. A NOAEL for parental, reproductive and offspring effects of 1000 mg/kg bw/day was derived.

4.11.1.1 Non-human information

Information on reproductive toxicity is available from a 2-generation study in Sprague-Dawley rats.

In the study no adverse effects on reproductive toxicity was observed. The only effect on offspring observed was slightly reduced bodyweight. However, when the individual weights of the pups were considered, the difference did not appear to be biologically significant. Overall, the results suggest pyroxsulam does not affect fertility or reproductive performance.

4.11.1.2 Human information

No information available.

4.11.2 Developmental toxicity

Table 20: Summary table of relevant reproductive toxicity studies - Development

Method	Dose levels	Observations and remarks (effects of major toxicological significance)
Developmental toxicity OECD 414 (2001) – dosing started on day 6 GLP 26 female Sprague-Dawley rats/dose Oral gavage Sloter (2005a)	0, 100, 300 or 1000 mg/kg bw/day from day 6 to day 20 Vehicle – 0.5% methylcellulose	Maternal toxicity No maternal toxicity was observed Fetal examination The incidence of testicular alternations was slightly increased at 1000 mg/kg bw/day compared to controls (concurrent and historical). The observations were observed in three litters: • Missing testes (malformation) in one foetus from one litter; • Hypoplastic testis (malformation) in one foetus from another litter • Cystic testis (variation) in three fetuses from another litter In addition, one foetus from the 300 mg/kg bw/day also had a missing testis. A NOAEL for maternal and Foetal toxicity of 1000 mg/kg bw/day was derived.
Developmental toxicity study OECD 414 (2001) GLP Oral gavage 26 New Zealand White rabbits Sloter (2005b)	0, 30, 100 and 300 mg/kg bw/day in 0.5% methylcellulose – doses based on the results of a preliminary study, in which slight toxicity was observed at 300 mg/kg bw/day (decreased faecal output, mean body weight and food consumption)	Maternal toxicity One female from each treatment group died – these deaths were not considered treatment related. No treatment-related effects on bodyweight were observed at any dose level. Transient ↓ in food consumption at 300 mg/kg bw/day Foetal examination Absence of small gall bladder was observed in several foetuses from treated groups (3.5%, 2.9, 2.8% of fetuses per litter, low to high dose), but not in the controls. Since the % affected foetuses per litter only exceeded the historical control range (0.8%; 0-3%) at the lowest dose, the effect is not considered treatment related. Slight increases in the incidence of a few skeletal variations were noted, principally in the top dose group, but these were not statistically significant and were either well within the historical control range or showed no clear effect in terms of total foetal or litter incidence. No testicular effects were observed. A NOAEL of 300 mg/kg bw/day for maternal and foetal toxicity was derived.

4.11.2.1 Non-human information

Information is available from developmental toxicity studies in rat and rabbit.

In the rat study, conducted up to 1000 mg/kg bw/day, the only effects of concern were in the testes (see table for details). These effects were dismissed by the study authors on the basis of their low incidence and the fact that similar effects were not noted in the 2-generation study conducted at equivalent doses (although the 2-generation study was a dietary study whereas the developmental study was via oral gavage). In addition, the applicants also provided additional arguments to support their opinion why they were not substance related.

1) "...compounds known to produce hypoplastic testis and/or missing testis are androgen receptor antagonists or endocrine active agents (Foster and Harris, 2005; Carruthers and Foster, 2005; Anway et al, 2005). These compounds have been shown to interfere with the development of the male reproductive tract, embryonic testis development and male fertility. Male fertility in these particular studies was measured by different parameters (e.g. sperm mobility, sperm counts, testis and epididymal weights, anogenitial distance). Pyroxsulam had no effect on any of these parameters; this lack of correlation is another piece of the supportive data to consider these findings in the rat developmental study as not treatment related".

2) Reproductive alterations are rarely observed in isolation, but instead individual pups and multiple pups, within a litter, will have a suite of treatment-related effects (Foster and Harris, 2005, Carruthers ND Foster, 2005). In addition, for pyroxsulam, the absence of less serious effects that would be expected to precede the more serious effects of missing or hypoplastic testes was noted (reference to Bay, 2006). In particular, Rasoulpour proposes that cryptochrism, hypospadias and decreased testes and accessory organ weight and sperm counts would occur long before any treatment-induced missing or hypoplastic testes.

3) Testis cysts (clear sacs with a bubble like appearance) are incidental observations and not related to the hypoplastic or missing testes. This conclusion was based on data mining (no reference to similar testis cysts on normal or treated rats was found) and consultation with US and European test laboratories (most laboratories do not record these cysts). The consensus of the reproductive toxicologists consulted was that because the effect occurred in three pups from one litter it was an incidental finding.

Given the low incidence of the effects observed at the limit dose (1000 mg/kg bw/day), the absence of associated findings and the fact that similar findings were not observed in the 2-generation study or the rabbit developmental study, the effects are considered spontaneous and not treatment related. Overall, the results suggest that pyroxsulam does not cause developmental toxicity in rats.

In the rabbit developmental toxicity study, no significant maternal toxicity or evidence of treatment related effects were observed, suggesting pyroxsulam is not a developmental toxicant in rabbits.

4.11.2.2 Human information

No information available

4.11.3 Other relevant information

Not applicable

4.11.4 Summary and discussion of reproductive toxicity

Effects on fertility were investigated in a two-generation study in rats. In the study no adverse effects on reproductive toxicity was observed up to a dose of 1000 mg/kg bw/day. The only effect on offspring observed was slightly reduced bodyweight. However, when the individual weights of the pups were considered, the difference did not appear to be biologically significant. Overall, the results suggest pyroxsulam does not affect fertility or reproductive performance.

The developmental toxicity of pyroxsulam has been investigated in a developmental toxicity study in rats and rabbits. In rats, the only effects were testicular effects (missing testes, hypoplastic testes) in offspring. However, given the low incidence, the lack of related effects and failure to see similar

effects in the 2-generation study or the rabbit developmental study, these findings were not considered treatment related. In rabbits, no malformations of concern were observed. Overall, there was no evidence of a direct adverse effect on development.

4.11.5 Comparison with criteria

No effects were observed that provide sufficient evidence to cause a strong suspicion of impaired fertility or developmental toxicity.

