Committee for Risk Assessment

RAC

Annex 1

Background document

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

clethodim (ISO); (5RS)-2-{(1EZ)-1-[(2E)-3-chloroallyloxyimino] propyl}-5-[(2RS)-2-(ethylthio)propyl]-3-hydroxycyclohex-2-en-1-one

EC Number: -

CAS Number: 99129-21-2

CLH-O-0000001412-86-91/F

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

Adopted

4 December 2015

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Clethodim

EC Number: not available

CAS Number: 99129-21-2

Index Number: not available

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Clethodim
EC number:	Not available
CAS number:	99129-21-2
Annex VI Index number:	Not available
Degree of purity:	≥ 930 g/kg
Impurities:	toluene; max. 4 g/kg

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	Acute Tox. 4, H302 Skin sens. Cat 1, H317 Aquatic chronic 3, H412
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox. 4, H302 Skin sens. Cat 1, H317 Aquatic chronic 3, H412

As clethodim is an active substance used in plant protection products and not included yet in Annex VI of CLP, RAC is also asked to confirm the non-classification for the other hazard classes.

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	Not classified	none	Not classified	conclusive but not sufficient for classification
2.2.	Flammable gases	Not classified	none	Not classified	conclusive but not sufficient for classification
2.3.	Flammable aerosols	Not classified	none	Not classified	conclusive but not sufficient for classification
2.4.	Oxidising gases	Not classified	none	Not classified	conclusive but not sufficient for classification
2.5.	Gases under pressure	Not classified	none	Not classified	conclusive but not sufficient for classification
2.6.	Flammable liquids	Not classified	none	Not classified	conclusive but not sufficient for classification
2.7.	Flammable solids	Not classified	none	Not classified	conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	Not classified	none	Not classified	conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	Not classified	none	Not classified	conclusive but not sufficient for classification
2.10.	Pyrophoric solids	Not classified	none	Not classified	conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	Not classified	none	Not classified	conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	Not classified	none	Not classified	conclusive but not sufficient for classification
2.13.	Oxidising liquids	Not classified	none	Not classified	conclusive but not sufficient for classification
2.14.	Oxidising solids	Not classified	none	Not classified	conclusive but not sufficient for classification
2.15.	Organic peroxides	Not classified	none	Not classified	conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	Not classified	none	Not classified	conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	Acute Tox. 4	none	Not classified	

	Acute toxicity - dermal	Not classified	none	Not classified	conclusive but not sufficient for classification
	Acute toxicity - inhalation	Not classified	none	Not classified	conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	Not classified	none	Not classified	conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	Not classified	none	Not classified	conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	Not classified	none	Not classified	conclusive but not sufficient for classification
3.4.	Skin sensitisation	Skin sens. Cat 1	none	Not classified	
3.5.	Germ cell mutagenicity	Not classified	none	Not classified	conclusive but not sufficient for classification
3.6.	Carcinogenicity	Not classified	none	Not classified	conclusive but not sufficient for classification
3.7.	Reproductive toxicity	Not classified	none	Not classified	conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	Not classified	none	Not classified	conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	Not classified	none	Not classified	conclusive but not sufficient for classification
3.10.	Aspiration hazard	Not classified	none	Not classified	conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Aquatic chronic 3	none	Not classified	
5.1.	Hazardous to the ozone layer	Not classified	None	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: Signal word: warning
Hazard statements: H302, H317, H412, EUH066
Precautionary statements: not relevant to Annex VI.

Proposed notes assigned to an entry: none

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2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Clethodim has not been included in Annex VI of the CLP regulation.

2.2 Short summary of the scientific justification for the CLH proposal

The substance should be classified as acute Tox. 4, H302 based on the results of the acute oral toxicity study (LD_{50} 1133 mg a.i./kg bw).

Clethodim should be classified as a skin sensitiser (category 1, H317) because a positive response in a GPMT test higher than >30% is observed. Subcategory 1B is required when ≥30% responses at 1% intradermal induction dose. However, as category 1A cannot be excluded category 1 is proposed.

Clethodim needs to be classified as Aquatic Chronic 3, H412 for the environment according to CLP because it is rapidly degradable and chronic toxicity NOEC value for aquatic plant < 1 mg/l.

2.3 Current harmonised classification and labelling

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

None.

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

This paragraph is considered irrelevant seen the repeal of Directive 67/548/EEC with effect from 1 June 2015.

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Number of Notifiers
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms Signal Word Code(s)			
Aquatic Chronic 3	H412	H412					24
Acute Tox. 4	H302	H302		GHS07			19

Aquatic Chronic 2	H411	H411		GHS09 Wng			
Acute Tox. 4	H302	H302	EUH401	GHS07 Wng			4
Skin Irrit. 2	H315	H315					
Skin Sens. 1	H317	H317					
Acute Tox. 4	H302	H302		GHS07 Wng			1
Aquatic Chronic 3	H412	H412					

ECHA C&L inventory update 31/05/2012.

2.4.2 Current self-classification and labelling based on DSD criteria

This paragraph is considered irrelevant seen the repeal of Directive 67/548/EEC with effect from 1 June 2015.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Clethodim is an active substance used in plant protection products and is placed on Annex I of EC/1107/2009 (EC/87/2012). Therefore, clethodim shall normally be subject to harmonised classification and labelling (CLP article 36.2).

Part B.

SCIENTIFIC EVALUATION OF THE DATA

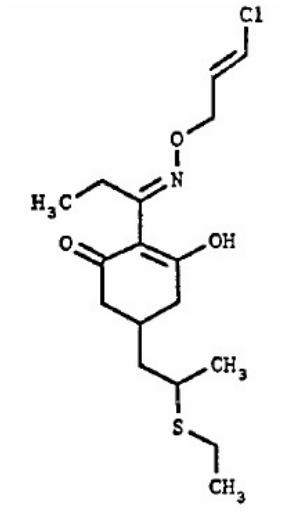
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 4: Substance identity

EC number:	
EC name:	
CAS number (EC inventory):	
CAS number:	99129-21-2
CAS name:	2-Cyclohexen-1-one, 2-[1-[[[(2E)-3-chloro-2-propen-1-yl]oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydrox-
IUPAC name:	(5*RS*)-2-{(1*EZ*)-1-[(2*E*)-3-chloroallyloxyimino]propyl}-5-[(2*RS*)-2-(ethylthio)propyl]-3-hydroxycyclohex-2-en-1-one
ISO name:	Clethodim
CLP Annex VI Index number:	Not available
Molecular formula:	$C_{17}H_{26}ClNO_3S$
Molecular weight range:	359.92 g/mol

Structural formula:



1.2 Composition of the substance

Table 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Clethodim	≥930 g/kg		

Current Annex VI entry: none

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Toluene	≤ 4 g/kg.		This concentration of toluene will not affect the classification of clethodim.
Confidential			These impurities do, as far as known, not affect the classification of clethodim.