4.11.6 Conclusions on classification and labelling

Not Classified: conclusive but not sufficient for classification

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Method	Dose Levels	Observations and Remarks	Reference
Chronic neurotoxicity study (one-year) OECD 424 (1997) GLP Dietary exposure 10 Fischer 344 rats/sex/dose	0, 10, 100 and 1000 mg/kg bw/day	4.4% ↓ bodyweight (based on all animals in this combined chronic/carcinogenicity and neurotoxicity study) was slightly reduced in females. Increased perineal staining in females and limited evidence of this effect in males There were no substance related effects on FOB findings or motor activity. There were no macroscopic or microscopic effects observed in the central or peripheral nervous systems. A NOAEL of 1000 mg/kg bw/day was derived for neurotoxicity	Maurissen, Andrus, Yano and Brooks (2005)

In a one-year neurotoxicity study in rats, there were no neuropathological findings in the central and peripheral nervous systems or any effects in the functional observation battery or on motor activity suggestive of neurotoxicity. Overall, pyroxsulam does not appear to be neurotoxic.

4.12.1.2 Immunotoxicity

No information available

4.12.1.3 Specific investigations: other studies

Not applicable

4.12.1.4 Human information

4.12.2 Summary and discussion

No neurotoxic effects were observed in a one year neurotoxicity study in rats up to a dose of 1000 mg/kg bw/day (Maurissen *et al*, 2005).

4.12.3 Comparison with criteria

No neurotoxic effects were observed in a one year neurotoxicity study in rats up to a dose of 1000 mg/kg bw/day (Maurissen *et al*, 2005).

4.12.4 Conclusions on classification and labelling

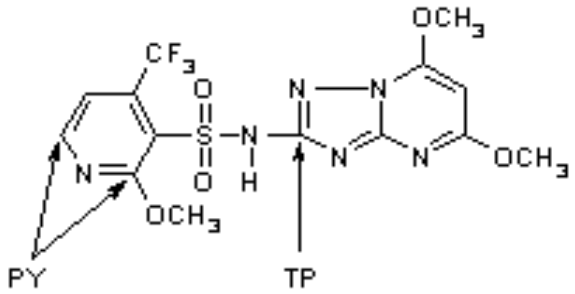
Not Classified: conclusive but not sufficient for classification

5 ENVIRONMENTAL HAZARD ASSESSMENT

Pyroxsulam (referred to in test reports as XDE-742) is a systemic post-emergence herbicide used for weed control. It is absorbed by foliage but also plant roots. Available environmental fate and hazard studies have been considered under Directive 91/414/EEC (subsequently replaced by EU Regulation 1107/2009) and summarised in the Draft Assessment Report, 2012 and subsequent DAR Addenda (Volume 3, B8; Environmental Fate and Behaviour and Volume 3, B9: Ecotoxicology). The agreed endpoints from the peer review of pyroxsulam under Directive 91/414/EEC are also included in the 2013 EFSA Conclusion.

The key information pertinent to determining a classification is presented below. All radiolabelled studies used ^{14}C-pyroxsulam with a purity of >97% and up to two labels as shown in Figure 1.

Figure 1: Structure of pyroxsulam indicating positions of the ^{14}C labels.



PY = 2- and 6- positions of pyridine ring
TP = 2-position of triazolopyrimidine ring

Pyroxsulam has a measured dissociation constant of 4.67 at 20^{o}C (Cathie, 2004). It is anticipated pyroxsulam will exist in its dissociated form at environmentally relevant pH (e.g. estimated 17.5% ionized at pH4, 68% ionised at pH 5, 95.5% ionised at pH 6, and 99.5% ionised at pH 7).

Where available information on degradation products is included – full details of degradant names and structures are presented in Annex I.

5.1 Degradation

A summary of available valid information on the fate of pyroxsulam is presented in Table 21 below.

Table 21: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Aquatic hydrolysis EPA Guideline (Subdivision N, 161-1) and SETAC Guideline (Part 1, section 9), GLP	Stable at pH 5, 7 and 9 at 20 °C	Valid	Yoder, 2004
Aquatic photolysis EPA (Subdivision N, 161-2) and SETAC Guideline (Part 1, section 10.1), GLP	Pyroxsulam DT_{50} = 4.1 days at 40°N in summer sunlight. Degradant pyridine sulfinic acid DT_{50} = 32 days at 40°N in summer sunlight. Degradant ADTP DT_{50} = 32 to 41 days at 40°N in summer sunlight.	Valid	Byrne *et al*, 2006
Ready biodegradation OECD Guideline 301B, GLP	Not rapidly biodegradable 19-23% degradation after 28 days	Valid	Schwarz, 2003
Water/sediment simulation SETAC Guideline (Part 1, section 8.2) and BBA Guideline (Part IV, section 5-1), GLP	Dissipation DT_{50} days based on whole system: 12 to 24 days Degradation DT_{50} days based on whole system: 17 to 33 days Mineralisation: 0.8 to 2% AR at 101 days	Valid Aerobic system	Yoder *et al*, 2006c

5.1.1 Stability

Aqueous hydrolysis

An aqueous hydrolysis study (Yoder, 2004) is available following GLP, US EPA Guideline Subdivision N, Series 161-1 and SETAC Guideline part 1, section 9. The study used ^{14}C radio labelled pyroxsulam (0.1 mg a.s./l). Test solutions were incubated at 20 °C in the dark for 32 days. No significant degradation was observed and analysis showed 100% radioactivity as pyroxsulam at study termination. On this basis, pyroxsulam is considered hydrolytically stable.

Aqueous photolysis

An aqueous photolysis study (Byrne *et al*, 2006) is available following GLP, US EPA Guideline Subdivision N, Series 161-2 and SETAC Guideline part 1, section 10.1. The study used ^{14}C radio labelled pyroxsulam (1.0 mg a.s./l). Test solutions were incubated at pH 7 for 15 days at 20 °C under constant irradiation using a xenon lamp (wavelengths below 290 nm filtered out). This is considered equivalent to 73.5 days of non-continuous irradiation in summer sun at 40°N.

The quantum yield of pyroxsulam was determined using an actinometer to be 4.41 $x10^{-1}$. This results in a predicted DT_{50} of 3.2 days at 40°N in summer sunlight. Correcting for lamp intensity, the experimental DT_{50} for pyroxsulam at 40°N in summer sunlight was 4.1 days.