Current Annex VI entry: index number 601-021-00-3 (Flam. Liq. 2, H225; Repr. 2, H361d ***Asp. Tox. 1, H304; STOT RE 2 *, H373 **; Skin Irrit. 2, H315; STOT SE 3, H336)

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
None				

1.2.1 Composition of test material

The purity of clethodim used in the studies of the section toxicology and metabolism was approximately 83%. Clethodim is also manufactured at a purity of approximately 93%. Comparison of the 5-batch analysis of 2002 with the 5-analysis of 1987 indicate that the identity of the majority of impurities is equal. However, two impurities, RE-50330 and ODD, are present in the 2002 batches, but not in the 1987 batches. The amount of RE-50030 in the 5 batch analysis was < 0.001% and is no reason for concern. ODD is present at higher concentration (mean: 0.143 %). According to the notifier this impurity was not looked for in the 5 batch analysis of 1987. However, it is formed during synthesis steps, which are identical for both batches and is therefore likely to have been present in the older batches used in the toxicity studies. Therefore, there are no difference in impurities that are expected to result in a difference in toxicity between the tested substance and the substance as put on the market.

1.3 Physico-chemical properties

Table 8: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	green yellow liquid (98.3%), amber viscous liquid (technical material)	Ashworth, 1988[a]	
Melting/freezing point	-80°C (98.3%)	Mak, 2003[a]	Freezing temperature
Boiling point	not available (thermal decomposition below the boiling temperature)	Lezberg, 2003[a]	The material used is not pure enough in accordance to the guidance (at least 98%). However the result of this test is not an exact boiling point. It is not expected that the impurities will influence the result of decomposition much, and the results are acceptable.

Relative density	Density: 1.16 g/ml at 20°C	Lezberg, 2003[a]	Purity 98.3%
Vapour pressure	2.08×10^{-6} at 20°C 4.92×10^{-6} at 25°C (98.5%)	Franke, 2006[b]	Purity 98.5%
Surface tension	purity 100%: 52.9 mN/m at 21°C (70% saturated aqueous solution), 59.2 mN/m at 18°C (35% saturated aqueous solution), 64.3 mN/m at 18°C (14% saturated aqueous solution) 32.1 mN/m at 24.6±0.5°C 30.5 mN/m at 39.8±0.5°C.	Bohle, 1989[a] Butler, 2009[b]	Tests were performed on neat product without any dilution into water.
Water solubility	Purity 98.3%, at 20°C: At pH 4: 0.0530 g/L At pH 7: 5.45 g/L At pH 9: 58.9 g/L At pH 10: 30.0 g/L	Li and Baldwin, 2003[a] Weissenfeld, 2006[b]	
Partition coefficient n-octanol/water	Log P_{ow} = 4.14 at pH 7 (99,0%) Log P_{ow} = 4.22 at pH 9 (99,0%) => Log P_{ow} = 4.2 for the non-dissociated form of clethodim	Ashworth, 1988[a]	Log P_{ow} = 4.2 is the estimation using the EPIWIN/KOWWIN program.
Flash point	no flash point up to 78°C (degradation, 93.8%).	Updyke, 1990[a]	
Flammability	Self-ignition temperature: 280° C (94.8%); no flash point up to 78°C (degradation, 93.8%).	Lezberg, 2003[a]	Not required since test substance is a liquid
Explosive properties	not explosive (92.4%)	Franke, 2005[b]	
Self-ignition temperature	280°C (94.8%)	Lezberg, 2003[a]	
Oxidising properties	not oxidizing (statement)	Lezberg, 2003[a]	
Granulometry	No data		
Stability in organic solvents and identity of relevant degradation products	At 25°C: acetone: >900 g/L hexane: >900 g/L ethylacetate: >900 g/L dimethylformamide: >900 g/L. methanol >100 g/L 1,2-Dichloroethane: >100 g/L xylene: >100 g/L.	Lezberg, 2003[a]	
Dissociation constant	purity 98.5%, at 20°C: pKa = 4.47	Franke, 2005[b]	
Viscosity	5.71 mPa.s at 20°C 4.31 mPa.s at 40°C	Lezberg, 2003[a]	

[a] as summarized in the DAR 2005; [b] as summarized in the DAR 2009

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for this type of report.

2.2 Identified uses

Clethodim is a selective herbicide for use on sugar beet.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

The data for classification of clethodim are based on the summaries as provided in the DAR of clethodim (2005) and its addenda and revisions (2009 and 2010). There is no REACH registration for clethodim (checked 13 May 2013).

3.1 Physico-chemical properties

3.1.1 Summary and discussion of physico-chemical properties

Clethodim has no flash point up to 78^0C, is not explosive and not oxidising (table 8).

3.1.2 Comparison with criteria

A liquid should be classified as flammable when the flash point is at or below 60^0C. Clethodim does not meet this criterion.

3.1.3 Conclusions on classification and labelling

Clethodim does not need to be classified for physico-chemical properties according to the CLP Regulation.

RAC evaluation of physical hazards
Summary of the Dossier submitter's proposal Clethodim has no flash point up to 78 °C, is not explosive and not oxidising. As such, clethodim does not meet the criteria for classification for physico-chemical properties according to CLP. **Comments received during public consultation** There were no comments regarding the classification for physico-chemical hazards. **Assessment and comparison with the classification criteria** Clethodim does not have a flash point below 78 °C and was shown to decompose before reaching boiling point. Therefore, clethodim does not meet the classification criteria for a flammable liquid. Examination of the chemical structure did not indicate that clethodim would have any explosive or oxidising properties and so it does not meet the criteria for classification as an explosive substance or an oxidising liquid. RAC is in agreement with the Dossier Submitter (DS) that **classification is not required for physico-chemical hazards**.

4 HUMAN HEALTH HAZARD ASSESSMENT

The data for classification of clethodim are based on the summaries as provided in the DAR of clethodim (2005) and its addenda and revisions (2007, 2009 and 2010). There is no REACH registration for clethodim (checked 26 June 2012).