Photodegradation is considered to occur through cleavage of the sulphonamide bridge resulting in the degradants pyridine sulfinic acid and ADTP. The DT_{50} of pyridine sulfinic acid was determined to be 32 days at 40°N in summer sunlight. The DT_{50} of ADTP was determined to be 32-41 days at 40°N in summer sunlight.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

Not available

5.1.2.2 Screening tests

A ready biodegradation study (Schwarz, 2003) is available following OECD Guideline 301B (CO_2 Evolution) and GLP using pyroxsulam. Activated sludge from a laboratory wastewater plant treating municipal sewage was used at 30 mg/l with 52 mg test item. Validation criteria for the Reference and Toxicity Controls were met. Ultimate biodegradation reached a maximum of 19 and 23% in the duplicate samples over 28 days. Overall, the substance is considered not readily biodegradable.

5.1.2.3 Simulation tests

A distribution and degradation in aerobic water-sediment system study (Yoder *et al*, 2006c) is available following SETAC Guideline (Part 1, section 8.2) and BBA Guideline (Part IV, section 5-1). The study used ^{14}C-pyroxsulam with two labels. Two aerobic systems were used: 'UK' and 'France'. The water and sediment test conditions are included in Table 22 below. The system was treated with 0.016 mg pyroxsulam per litre of water via the water surface.

Table 22: Water-sediment system test conditions

Criteria	River Roding, UK	Haut Languedoc, France
Water properties	pH: 8.3 Dissolved organic carbon: 4.8 ppm Oxygen: 0.2 mg/l at start to 2.1 mg/l at end Redox potential: 125.9 mV at start to 22.4 mV at end	pH: 8.1 Dissolved organic carbon: 5.8 ppm Oxygen: 5.0 mg/l at start to 2.0 mg/l at end Redox potential: 228.4 mV at start to 20.8 mV at end
Sediment properties	46% sand; 26% silt; 28% clay Organic carbon 2.2% at start pH: 7.3 Redox potential: -177.3mV at start to -149.2 mV at end	88% sand; 10% silt; 2% clay Organic carbon 2.9% at start pH: 4.8 Redox potential: -74.1 mV at start to -72.0 mV at end

The study was conducted at 20 °C, in the dark under aerobic conditions for up to 101 days.

Radioactivity was determined by Liquid Scintillation Counting (LSC) and subsequent analysis by High Performance Liquid Chromatography (HPLC) was undertaken. Total mean recoveries for both systems were >90% Applied Radioactivity (AR) for both labels at each sampling point.

Pyroxsulam dissipated from the water phase to the sediment phase in both systems where degradation to 7-OH-XDE-742 and ATSA occurred (Figure 2 shows the proposed aerobic degradation pathway). A third degradant was observed at >10% AR (max. 16.5% AR) but was unable to be identified. Further investigation was unable to recreate the compound and it was concluded that it was an experimental anomaly.

In water pyroxsulam decreased from initial 84-103.4% AR to 14.4-22.1% AR on day 101. In sediment pyroxsulam increased from initial 0.8–16.1% AR to peak between 17.2 and 42% AR by day 75.

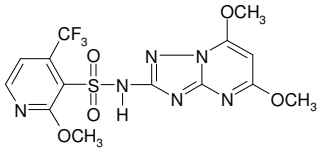
A Single First Order (SFO) kinetics approach was applied to calculated DT_{50} values. The study authors removed outliers and refitted the model to improve fit. While this approach was not statistically justified, overall slower rates were derived and the approach was accepted in the DAR.

Whole system dissipation DT_{50} values for both labels were as follows:

Pyroxsulam $DT_{50\ whole\ system}$: 24 days for UK system and 12 days for France system
7-OH-XDE-472 $DT_{50\ whole\ system}$: 16 days for UK system and 42 days for France system
ATSA $DT_{50\ whole\ system}$: 22 days for UK system and 71 days for France system

Minimal mineralisation was observed with a maximum of 2% AR in UK system and 0.8% AR in France system after 101 days.

Figure 2: Proposed degradation pathway of pyroxsulam in water-sediment systems under aerobic conditions (taken from DAR, Volume 3, Annex B8: Environmental Fate and Behaviour – January 2012)



Pyroxsulam (XDE-742)

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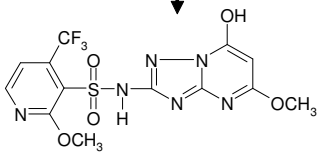
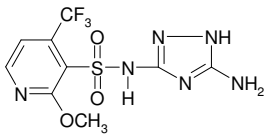


7-OH-XDE-742



XDE-742 ATSA

CO_2 (minor) + Bound residues

5.1.3 Summary and discussion of degradation

Pyroxsulam is considered hydrolytically stable.

Pyroxsulam is susceptible to photodegradation. The experimental DT_{50} in sterile pure water was 4.1 days at 40°N in summer sunlight. Two degradants were identified with DT_{50} values of 32 and 21-41 days 40°N in summer sunlight. The actual degree of photodegradation in the aquatic environment depends on local conditions and seasons. Therefore, in reality the potential for aquatic photolysis is likely to be limited.

In a ready biodegradation study a maximum of 23% degradation was observed over 28 days and pyroxsulam is considered to be 'not readily degradable'.

In an aerobic water-sediment study pyroxsulam was observed to dissipate from the water column to sediment in two systems where subsequent decline was also noted. Estimated whole system dissipation DT_{50} values for pyroxsulam were between 12 and 24 days. Two key degradants were observed with whole system DT_{50} values of 16 to 42 and 22 to 71 days. Minimal mineralisation (maximum 2% AR by day 101) was observed.

Overall, the degradation information does not provide sufficient data to show pyroxsulam is ultimately degraded within 28 days (equivalent to a half-life <16 days) or transformed to non classifiable products. Consequently, pyroxsulam is considered not rapidly degradable for the purpose of classification and labelling.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Following OECD Test Guideline 106 and GLP, a soil adsorption study (Smith, 2004) is available investigating the adsorption of pyroxsulam. The study used 10 soils from the UK and Germany and ^{14}C-pyroxsulam. Soil pH ranged from 5.4 to 7.9 and organic carbon from 0.8 to 3.8%. When normalised for organic carbon, adsorption was observed to be pH dependant with increasing adsorption with decreasing soil pH. The K_{oc} values ranged between 3.62 and 83.86 ml/g. This equates to log K_{oc} values between 0.56 and 1.92.

5.2.2 Volatilisation

Experimental data (Madsen and Kastel, 2003) indicate the vapour pressure for pyroxsulam is $<1 \times 10^{-7}$ Pa at 20 °C following OECD Test Guideline 104. The Henry's Law Constant (Madsen, 2006b) was calculated to be $<1.36 \times 10^{-8}$ Pa m^3 mol^{-1} at 20 °C, pH 7 indicating pyroxsulam is unlikely to partition from the water phase to air.

5.2.3 Distribution modelling

Not relevant for classification and labelling.

5.3 Aquatic Bioaccumulation

Table 23: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
Partition coefficient *n*-octanol/water (shake flask method)	Log K_{ow} 1.08 at pH 4, 20°C Log K_{ow} -1.01 at pH 7, 20°C Log K_{ow} -1.6 at pH 9, 20°C	Valid	Turner, (2004b)

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

No data available.

5.3.1.2 Measured bioaccumulation data

No data available.

5.3.2 Summary and discussion of aquatic bioaccumulation

The experimental log K_{ow} for pyroxsulam is 1.08 at pH 4 and -1.01 at pH 7 and 20°C (Turner, 2004b). The lower pH 4 value is anticipated to represent the non-ionised form while the pH 7 value is anticipated to reflect a predominantly ionised form likely to be present at environmentally relevant pH. Overall, the log K_{ow} is below the CLP logK_{ow} trigger value of ≥ 4 intended to identify substances with a potential to bioaccumulate. Given this low value, an experimental BCF study was not required.

5.4 Aquatic toxicity

A summary of available valid information on the aquatic toxicity of pyroxsulam (98% purity) is presented in Table 24. Where available, a summary of valid information for degradants is also included in Annex II, Table 1.

Studies were reviewed under Directive 91/414/EEC and considered valid and reliable. Further details are presented for studies conducted on the active substance pyroxsulam but not for its degradants as these are all of similar or lower toxicity and are not considered further for the environmental hazard classification of pyroxsulam.

The water solubility of pyroxsulam is pH dependant (16.4 mg/l at pH4, 3.2 g/l at pH 7 and 13.7 g/l at pH 9. The water pH during aquatic testing is noted in Table 24. Given experimental pH values, this is not anticipated to have affected key study results.

Table 24: Summary of relevant information on aquatic toxicity for pyroxsulam (XDE-742)

Guideline / GLP status	Species	Endpoint	Exposure		Results		Reference
			Design	Duration	Endpoint	Toxicity (mg a.s./l)	
Acute toxicity to fish OECD Guideline 203, GLP, purity: 98%	Rainbow Trout (*Oncorhynchus mykiss*)	Mortality	Static pH 7.5 to 8.5	96 hours	LC_{50}	>87 (mm)	Zok, 2003c
Acute toxicity to fish OECD Guideline 203, GLP, purity: 98%	Fathead Minnow (*Pimephales promelas*)	Mortality	Static pH 7.5 to 8.5	96 hours	LC_{50}	>94.4 (mm)	Zok, 2003d
Fish Early Life-Stage (FELS) toxicity OECD Guideline 210, GLP, purity: 98%	Fathead Minnow (*Pimephales promelas*)	Time to hatch, hatching success, survival and growth (length, wet weight and dry weight)	Flow-through pH 7.0 to 7.5	40 days	NOEC	10.1 (mm)	Marino *et al*, 2005
Daphnia sp Acute Immobilisation OECD Guideline, 202 GLP, purity: 98%	*Daphnia magna*	Acute immobilisation	Static pH 7.2 to 8.0	48 hours	EC_{50}	>100 (mm)	Marino *et al*, 2004
Daphnia magna Reproduction OECD Guideline 211, GLP, purity: 98%	*Daphnia magna*	Survival; reproduction; growth	Flow-through pH 7.2 to 7.9	21 days	NOEC	10.4 (mm)	Marino *et al*, 2005
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity: 98%	*Pseudo-kirchneriella subcapitata**	Cell multiplication inhibition	Static pH 7.5-7.7 to 8.6-10.5	72 hours	ErC_{50} NOErC	0.924 (mm) 0.055 (mm)	Hancock *et al*, 2004
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity: 98%	*Anabaena flos-aquae*	Cell multiplication inhibition	Static pH 5.0-7.4 to 5.1-7.6	72 hours	ErC_{50} NOErC	41 (mm) 13 (mm)	Hoberg, 2005a
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity: 98%	*Skeletonema costatum*	Cell multiplication inhibition	Static pH 7.9-8.2 to 8.2-8.7	96 hours	ErC_{50} NOErC	59 (mm) 3.4 (mm)	Hancock *et al*, 2005
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity: 98%	*Navicula pelliculosa*	Cell multiplication inhibition	Static pH 6.8-7.1 to 6.8-9.2	72 hours	ErC_{50} NOErC	6.9 (mm) 4 (mm)	Hoberg, 2005b
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP, purity: 98%	*Lemna gibba*	Growth	Semi-static pH 7.5-7.9 to 7.1-8.3	7 days	ErC_{50} NOErC	**0.00388 (mm)** **0.000681 (mm)**	Hancock *et al*, 2005b

Guideline / GLP status	Species	Endpoint	Exposure		Results		Reference
			Design	Duration	Endpoint	Toxicity (mg a.s./l)	
Sediment-water toxicity Test. OECD Guideline 219, purity: 98%	*Chrionomus riparius*	Emergence and survival	Static, spike water pH 7.4-8.3	28 days	NOEC	100 (n)	Henry *et al*, 2005

Notes:
mm refers to results based on mean measured test concentrations
n refers to nominal concentrations
*formerly *Selenastrum capricornutum*

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Two acute toxicity to fish studies using pyroxsulam (purity >98%) are available following GLP and OECD Guideline 203.