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

The absorption, distribution, metabolism and excretion of ^{14}C-clethodim (purity 99%) in rat was investigated after a single oral dose of 4.4 and 468 mg/kg/bw, and a single oral dose of 4.5 mg/kg bw after 14 daily pre-treatments at the same dose. After single (4.4 or 468 mg/kg) or repeated (4.5 mg/kg) oral administration of [Propyl-1-14C] clethodim, absorption was 88-95% AR, irrespective of dose regime, in males and females, respectively, based on radiolabel recovered from urine, expired CO2, tissues, cage wash and residual carcass. Within 24 hours after administration, males and females that had received the low or repeated dose excreted 80-86% and 8.5-14% of the administered dose in urine and faeces, respectively. Rats that had received the high dose excreted 53-59% and 3.2-4.9% of the administered dose in urine and faeces, respectively, within 24 hours. Excretion of radioactivity with expired air was small (0.5-1.0% the administered dose). Only 0.2-0.7% of the administered dose was retained in tissues (including residual carcass) of both females and males of all dose groups. In all dose groups, retention of radioactivity was highest in the adrenals, the liver and the kidneys (adrenals low and repeated dose: 0.068-0.22 mg eq/kg, high dose: 5.4-13 mg eq/kg; kidney and liver low and repeated dose: 0.020-0.063 mg eq/kg, high dose: 2.3-5.2 mg eq/kg). Radioactivity levels in tissues and organs of males were very similar to those in females. Distribution of radioactivity in tissues and organs in the single low dose group was comparable to the distribution of radioactivity in the repeated dose group. Clethodim was extensively metabolised in rats in all groups. Clethodim was detected in urine (high dose females only: 0.4%) and faeces (0.3-1% of the administered dose in all groups/sexes). The main metabolite in urine and faeces was clethodim sulfoxide. In urine samples of males and females, this metabolite represented 46-61% of the administered dose. The metabolites S-methyl sulfoxide and imine sulfoxide represented 6-11% and 6-9% of the administered dose, respectively, in urine. Other identified compounds in urine and faeces were 5-OH sulfoxide, oxazole sulfoxide, trione sulfoxide, 5-OH sulfone, clethodim sulfone, aromatic sulfone and S-methyl sulfone. None of these exceeded 5% of the administered dose. Additionally, oxazole sulfone was detected in the urine of the high dose male rats, but it was not quantified. One fraction remained unidentified and represented 5-9% of the administered dose in urine and 1-3% of the administered dose in the faeces extracts. The metabolite pattern in urine and faeces was comparable for both sexes and all dose regimes, with the exception that clethodim was detected in the urine of female rats only.

The percutaneous absorption and distribution of [^{14}C]-clethodim were studied in two groups of 16 males. Groups of 4 animals received a single topical application of 6, 62 or 476 µg a.s./cm^2, by application of 500 µl of the formulation test substance to the skin area within a rubber template of 10 cm^2. The treated skin area was not covered. At 2, 10 and 24 hours after application, the dose area was carefully washed with gauzed pads immersed in soapy water. This procedure was repeated three times, followed by one scrubbing with deionized water alone. All washings were collected for ^{14}C analysis. All animals were sacrificed after termination of the exposure period (2, 10 and 24 hours after application). After sacrifice, blood, urine and faeces were collected. Cage wash was performed at termination. After sacrifice, the skin was excised around the outside of the application template. A 1 cm strip of the skin around the outside of the application site was included. The skin

site was rinsed twice with 20 ml of acetone. The template was washed with methanol. The remaining carcass was retained.
The dermal absorption of clethodim in rats *in vivo*, under non-occlusive conditions, was 42% and 15% after a single dermal application of a spray dilution and undiluted formulation, respectively. Under occlusive conditions, dermal absorption might be higher.
No *in vitro* dermal absorption study with rat and human skin was available. In general, it can be stated that the absorption of substances through rat skin is higher than through human skin.
Based on above considerations it is concluded that for risk assessment purposes, 42% will be used for the spray dilution and 15% for the undiluted formulation.

4.1.2 Human information

None

4.1.3 Summary and discussion on toxicokinetics

Absorption was 88-95% of the administered dose, irrespective of dose regime, in males and females, respectively, based on radiolabel recovered from urine, expired CO2, tissues, cage wash and residual carcass. Only 0.2-0.7% of the administered dose was retained in tissues (including residual carcass) of both females and males of all dose groups. In all dose groups, retention of radioactivity was highest in the adrenals, the liver and the kidneys. There was no evidence of accumulation. Within 24 hours after administration, males and females rats excreted 80-86% and 8.5-14% of the administered dose in urine and faeces, respectively. Clethodim was extensively metabolised in rats. The main metabolite in urine and faeces was clethodim sulfoxide.

The dermal absorption of clethodim in rats *in vivo* was 42% and 15% for after a single dermal application of a spray dilution and undiluted formulation, respectively. Under occlusive conditions, dermal absorption might be higher.

4.2 Acute toxicity

Table 9: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
OECD TG 401	LD50 = 1133 mg a.i. /kg bw	Rats	Cushman, 1986 [a]
OECD TG 401	LD50 = 2024 mg a.i /kg bw	Mice	Cox, 1986[a]
OECD TG 402	LD50 > 4167 mg a.i. /kg bw	Rabbits	Cushman, 1986 [a]
OECD TG 403	LC50 > 3.25 mg a.i./L	Rats	Griffis, 1986[a]
Intraperitoneal treatment	LD50 = 868 mg a.i. /kg bw	Rats	Cox, 1987[a]

[a] as summarized in the DAR 2005, B6, toxicology and metabolism

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

reference	:	Cushman, J.R., 1986	exposure	:	Once by gavage
type of study	:	Acute oral toxicity study	doses	:	Males : 0, 1050, 1450, 1860 and 2500 mg/kg [1] Females : 0, 800, 1050, 1450 and 2000 mg/kg [1]
year of execution	:	1985	vehicle	:	Carboxymethyl cellulose (0.7%) and

					Tween 80 (1.0%) in distilled water
test substance	:	Chevron RE-45601 technical (Clethodim technical), lot no SX-1688, purity 83.3%	GLP statement	:	Yes
route	:	Oral	guideline	:	In accordance with OECD 401
species	:	Rat, Sprague-Dawley	acceptability	:	Acceptable
group size	:	5/sex/dose	**LD_{50}**	:	1358 mg a.i./kg bw (males) 1133 mg a.i./kg bw (females)

[1] equal to 875, 1208, 1550, 2083 mg a.i./kg bw (males) and 667, 875, 1208, 1667 mg a.i./kg bw (females) after correction for purity of the test substance

This study was performed in rats in accordance with OECD 401.

Mortality:

5/5 males given 2500 mg/kg, 4/5 males given 1860 mg/kg and 1/5 males given 1450 mg/kg were found dead within 1 day after treatment. 5/5 females given 2000 mg/kg were found dead within 1 day after treatment. 3/5 females given 1450 mg/kg were found dead within 3 days after treatment. No further mortality occurred.