Study 1 (Zok, 2003c)

Using Rainbow Trout (*Oncorhynchus mykiss*), a static limit test was performed using the nominal concentration 100 mg/l. Study conditions were within the test guideline range and validation criteria were met. Analytical verification was >86% of nominal. The study 96-h LC_{50} was >100 mg a.s./l (nominal), >87 mg a.s./l (mean measured). The study 96-h NOEC was 100 mg a.s./l (nominal), 87 mg a.s./l (mean measured).

Study 2 (Zok, 2003d)

Using Fathead Minnow (*Pimephales promelas*) a static limit test was performed using the nominal concentration 100 mg/l. Aside from one dissolved oxygen measurement dropping to 58% below the 60% guideline, study conditions were within the test guideline range and validation criteria were met. The study 96-h LC_{50} was >100 mg a.s./l (nominal), >94.4 mg a.s./l (mean measured). The study 96-h NOEC was 100 mg a.s./l (nominal), 94.4 mg a.s./l (mean measured).

5.4.1.2 Long-term toxicity to fish

A 40-day flow-through chronic toxicity to fish study (Marino *et al*, 2005) using pyroxsulam following GLP and OECD Guideline 210 is available. The study used Fathead Minnow (*Pimephales promelas*) and the following endpoints: time to hatch, hatching success, survival and growth. The nominal exposure range was 0.778, 1.3, 2.16, 3.69, 6 and 10 mg a.s./l. Results were based on mean measured values: 0.836, 1.28, 2.23, 3.62, 6.11 and 10.1 mg a.s./l. Validity criteria were met and the test is considered reliable. Significant effects were not observed for any parameter. The study 40-d NOEC was 10.1 mg a.s./l reflecting the highest mean measured exposure concentration.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

A static acute toxicity to *Daphnia magna* study (Marino *et al*, 2004) using pyroxsulam is available following GLP and OECD Guideline 202. The nominal exposure range was 13, 21.6, 36, 60 and 100 mg a.s./l. Results were based on mean measured values: 12.2, 20.6, 34.9, 58.8 and 100 mg a.s./l. Validity criteria were met and the test is considered reliable. As no significant effects were observed, the study 48-h LC_{50} was >100 mg a.s./l based on mean measured. The study 48-h NOEC was 100 mg a.s./l based on mean measured.

5.4.2.2 Long-term toxicity to aquatic invertebrates

A semi-static chronic toxicity to *Daphnia magna* study (Marino *et al*, 2005) using pyroxsulam is available following GLP and OECD Guideline 211. The study assessed the following endpoints: survival, reproduction, length and weight. The nominal exposure range was 0.0313, 0.625, 1.25, 2.5, 5 and 10 mg a.s./l. Results were based on mean measured values: 0.0353, 0.701, 1.37, 2.66, 5.27 and 10.4 mg a.s./l. Validity criteria were met and the test is considered reliable. Significant effects were not observed for any parameter. The study 21-d NOEC was 10.4 mg a.s./l reflecting the highest mean measured exposure concentration.

5.4.3 Algae and aquatic plants

Algae:

Four algal growth inhibition studies using pyroxsulam are available.

Study 1 (Hancock *et al*, 2004)

A static algal growth inhibition test using pyroxsulam (purity 98%) and *Pseudokirchneriella subcapitata* is available following GLP and OECD Guideline 201. The nominal exposure range was 0.0313, 0.0625, 0.125, 0.25, 0.5, 1 and 2 mg a.s./l. Results were based on mean measured values: 0.0261, 0.0550, 0.126, 0.252, 0.503, 1.01 and 2.04 mg a.s./l. Validity criteria were met and the test is considered reliable. The 72-h E_rC_{50} was 0.924 mg a.s./l and the 72-hour NOE_rC was 0.055 mg a.s./l based on mean measured concentrations.

Study 2 (Hoberg *et al*, 2005a)

A static algal growth inhibition test using pyroxsulam (purity 98%) and the cyanobacteria *Anabaena flos-aquae* is available following GLP and OECD Guideline 201. The nominal exposure range was 0.041, 1.0, 2.6, 6.4, 16, 40 and 100 mg a.s./l. Results were based on mean measured values: 0.036, 0.89, 2.2, 5.4, 13, 28 and 85 mg a.s./l. Validity criteria were met and the test is considered reliable. Initial pH values were 5 to 7.4 and final pH values 5.1 to 7.6. Study observations did not include undissolved material and the lower range pH is not anticipated to have affected study results. The 72-h E_rC_{50} was 41 mg a.s./l and the 72-hour NOE_rC was 13 mg a.s./l based on mean measured concentrations.

Study 3 (Hancock *et al*, 2005)

A static algal growth inhibition test using pyroxsulam (purity 98%) and diatom *Skeletonema costatum* is available following GLP and OECD Guideline 201. The nominal exposure range was 3.13, 6.25, 12.5, 25, 50 and 100 mg a.s./l. Results were based on mean measured values: 3.4, 6.8, 13.6, 26.7, 52.8 and 105 mg a.s./l. Validity criteria were met and the test is considered reliable. The

96-h E_rC_{50} was 59 mg a.s./l and the 96-hour NOE_rC was 3.4 mg a.s./l based on mean measured concentrations.

Study 4 (Hoberg, 2005b)

A static algal growth inhibition test using pyroxsulam (purity 98%) and *Navicula pelliculosa* is available following GLP and OECD Guideline 201. The nominal exposure range was 0.1, 0.26, 0.64, 1.6, 4 and 10 mg a.s./l. Results were based on mean measured values: 0.1, 0.29, 0.67, 1.7, 4 and 10 mg a.s./l. Validity criteria were met and the test is considered reliable. The 72-h E_rC_{50} was 6.9 mg a.s./l and the 72-hour NOE_rC was 4 mg a.s./l based on mean measured concentrations.

Aquatic plants:

A semi-static 7-day toxicity to *Lemna gibba* study (Hancock *et al*, 2005b) using pyroxsulam is available following GLP and OECD Guideline 221.

Exposure solutions were prepared with the aid of the solvent DMF (0.1ml/l) and a solvent control was included. The nominal exposure range was 0.313, 0.625, 1.25, 2.5, 5 and 10 µg a.s./l. Analytical measurement used liquid chromatography positive electrospray ionization mass spectrometry (LC/PESI-MS). Results were based on mean measured fresh media concentrations from days 0, 3 and 5 as pyroxsulam was considered stable based on analytical concentrations of expired solutions which were 89.5 to 117% nominal. This resulted in a mean measured test concentration range of: 0.335, 0.681, 1.34, 2.81, 5.23 and 10.3 µg/l.