Symptoms of toxicity:

Salivation, decreased motor activity, unsteady gait, hyperreactivity, lacrimation, clonic convulsions, red nasal discharge, ocular discharge and collapse were observed in almost all dose groups. Reduced food consumption and yellow anogenital stains were noticed in surviving treated animals. On day 6 all treated animals surviving were normal. No treatment-related findings were noted in the animals in the control group.

Body weight:

A decrease of body weight gain was noted among the surviving males given 1450 mg/kg at day 7 of the study. Body weight of these animals returned to control values at day 14. No treatment related findings were noted in the surviving animals of other dose groups.

Pathology:

Red gelatinous material beneath the meninges, reddened, darkened and/or mottled lungs with foam in the trachea, reddened meninges, white or black material in stomach, fluid in stomach, small intestine, enlarged adrenals and dilated renal pelvis were found among the animals that died during the study at macroscopic post mortem examination.

Two surviving females, given 1450 mg/kg, showed small lesions of gliosis in a single spinal nerve at microscopic examination. Macroscopic post mortem examination of the other surviving animals at termination did not reveal any abnormalities

The acute oral LD_{50} of RE-45601 technical was found to be 1630 mg/kg bw in males and 1360 mg/kg bw for females. After correction for the purity, this is equal to an oral LD_{50} of 1358 mg a.i./kg bw for males and 1133 mg a.i./kg bw for females.

reference	:	Cox, R.H., 1986	exposure	:	Once by gavage
type of study	:	Acute oral toxicity study	doses	:	Males : 0, 1500, 2000, 2500, 3000 mg/kg [1] Females : 0, 2000, 2500, 3000, 3500 mg/kg [1]
year of execution	:	1986	vehicle	:	Carboxymethyl cellulose sodium salt, distilled water and Tween 80
test substance	:	Chevron RE-45601 technical (Clethodim technical), lot no SX-1688, purity 83.3%	GLP statement	:	Yes
route	:	Oral	guideline	:	in accordance with OECD 401
species	:	Mice, Charles River CD-1	acceptability	:	Acceptable
group size	:	5/sex/dose	**LD_{50}**	:	2143 mg a.i./kg bw (males) 2024 mg a.i./kg bw (females)

[1] equal to 1250, 1667, 2083, 2500 mg a.i./kg bw (males) and 1667, 2083, 2500, 2917 a.i./kg bw (females) after correction for purity of the test substance

This study was performed in rats in accordance with OECD 401.
Mortality:
3/5 males given 3.0 g/kg and 2.5 g/kg and 1/5 males given 2.0 g/kg were found dead within one and two days after treatment. 2/5 females given 2.0 g/kg, 1/5 females given 2.5 g/kg, 5/5 females given 3.0 g/kg and 4/5 females given 3.5 g/kg were found dead within one and two days after treatment. No further mortality occurred.
Symptoms of toxicity:
Hypoactivity, rough coat, hunched appearance, ataxia, tremors, salivation, laboured respiration, soft faeces, urine stains were noted in all dose groups between days 1-4. No abnormal clinical signs were observed for males after day 2. For females most clinical signs subsided by day 3.
Body weight:
No treatment-related findings were noted.
Pathology:
Slightly dark red lungs and compound-like material in the stomach and intestines were noted among the animals that died during the study. Macroscopic post mortem examination of the surviving animals at termination did not reveal any abnormalities.
The acute oral LD_{50} of RE-45601 technical was found to be 2573 mg/kg bw in males and 2430 mg/kg bw for females.
After correction for the purity, this is equal to an oral LD_{50} of 2143 mg a.i./kg bw for males and 2024 mg a.i./kg bw for females.

4.2.1.2 Acute toxicity: inhalation

reference	:	Griffis, L.C., 1986	exposure	:	4 hours, whole body
type of study	:	Acute inhalation toxicity study	doses	:	0, 3.9 mg/L (maximal attainable concentration) [1], MMAD 2.8 µm, GSD 1.9 µm
year of execution	:	1986	vehicle	:	acetone
test substance	:	Chevron RE-45601 technical (Clethodim technical), lot no SX-1688, purity 83.3%	GLP statement	:	Yes
route	:	Inhalation	guideline	:	In accordance with OECD 403
species	:	Rats, white New Zealand	acceptability	:	Acceptable
group size	:	5/sex/dose	**LD_{50}**	:	> 3.25 mg a.i./L (males and females)

[1] equal to 3.25 mg a.i./L after correction for purity of the test substance

Mortality: No mortality occurred.
Symptoms of toxicity:
During exposure squinted or closed eyes (all animals) and salivation (2/5 males and 1/5 female) were noticed. After exposure salivation, red nasal discharge, abnormal respiratory sounds, mydriasis, decreased faeces, unkempt appearance, yellow/red anogenital discharge were observed. All animals appeared normal within 8 days of exposure.
Body weight:
No treatment related findings.
Pathology:
No treatment related findings.
The acute inhalation LD_{50} of clethodim (purity of 83.3%) was found to be greater than 3.9 mg/L for males and females. After correction for the purity, this is equal to an inhalation LD_{50} of >3.25 mg a.i./L for males and females.

4.2.1.3 Acute toxicity: dermal

reference	:	Cushman, J.R., 1986	exposure	:	24 hours (semi-occlusive exposure)
type of study	:	Acute dermal toxicity study	doses	:	Males and females : 5000 mg/kg bw [1] Males : 2000 mg/kg bw [1]
year of execution	:	1986	vehicle	:	None
test substance	:	Chevron RE-45601 technical (Clethodim technical), lot no SX-1688, purity 83.3%	GLP statement	:	Yes
route	:	Dermal	guideline	:	In accordance with OECD 402
species	:	Rabbits, white New Zealand	acceptability	:	Acceptable
group size	:	5/sex/dose	**LD_{50}**	:	> 4167 mg/kg (males and females)

[1] equal to 4167 mg a.i./bw (males and females) and 1667 mg a.i./kg bw (females) after correction for purity of the test substance

This study was performed in rats in accordance with OECD 402.
Mortality: 1/5 males given 5.0 g/kg were found dead on day 6. No further mortality occurred.
Symptoms of toxicity:
Abraded, thickened, blackened/darkened, crusty and/or cracked skin, erythema and/or oedema, were seen in the treated animals during the observation period. Reduced food intake, decreased motor activity, decreased body temperature, unkempt appearance, diarrhoea, no faeces and collapse were noted in the male given 5.0 g/kg that died during the study.
Slight to severe erythema twenty-four hours after dosing (treated and control animals) and severe oedema (treated animals). After 7 days no to severe erythema and no to well-defined oedema (treated animals). In one female dosed with 5000 mg/kg erythema persisted after 14 days. After 7 and 14 days controls showed no erythema or oedema.
Body weight:
No treatment related findings.
Pathology:
Macroscopic post mortem examination of the animals at termination showed flaky, dry and/or reddened skin. Microscopic examination revealed trace to mild hyperkeratosis among the treated animals.
The acute oral LD_{50} of clethodim (purity of 83.3%) was found to be greater than 5000 mg/kg bw for males and females. After correction for the purity, this is equal to a dermal LD_{50} greater than 4167 mg a.i./kg bw for males and for females.