The study pH was 7.5 – 7.9 initially and 7.1 – 8.3 for expired solutions with plants. Validity criteria were met and the test is considered reliable. The study endpoints were percentage reduction in frond number, biomass, growth rate based on frond number and growth rate based on biomass. Table 25 shows growth rates in relation to exposure concentrations. Table 26 shows effect concentrations and NOEC values for assessed endpoints.

Table 25: Summary of pyroxsulam (XDE-742) effects on growth rate of the aquatic plant, *Lemna gibba*

Mean Measured Concentration (µg a.s./L)	Mean growth rate per day	% Difference [a]
Control	0.404	---
Vehicle Control	0.393	---
Pooled Control	0.398	---
0.335	0.411	-3
0.681	0.405	-2
1.34	0.376*	5
2.81	0.249*	37
5.23	0.131*	67
10.3	0.0844*	79

[a] Percent difference as compared to the pooled control was determined on day 7

* Growth was significantly less than the pooled control (Dunnett's test, p = 0.05).

Table 26: Summary of pyroxsulam (XDE-742) effect concentrations for the aquatic plant, *Lemna gibba* - based on mean measured test concentrations over 7 days exposure

Endpoint	Parameter Effect Concentration as µg a.s./L		
	EC_{50}	95% confidence limit	NOEC
Frond Number	2.57	1.16 - 5.70	0.681
Growth Rate	3.88	1.68 - 8.97	0.681
Biomass as Dry Weight	3.82	2.23 - 6.56	0.681

The key growth rate endpoint for acute hazard classification purposes is the 7-d E_rC_{50} of 0.00388 mg a.s./l (95% confidence intervals 0.00168 to 0.00897 mg a.s./l) based on mean measured. The key growth rate endpoint for chronic classification is the 7-d NOE_rC of 0.000681 mg a.s./l, also based on mean measured test concentrations.

5.4.4 Other aquatic organisms (including sediment)

A static 28-day toxicity to *Chrironomus riparius* (midge larvae) study (Henry *et al*, 2005) is available using pyroxsulam (98% purity) following OECD Guideline 219. The nominal exposure range was 6.25, 12.5, 25, 50 and 100 mg a.s./l. Exposure was via the water phase and a sediment phase was present. Concentrations of pyroxsulam (as a percentage of nominal) in the water phase were 104% on day 0, 86.3% on day 7 and 99% on day 28. Validity criteria were met and the test is considered reliable. No statistical differences were observed between exposure and control systems. The 28-day NOEC was 100 mg a.s./l based on nominal.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

For the purpose of classification, pyroxsulam is considered not rapidly degradable.

The experimental log K_{ow} for pyroxsulam is 1.08 at pH 4 and -1.01 at pH 7 and 20°C. The lower pH 4 value is anticipated to represent the non-ionised form while the pH 7 value is anticipated to reflect a predominantly ionised form likely to be present at environmentally relevant pH. Overall, the log K_{ow} is considered to be below the CLP log K_{ow} trigger value of ≥ 4 intended to identify substances with a potential to bioaccumulate.

Identified degradants are of similar or lower toxicity to the parent substance (see Annex II) and are not considered further for the environmental classification of pyroxsulam.

Aquatic acute toxicity data on pyroxsulam are available for fish, invertebrates, algae and aquatic plants. Aquatic plants are the most acutely sensitive trophic group. The lowest $L(E)C_{50}$ value is a 7-day E_rC_{50} of 0.00388 mg/l for *Lemna minor* in the range 0.001 to ≤0.01 mg/l. On this basis pyroxsulam should be classified as Aquatic Acute 1 with an M factor of 100.

Adequate chronic toxicity data on pyroxsulam are available for fish, invertebrates, algae and aquatic plants. The lowest value is a 7-day NOE_rC for *Lemna minor* of 0.0007 mg/l. Given this is in the range 0.0001 to ≤0.001 mg/l and the substance is considered non-rapidly degradable, pyroxsulam should be classified as Aquatic Chronic 1 with an M factor of 100.

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Aquatic Acute 1; H400: Very toxic to aquatic life
Acute M factor = 100
Aquatic Chronic 1; H410: Very toxic to aquatic life with long lasting effects
Chronic M factor = 100

6 OTHER INFORMATION

None

7 REFERENCES

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Toxicology and metabolism

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KIIA 8.4.1/06	Hoberg, J.R.	2005d	7-OH Metabolite of XDE-742 - Acute Toxicity to the Freshwater Green Alga, Pseudokirchneriella Subcapitata Springborn Smithers Laboratories DAS Report No.: 50108 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.4.1/07	Hancock, G.A.; Arnold, B.H.; Najar, B.S.; Sushynski, J.M.	2006a	ATSA Metabolite of XDE-742 Growth Inhibition Test with the Freshwater Green Alga, Pseudokirchneriella Subcapitata The Dow Chemical Company DAS Report No.: 61002 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.4.1/08	Hoberg, J.R.	2006a	5-OH Metabolite of XDE-742 - Acute Toxicity to the Freshwater Green Alga, Pseudokirchneriella Subcapitata Springborn Smithers Laboratory DAS Report No.: 50107 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.4.1/09	Hoberg, J.R.	2006b	5,7-Di-OH Metabolite of XDE-742 - Acute Toxicity to the Freshwater Green Alga, Pseudokirchneriella Subcapitata Sprinborn Smithers Laboratories DAS Report No.: 50109 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N