4.2.1.4 Acute toxicity: other routes

reference	:	Cox, R.H., 1987	exposure	:	Once (5 ml/kg)
type of study	:	Acute intraperitoneal toxicity study	doses	:	0, 700, 1000, 1400, 2000 mg/kg bw (both sexes) [1]
year of execution	:	1986 - 1987	vehicle	:	Tween 80, carboxymethyl cellulose sodium salt high viscosity and distilled water
test substance	:	Chevron RE-45601 technical (Clethodim technical), lot no SX-1688, purity 83.2%	GLP statement	:	Yes
route	:	Intraperitoneal injection	guideline	:	Not applicable
species	:	Rat, Sprague-Dawley, Crl:CD (SD)BR	acceptability	:	Acceptable
group size	:	5/sex/dose	**LD_{50}**	:	868 mg a.i./kg bw (male) 1001 mg a.i./kg bw (female)

[1] equal to 583, 833, 1167, 1667 mg a.i./L (males and females) after correction for purity of the test substance

Two ranging finding studies were performed to select the appropriate dosage levels. The first range finding study was conducted with 2 animals per sex per dose with dose levels 30, 100, 300, 500 and 700 mg/kg bw and a dosing factor of 2.0 ml/kg. The second range finding study was conducted with 2 animals per sex per dose with dose levels 700, 1000 and 1400 mg/kg bw and a dosing factor of 5.0 ml/kg.

Five rats per sex per dose level were intraperitoneal exposed to the test item at four dose levels. Five additional rats per sex were injected with 5 ml/kg of the vehicle and served as control animals. All animals were observed for signs of toxicity. Individual body weights, pupillary response were recorded. Complete necropsy was performed.
Mortality:
5/5 males given 2000 mg/kg, 4/5 males given 1400 mg/kg, 3/5 males given 1000 mg/kg were found dead within 1 days after treatment. 4/5 females given 2000 mg/kg and 1400 mg/kg and 2/5 females given 1000 mg/kg were found dead within 14 days after treatment. No further mortality occurred.
Symptoms of toxicity:
Among the test substance treated animals, clinical signs observed included hypoactivity, rough coat, hunched posture, urine staining of the fur, soft faeces, salivation, ataxia, red stains on nose and eyes and prostration. Most of the clinical signs disappeared by day 4. Pupillary responses were normal for all animals except for 2 animals on day 1 after dosing.
Body weight:
No treatment related findings, except for one female animal in the 700 mg/kg dose group, which showed weight loss.
Pathology:
A pale liver and bright red lung was observed for animals which died during the study. Pale left lateral lobes and rounded margins of the liver were observed in two 700 mg/kg dose group animals which survived. Compound-like material was found in the abdominal cavity of all animals that died in the 2000 mg/kg dose group. No further treatment-related effects.
The acute intraperitoneal LD50 of clethodim (purity of 83.2%) was found to be 1041 mg/kg bw for males and 1201 mg/kg bw for females. After correction for the purity, this is equal to an intraperitoneal LD_{50} of 868 mg a.i./kg bw for males and 1001 mg a.i./kg bw for females.

4.2.2 Human information

No data available.

4.2.3 Summary and discussion of acute toxicity

The oral LD50 in rat was LD_{50} 1133 mg a.i./kg bw, the dermal LD50 in rat was > 4167 mg a.i./kg bw/day, and the inhalation LC50 in rat was > 3.25 mg a.i./L.

4.2.4 Comparison with criteria

According to the criteria of the CLP Regulation, substances should be classified as acute Tox. 4, H302 when the oral LD_{50} is between 300 and 2000 mg/kg bw. According to an acute oral rat toxicity study, the LD_{50} of clethodim is 1133 mg a.i./kg bw.

According to the criteria of the CLP Regulation, substances should be classified for acute inhalation toxicity when the LC_{50} (dust/mist) ≤ 5 mg/L. No mortality was observed in the inhalation toxicity test in rats up to the maximal attainable concentration of 3.25 mg a.i./L. As no mortality occurred up to the maximal attainable concentration, no classification for acute inhalation toxicity is required.

According to the criteria of the CLP Regulation, substances should be classified when the dermal LD50 < 2000 mg/kg bw. The LD_{50} of clethodim is >4167 mg a.i./kg bw in rats. Clethodim does therefore not meet the CLP criteria.

4.2.5 Conclusions on classification and labelling

Clethodim needs to be classified for acute oral Tox. 4; H302. No classification is required for acute dermal and inhalation toxicity.

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The oral LD_{50} in rats was 1133 mg/kg bw. According to the CLP criteria, substances should be classified Acute Tox. 4 when the oral LD_{50} value is between 300 and 2000 mg/kg bw.

The dermal LD_{50} in rats was > 4167 mg/kg bw. According to the CLP criteria, substances should be classified when the dermal LD_{50} is ≤ 2000 mg/kg bw. Therefore, clethodim does not meet the criteria for classification for acute dermal toxicity.

The inhalation LC_{50} in the rat was > 3.25 mg/L (the maximum attainable concentration). According to the criteria, substances should be classified for acute inhalation toxicity when the LC_{50} (dust/mists) ≤ 5 mg/L. As no mortality occurred at the maximum concentration tested, clethodim should not be classified for acute inhalation toxicity.

According to the DS, Clethodim meets the criteria for classification with Acute Oral Toxicity, Category 4 (H302). No classification was proposed for acute dermal or inhalation toxicity.

Comments received during public consultation

There were two comments relating to acute toxicity received from Member States. One was in general agreement with the classification for toxicological hazards and the other specifically supported the classification of clethodim for acute oral toxicity.

Assessment and comparison with the classification criteria

Clethodim was tested by the oral route in both rats and mice. In each study, the substance tested was 83.3 % pure. The LD_{50} values were corrected to take into account the actual amount of active ingredient dosed.

In rats, the oral LD_{50} for males was 1358 mg/kg bw and for females was 1133 mg/kg bw. In mice, the oral LD_{50} values for males and females were 2143 mg/kg bw and 2024 mg/kg bw, respectively. Both the values for male and female rats justify the classification Acute Toxicity Category 4 ($300 < LD_{50} \leq 2000$ mg/kg).

Clethodim was also tested in rats by the inhalation route. No mortality occurred; the LC_{50} was > 3.25 mg/L. No classification for acute inhalation toxicity is appropriate as an LC_{50} equal to or below 5 mg/L has not been demonstrated. There was no mortality at exposure levels relevant to classification.

Groups of 5 male and female rabbits were exposed dermally to 4167 mg/kg bw clethodim for 24 h. There was 1 death among the male rabbits during the study. Therefore the resulting LD_{50} was > 4167 mg/kg bw/day for both males and females. This is above the cut-off of 2000 mg/kg for acute dermal toxicity classification.

The data support no classification for acute toxicity by the inhalation and dermal routes and classification of clethodim as **Acute Toxicity 4 by the oral route (H302 – harmful if swallowed)**.

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

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

The oral LD50 in rat was LD50 1133 mg a.i./kg bw. Salivation, decreased motor activity, unsteady gait, hyperreactivity, lacrimation, clonic convulsions, red nasal discharge, ocular discharge and collapse were observed in almost all dose groups. Reduced food consumption and yellow anogenital stains were noticed in surviving treated animals.
The dermal LD50 in rat was > 4167 mg a.i./kg bw/day. Abraded, thickened, blackened/darkened, crusty and/or cracked skin, erythema and/or oedema, were seen in the treated animals during the observation period. Reduced food intake, decreased motor activity, decreased body temperature, unkempt appearance, diarrhoea, no faeces and collapse were noted in the male given 5.0 g/kg that died during the study. Slight to severe erythema twenty-four hours after dosing (treated and control animals) and severe oedema (treated animals). After 7 days no to severe erythema and no to well-defined oedema (treated animals). In one female dosed with 5000 mg/kg erythema persisted after 14 days. After 7 and 14 days controls showed no erythema or oedema.
The inhalation LD50 in rat was > 3.25 mg a.i./L. During inhalation exposure squinted or closed eyes (all animals) and salivation (2/5 males and 1/5 female) were noticed. After exposure salivation, red nasal discharge, abnormal respiratory sounds, mydriasis, decreased faeces, unkempt appearance, yellow/red anogenital discharge were observed. All animals appeared normal within 8 days of exposure.

4.3.2 Comparison with criteria

According to the criteria of the CLP Regulation for single dose exposure, substances should be classified as cat. 2 when there is evidence for toxicity at a single oral dose between 300 and 2000 mg/kg bw. However, at the same dose range, clethodim has been classified as acute Tox. 4, H302. To prevent double classification, clethodim does not need to be classified for oral STOT SE.

For single dose exposure, substances should not be classified when: inhalation toxicity test (dust/mist) LC50 $\leq$ 5 mg/L. If there is evidence from animal studies or from human experience showing that corrosive substances may cause respiratory tract irritation, then STOT SE Category 3 may be appropriate. For clethodium, no mortality was observed in the inhalation toxicity test up to the concentration of 3.25 mg a.i./L. No significant toxicity was observed up to the maximal attainable concentration. Therefore,no classification is needed for acute inhalation STOT SE.

For single dose exposure, substances should be classified when there is evidence for toxicity at a single dermal dose between 1000 and 2000 mg/kg bw. Since there is no evidence for specific target organ toxicity in the dermal study at 2000 mg/kg bw, clethodim does not need to be classified for dermal exposure.

4.3.3 Conclusions on classification and labelling

Clethodim does not need to be classified for STOT SE.

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

Summary of the Dossier submitter's proposal

In a rat acute oral toxicity study, salivation, decreased motor activity, unsteady gait, hyperreactivity, lacrimation, clonic convulsions, red nasal discharge, ocular discharge and collapse were observed in almost all dose groups. Reduced food consumption and yellow anogenital stains were noticed in surviving treated animals. As increased mortality was seen in the dose range relevant for classification with STOT SE, no further classification was proposed in order to prevent "double classification" [i.e. a second classification for the same hazard].

In an acute inhalation study in rats, no mortality or significant toxicity was observed up to the maximal attainable concentration of 3.25 mg/L. Therefore, no classification was needed for acute inhalation STOT SE. There was no evidence of respiratory tract irritation in the available studies; therefore, classification with STOT SE Category 3 was not proposed.

For dermal exposure, substances should be classified when there is evidence for toxicity between 1000 and 2000 mg/kg bw after a single exposure. Since there is no evidence for specific target organ toxicity in the acute dermal study at 2000 mg/kg bw, no classification was proposed.

It was not proposed to classify clethodim for STOT SE.

Comments received during public consultation

There were no comments pertaining to STOT-SE during the public consultation.

Assessment and comparison with the classification criteria

Following oral dosing, signs of toxicity in surviving treated rats included reduced food consumption, convulsions and red nasal discharge. Two surviving females were noted to have small lesions of the gliosis in a single spinal nerve at microscopic examination. There were no abnormalities in other surviving animals. In isolation, these limited findings are not considered sufficient to demonstrate specific toxicity of the central nervous system.

Following inhalation exposure of rats to clethodim, signs of toxicity included salivation, red nasal discharge, abnormal respiration sounds, decreased faeces and yellow/red anogenital discharge.

In the dermal study in rabbits, signs of toxicity were limited to the local area of exposure. These included abraded, thickened, blackened, crusty and/or cracked skin. These signs of local skin damage were accompanied by erythema and oedema.

The effects that occurred in the absence of lethality following acute oral, inhalation and dermal exposure to clethodim were all indicative of non-specific signs of general toxicity. As there was no significant or severe organ toxicity noted, no respiratory tract irritation or narcotic effects, RAC agrees with the DS that **no classification for STOT-SE is appropriate**.

4.4 Irritation

4.4.1 Skin irritation

4.4.1.1 Non-human information

Characteristics reference	:	Pelcot, 2005a	exposure	:	3 minutes, 1 hour and 4 hours on one animal, 4 hours on two animals, application area 6 cm_2, semi-occlusive
type of study	:	Skin irritation	doses	:	0.5 ml
year of execution	:	2005	vehicle	:	None
test substance	:	Clethodim technical, lot no. 6F50568000, purity 93.4%	GLP statement	:	Yes
route	:	Dermal	guideline	:	OECD 404
species	:	Rabbit, New Zealand White	acceptability	:	Acceptable
group size	:	3 males	**Effect**	:	Skin irritating

The study is performed in accordance with OECD guideline 404. After a 3-mintue exposure period, the animal showed very slight erythema (grade 1) on day 2 only. After a 1 hour exposure period, the animal showed very slight erythema (grade 1) and dryness of the skin from day 2 up to day 7.
The results after a 4 hour exposure period are summarized in table 10.