Annex Point/ Reference Number	Author(s)	Year	Title Source (where different from the Company), Company, Report Number, GLP or GEP status (where relevant), Published or not
KIIA 8.4.1/10	Hoberg, J.R.	2006c	6-C1-7-OH Metabolite of XDE-742 - Acute Toxicity to the Freshwater Green Alga, Pseudokirchneriella Subcapitata Springborn Smithers Laboratory DAS Report No.: 50112 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.4.1/11	Hoberg, J.R.	2006d	ADTP Metabolite of XDE-742 - Acute Toxicity to the Freshwater Green Alga, Pseudokirchneriella Subcapitata Springborn Smithers Laboratories DAS Report No.: 50111 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.4.1/12	Aufderheide, J.	2007	Sulfonamide Metabolite of XDE-742: Growth Inhibition Test with the Unicellular Green Alga, *Pseudokirchneriella subcapitata* ABC Laboratories DAS Report No.: 070314 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.5.2/01	Henry, K.S.; McClymont, E.L.; Najar, J.R.	2005	XDE-742: 28-Day Chronic Toxicity Study with the Midge, Chironomus riparius, Using Spiked Water in a Sediment-Water Exposure System The Dow Chemical Company DAS Report No.: 41061 (Masterfile Number): 149503 GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.5.2/02	Putt, A.E.	2006	7-OH Metabolite of XDE-742 - Chironomid Toxicity Test with Midge (Chironomus Riparius) Under Static Conditions Using Spiked Water Springborn Smithers Laboratories DAS Report No.: 50166 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.6/01	Hancock, G.A.; McClymont, E.L.; Najar, J.R.	2005	XDE-742: Growth Inhibition Test with the Aquatic Plant Duckweed, Lemna gibba The Dow Chemical Company DAS Report No.: 41124 (Masterfile Number): 207218 GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.6/03	Hoberg, J.R.	2005e	XDE-742 Sulfinic Acid Metabolite Toxicity to Duckweed, Lemna Gibba Springborn Smithers Laboratories, USA DAS Report No.: 50122 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N

Annex Point/ Reference Number	Author(s)	Year	Title Source (where different from the Company), Company, Report Number, GLP or GEP status (where relevant), Published or not
KIIA 8.6/04	Hoberg, J.R.	2006e	7-OH Metabolite of XDE-742 - Toxicity to Duckweed, Lemna Gibba Springborn Smithers Laboratories DAS Report No.: 50119 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.6/05	Hancock, G.A.; Arnold, B.H.; Najar, J.R.; Sushynski, J.M.	2006b	ATSA Metabolite of XDE-742: Growth Inhibition Test with the Aquatic Plant Duckweed, Lemna Gibba The Dow Chemical Company DAS Report No.: 61006 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.6/06	Hoberg, J.R.	2006f	5-OH Metabolite of XDE-742 - Toxicity to Duckweed, Lemna Gibba Springborn Smithers Laboratories DAS Report No.: 50120 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.6/07	Hoberg, J.R.	2006g	5,7-Di-OH Metabolite of XDE-742 - Toxicity to Duckweed, Lemna Gibba Springborn Smithers Laboratories DAS Report No.: 50121 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.6/08	Hoberg, J.R.	2006h	6-C1-7-OH Metabolite of XDE-742 - Toxicity to Duckweed, Lemna Gibba Springborn Smithers Laboratories DAS Report No.: 50124 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.6/09	Hoberg, J.R.	2006i	ADTP Metabolite of XDE-742 - Toxicity to Duckweed, Lemna Gibba Springborn Smithers Laboratories DAS Report No.: 50123 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N
KIIA 8.6/10	Hicks, S.L.	2007	Sulfonamide Metabolite of XDE-742: Growth Inhibition Test with the Freshwater Aquatic Plant, Duckweed, *Lemna gibba* ABC Laboratories DAS Report No.: 070315 (Masterfile Number): n/a GLP/GEP (Y/N): Y Published (Y/N): N

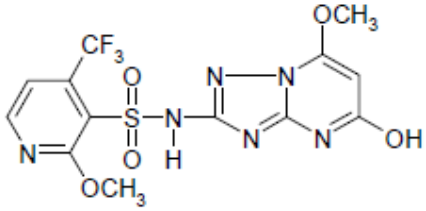
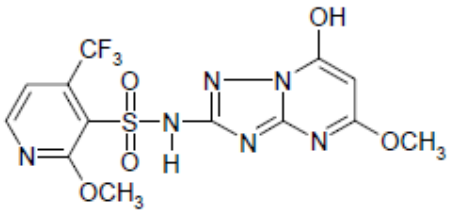
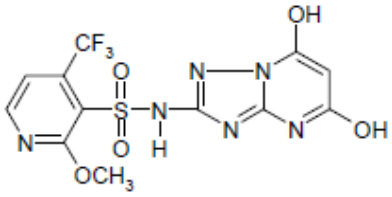
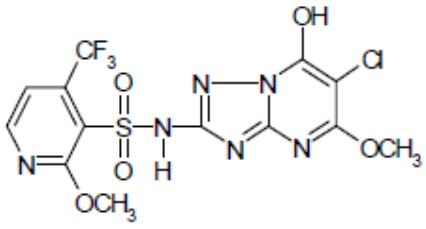
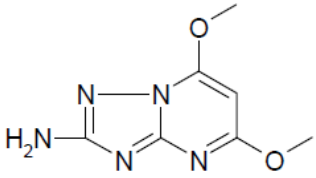
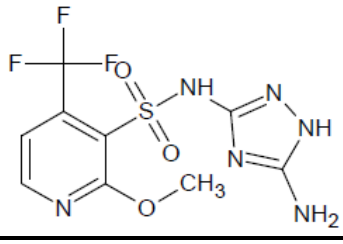
8 ANNEXES

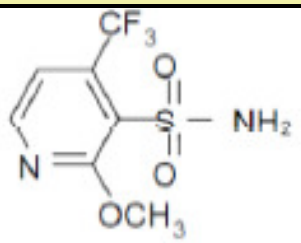
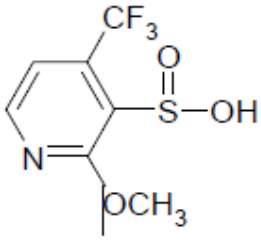
Annex I - Degradant code, chemical name and structure.

Annex II - Aquatic toxicity data for pyroxsulam degradants

ANNEX I – Degradant code, chemical name and structure.

Table 1: Identity of degradants

Name / code name	Chemical name	Structural formula
5-OH-pyroxsulam 5-OH-XDE-742	*N*-(5-hydroxy-7-methoxy[1,2,4] triazolo[1,5-*a*]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-3-pyridinesulfonamide	
7-OH-pyroxsulam 7-OH-XDE-742	*N*-(7-hydroxy-5-methoxy[1,2,4] triazolo[1,5-*a*]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)pyridine-3-sulfonamide	
5,7-OH-pyroxsulam 5,7-diOH-XDE-742	*N*-(5,7-dihydroxy[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl)-3-pyridinesulfonamide	
6-Cl-7-OH-pyroxsulam 6-Cl-7-OH-XDE-742	*N*-(6-chloro-7-hydroxy-5-methoxy [1,2,4] triazolo[1,5-*a*]pyrimidin-2-yl)-2-methoxy-4-(trifluoromethyl) pyridine -3-sulfonamide	
ATDP	5,7-dimethoxy[1,2,4]triazolo[1,5-a]pyrimidin-2-amine	
ATSA	*N*-(5-amino-1*H*-1,2,4-triazol-3-yl)-2-methoxy-4-(trifluoromethyl)-3-pyridinesulfonamide	

Name / code name	Chemical name	Structural formula
Pyridine sulfonamide	2-methoxy-4-(trifluoromethyl)pyridine-3-sulfonamide (IUPAC)	
Pyridine sulfinic acid	2-methoxy-4-(trifluoromethyl)pyridine-3-sulfinic acid (IUPAC) 3-pyridinesulfinic acid, 2-methoxy-3-trifluoromethyl (CAS)	

ANNEX II – Aquatic toxicity data for pyroxsulam degradants

Table 1: Summary of relevant information on aquatic toxicity for pyroxsulam degradants

Degradant / Guideline / GLP status	Species	Endpoint	Exposure		Results		Reference
			Design	Duration	Endpoint	Toxicity (mg/l)	
7-OH-XDE-742							
Acute toxicity to fish OECD Guideline 203, GLP, purity 99%)	Rainbow Trout (*Oncorhynchus mykiss*)	Mortality	Static	96 hours	LC_{50}	>120 (mm)	Sayers, 2006a
Daphnia sp Acute Immobilisation OECD Guideline, 202, GLP, purity 99%)	*Daphnia magna*	Acute immobilisation	Static	48 hours	EC_{50}	>99 (mm)	Sayers, 2006b
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity 96%)	*Pseudokirchneriella subcapitata**	Cell multiplication inhibition	Static	72 hours	ErC_{50} NOErC	65 (mm) 16 (mm)	Hoberg, 2005d
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP, purity 99%)	*Lemna gibba*	Growth	Semi-static	7 days	ErC_{50} NOErC	4.0 (mm) 0.74 (mm)	Hoberg, 2006e
Sediment-water toxicity Test. OECD Guideline 219, purity: 99%	*Chrionomus riparius*	Emergence and survival	Static, spike water	28 days	NOEC	30 (n)	Putt, 2006
ATSA							
Acute toxicity to fish OECD Guideline 203, GLP, purity 99%)	Rainbow Trout (*Oncorhynchus mykiss*)	Mortality	Static	96 hours	LC_{50}	>119 (mm)	Marino *et al*, 2006a
Daphnia sp Acute Immobilisation OECD Guideline, 202, GLP, purity 100%)	*Daphnia magna*	Acute immobilisation	Static	48 hours	EC_{50}	>121 (mm)	Marino *et al*, 2006b
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity 100%)	*Pseudokirchneriella subcapitata**	Cell multiplication inhibition	Static	72 hours	ErC_{50} NOErC	42.8 (mm) <3.06 (mm)	Hancock *et al*, 2006a
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP, purity 99%)	*Lemna gibba*	Growth	Semi-static	7 days	ErC_{50} NOErC	>120 (mm) 120 (mm)	Hancock *et al*, 2006b

Pyridine sulfinic acid							
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity 98%)	*Pseudokirchneriella subcapitata**	Cell multiplication inhibition	Static	72 hours	ErC_{50} NOErC	>97 (mm) 55 (mm)	Hoberg, 2005c
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP, purity 98%)	*Lemna gibba*	Growth	Semi-static	7 days	ErC_{50} NOErC	>110 (mm) 110 (mm)	Hoberg, 2005e
5-OH-XDE-742							
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity 100%)	*Pseudokirchneriella subcapitata**	Cell multiplication inhibition	Static	72 hours	ErC_{50} NOErC	>80 (mm) 80 (mm)	Hoberg, 2006a
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP, purity 100%)	*Lemna gibba*	Growth	Semi-static	7 days	ErC_{50} NOErC	7.4 (mm) 1.7 (mm)	Hoberg, 2005f
6-Cl-7-OH-XDE-742							
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity 99%)	*Pseudokirchneriella subcapitata**	Cell multiplication inhibition	Static	72 hours	ErC_{50} NOErC	85 (mm) 39 (mm)	Hoberg, 2006c
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP, purity 99%)	*Lemna gibba*	Growth	Semi-static	7 days	ErC_{50} NOErC	46 (mm) 16 (mm)	Hoberg, 2005h
ADTP							
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity 98%)	*Pseudokirchneriella subcapitata**	Cell multiplication inhibition	Static	72 hours	ErC_{50} NOErC	>92 (mm) 92 (mm)	Hoberg, 2006d
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP, purity 98%)	*Lemna gibba*	Growth	Semi-static	7 days	ErC_{50} NOErC	>93 (mm) 93 (mm)	Hoberg, 2006i
5,7-di-OH-XDE-742							
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity 98%)	*Pseudokirchneriella subcapitata**	Cell multiplication inhibition	Static	72 hours	ErC_{50} NOErC	60 (mm) 36 (mm)	Hoberg, 2006b
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP, purity 98%)	*Lemna gibba*	Growth	Semi-static	7 days	ErC_{50} NOErC	>95 (mm) 37 (mm)	Hoberg, 2006g

Pyridine sulfonamide							
Freshwater Algal Growth Inhibition OECD Guideline 201, GLP, purity 96%)	*Pseudokirchneriella subcapitata**	Cell multiplication inhibition	Static	72 hours	ErC_{50} NOErC	>114 (mm) 114 (mm)	Auferheide, 2007
Lemna sp. Growth Inhibition Test OECD Guideline 221, GLP, purity 96%)	*Lemna gibba*	Growth	Semi-static	7 days	ErC_{50} NOErC	>114 (mm) 114 (mm)	Hicks, 2007

Notes:
mm refers to mean measured
*formerly *Selenastrum capricornutum*