In an acute dermal toxicity test, abraded, thickened, blackened/darkened, crusty and/or cracked skin, erythema and/or oedema, were seen in the treated animals during the observation period. Reduced food intake, decreased motor activity, decreased body temperature, unkempt appearance, diarrhoea, no faeces and collapse were noted in the male given 5.0 g/kg that died during the study. Slight to severe erythema twenty-four hours after dosing (treated and control animals) and severe oedema (treated animals). After 7 days no to severe erythema and no to well-defined oedema (treated animals). In one female dosed with 5000 mg/kg erythema persisted after 14 days. After 7 and 14 days controls showed no erythema or oedema. Macroscopic post mortem examination of the animals at termination showed flaky, dry and/or reddened skin. Microscopic examination revealed trace to mild hyperkeratosis among the treated animals.

Table 10: Summary table of the skin irritation study

Scores observed after	1 hour	24 hours	48 hours	72 hours
Erythema	1,1,1	1,2,2	1,2,2	0,2,2
Edema	0,0,0	0,2,2	0,2,2	0,1,0

4.4.1.2 Human information

No data available.

4.4.1.3 Summary and discussion of skin irritation

Mean value irritation scores of clethodim (purity of 93.4%) for erythema and edema are ≤ 2 at all time points. All effects were reversible within 9 days.

4.4.1.4 Comparison with criteria

Clethodim does not fullfil the criteria for classification as a skin irritant (category 2, H315) of the CLP Regulation, because mean values for erythema and edema are <2.3 in three tested animals and all effects were reversible within 9 days. However, Clethodim needs to be labelled as EUH066; because dryness of the skin from day 2 up to day 7 was observed in the irritation test and abraded, thickened, blackened/darkened, crusty and/or cracked skin was seen in the treated animals during the observation period of an acute dermal toxicity test.

4.4.1.5 Conclusions on classification and labelling

No classification for skin irritation is required for clethodim. This substance needs to be labelled as EUH066; Repeated exposure may cause skin dryness or cracking.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

In a rabbit skin irritation study, mean scores for erythema and oedema in treated animals were ≤ 2 at all time points. All effects were reversible within 9 days.

Clethodim does not meet the CLP criteria for classification as a skin irritant because mean values for erythema and oedema were < 2.3 in three tested animals and all effects were reversible within 9 days. However, clethodim needs to be labelled with EUH066 (Repeated exposure may cause skin dryness and cracking) as dryness of the skin from day 2 up to day 7 was observed and abraded, thickened, blackened, crusty and/or cracked skin was seen in treated animals during the observation period of an acute dermal toxicity test.

Comments received during public consultation

Two Member States supported the proposal for no classification for skin irritation. Further, both supported use of the supplementary labelling phrase EUH066 (Repeated exposure may cause skin dryness and cracking). In contrast, one Member State commented that clethodim had produced flaky, dry and/or reddened skin at termination of the study and microscopic examination revealed trace to mild hyperkeratosis among the treated animals. On this basis, the Member State suggested classification with Skin Irrit. Cat. 2.

Assessment and comparison with the classification criteria

Clethodim was tested in a guideline compliant rabbit skin irritation study (OECD/GLP). This involved use of a 3 min. exposure period in 1 animal, a 1 h exposure period in another animal and a 4 h exposure period in 3 animals. All animals were observed for a period of 14 days following removal of the dressing.

After 3 min exposure, grade 1 erythema was observed on Day 2 only. After 1 h exposure, grade 1 erythema and dryness of the skin was observed from Days 2 – 7.

Following 4 h exposure, no individual scores for either erythema or oedema were above 2 at 24, 48 or 72 h. The mean individual animal scores for erythema and oedema are shown in the table below. All effects were reversible by Day 9.

	Individual animal scores - average (24 - 72 h)
Erythema	0.67 - 2 – 2
Oedema	0 - 1.67 - 1.33

Further information on the potential for clethodim to cause skin irritation was available from an acute dermal study in rabbits and a skin sensitisation study in guinea pigs.

In the acute dermal study, thickened, blackened, crusty and/or cracked skin and erythema and oedema were noted in all treated rats during the observation period following 24 h exposure to clethodim (4167 mg/kg bw). Twenty-four hours after removal of the dressing slight to severe erthyema and oedema were noted in treated animals. After 7 days, none to severe erythema and oedema were noted, although in one female the erythema persisted after 14 days. Macroscopic examination at termination revealed flaky, dry and/or reddened skin. Microscopic examination revealed trace to mild hyperkeratosis among treated animals.

In a Guinea Pig Maximisation test, discrete or patchy erythema was noted in 5/10 animals at 24 h and 6/10 animals at 48 h.

Comparison with the criteria

In the rabbit skin irritation study the scores obtained following 4 h (or less) treatment with clethodim did not meet the criteria for classification as Skin Irrit. 2 (mean value of ≥ 2.3 - ≤ 4.0 for erythema or oedema in at least 2/3 animals from gradings at 24, 48 and 72 h after patch removal). There was no evidence of full thickness destruction of the skin. The effects observed were not sufficiently severe to justify classification. Additionally, all effects were found to be reversible within 9 days and there was no evidence of alopecia, hyperkeratosis, hyperplasia or scaling. Therefore, the data from this study indicate that no classification for skin irritation is warranted.

Labelling phrase EUH066 (Repeated exposure may cause skin dryness or cracking) can be applied to substances which may cause concern as a result of skin dryness, flaking or cracking following exposure but which do not meet the criteria for classification.

In the acute dermal toxicity study with clethodim, there were signs of skin irritation noted during the initial 24 h observation period and flaky, dry and/or reddened skin was observed at termination. In the guinea pig skin sensitisation study, discrete or patchy erythema was noted in 60 % of animals 48 h after topical induction. Given these results and the fact that this substance is clearly lipophilic (LogP 4.2), it would seem appropriate to apply EUH066 to clethodim.

Therefore, RAC agrees with the DS that **clethodim should not be classified for skin irritation but should bear the supplemental labelling phrase, EUH066**.

4.4.2 Eye irritation

4.4.2.1 Non-human information

reference	:	Cushman, J.R., 1986	exposure	:	Single application
type of study	:	Eye irritation study	doses	:	0.1 ml
year of execution	:	1986	vehicle	:	None
test substance	:	Chevron RE-45601 technical (Clethodim technical), lot no SX-1688, purity 83.3%	GLP statement	:	Yes
route	:	Ocular	guideline	:	In accordance with OECD 405
species	:	Rabbits, New Zealand White	acceptability	:	Acceptable
group size	:	9 rabbits (males)	**Effect**	:	Not irritating to eyes

The study was performed in accordance with OECD 405. Single samples of 0.1 ml clethodim (purity of 83.3%) were instilled into one eye of each of six rabbits. Single samples of 0.1 ml test substance were instilled into one eye of each of three rabbits; the treated and control eyes of these rabbits were rinsed for one minute after a 30-seconds exposure period. Observations were made 1, 24, 48 and 72 hours after instillation. Clethodim was found to be mildly irritating to the rabbit eye. All effects were reversible within 3 days (Table 11).

Table 11: Summary table of the eye irritation study

Scores observed after	1 hour	1 day	2 days	3 days
Cornea/opacity	0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0 (0)	0, 0, 0, 0, 0, 0 (0)	0, 0, 0, 0, 0, 0 (0)
Iris	0, 0, 0, 0, 0, 0	0, 0, 0, 0, 0, 0 (0)	0, 0, 0, 0, 0, 0 (0)	0, 0, 0, 0, 0, 0 (0)
Conjunctiva redness	3, 2, 2, 2, 3, 2	2, 1, 2, 2, 2, 2 (1.8)	1, 0, 1, 2, 1, 1 (1.0)	0, 0, 0, 0, 0, 0 (0)
Conjunctiva chemosis	2, 1, 2, 1, 2, 1	1, 1, 1, 0, 1, 1 (0.8)	0, 0, 0, 0, 0, 0 (0)	0, 0, 0, 0, 0, 0 (0)

( ): mean values

4.4.2.2 Human information

No data available.

4.4.2.3 Summary and discussion of eye irritation

Clethodim was found to be mildly irritating to the rabbit eye. All effects were reversible within 3 days.

4.4.2.4 Comparison with criteria

Clethodim was found to be mildly irritating to the rabbit eye (Cushman, 1986). No effects on the iris and cornea were observed and the effects on conjuntiva redness and chemosis were below 2 (average over time per animal). All effects were reversible within 3 days. Clethodim does not fulfil the criteria for classification according to the CLP Regulation.

4.4.2.5 Conclusions on classification and labelling

Clethodim does not need to be classified for eye irritation in the CLP Regulation.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier submitter's proposal

In an eye irritation study, clethodim was found to be mildly irritating to rabbits. All effects were reversible within 3 days. No effects on the iris or cornea were observed and the effects on conjunctiva redness and chemosis were below 2. Clethodim does not meet the criteria for classification.

Comments received during public consultation

Two Member States agreed with the classification proposal for toxicological hazards in general.

Assessment and comparison with the classification criteria

In a guideline eye irritation study clethodim was instilled into the eye of 6 rabbits. All observed effects were reversible within 3 days. The results are summarised in the table below.

	Individual animal scores - average (24 - 72 h)
Cornea/opacity	0 - 0 - 0 - 0 - 0 - 0
Iris	0 - 0 - 0 - 0 - 0 - 0
Conjunctiva redness	1 - 0.33 – 1 - 1.33 – 1 - 1
Conjunctiva chemosis	0.33 - 0.33 - 0.33 – 0 - 0.33 - 0.33

These scores are below the cut-off values required for classification:
- corneal opacity ≥ 1 and/or
- iritis ≥ 1 and/or
- conjunctival redness ≥ 2 and/or
- conjunctival oedema ≥ 2

Given also the reversibility of the effects that were observed, RAC is in agreement with the DS that there should be **no classification for serious eye damage/irritation**.

4.4.3 Respiratory tract irritation

This paragraph is considered irrelevant seen the repeal of Directive 67/548/EEC with effect from 1 June 2015.

4.5 Corrosivity

4.5.1 Non-human information

See 4.4.1

4.5.2 Human information

No data available.

4.5.3 Summary and discussion of corrosivity

The skin irritation study (4.4.1) shows no signs of corrosion.

4.5.4 Comparison with criteria

The skin irritation study (4.4.1) shows no need for classification for corrosion in the CLP Regulation.

4.5.5 Conclusions on classification and labelling

Clethodim does not need to be classified for corrosivity in the CLP Regulation.

4.6 Sensitisation

4.6.1 Skin sensititsation

4.6.1.1 Non-human information

reference	:	Arcelin, 2005	exposure	:	Intradermal and topical induction, topical challenge (occlusive, 24 h)
type of study	:	skin sensitisation study (Maximisation test)	doses	:	50% intradermal injection 62.5% epidermal application 50% challenge application
year of execution	:	2005-2006	vehicle	:	PEG 300
test substance	:	Clethodim technical, 6F57523000, purity 92.4%	GLP statement	:	Yes
route	:	Dermal	guideline	:	OECD 406
species	:	Guinea pig, Albino Dunkin Hartley	acceptability	:	Acceptable
group size	:	Pretest: 3 females Main, control: 5 females Main, test: 10 females	**Effect**	:	Skin sensitizer

The study was performed in accordance with OECD 406. α-hexylcinnamaldehyde (HCA) was used as the positive control. Dose levels were based on the results of a range-finding study using 15, 25 and 50% for intradermal injections and 15, 25, 50 and 75% (technically highest concentration) for topical applications. Intradermal injection with 25 and 50% induced moderate and confluent erythema and 15% induced discrete or patchy erythema. Topical application with 75% induced no or discrete erythema. Intradermal induction was performed with 50% test substance in PEG 300. Topical induction was initiated after intradermal induction with treatment of 62.5% concentration of test substance 7 days after the first induction (62.5% instead of 75% due to a technical error). Fourteen days later, challenge was performed with dermal application of 50% test substance in PEG 300.
Results after intradermal induction with 50% clethodim technical were not included in the study report. After topical induction with 62.5% Clethodim technical, discrete or patchy erythema was noted in 5/10 animals at 24 hours and 6/10 animals at 48 hours after removal of the test substance. After topical challenge with 50% clethodim technical, skin reactions (discrete or patchy erythema to moderate and confluent erythema) were noted in 9/10 animals at 24 hours and 8/10 animals at 48 hours after removal of the test substance. Topical challenge in control animals did not induce any dermal reaction.

4.6.1.2 Human information

No data available.

4.6.1.3 Summary and discussion of skin sensitisation

Clethodim scored positive in a GPMT test (9/10 positive) after intradermal induction with 50% clethodim.

4.6.1.4 Comparison with criteria

In the CLP Regulation, a substance should be classified as a skin sensitiser (category 1B, H317) when a positive response in a GPMT test (in >30% of the animals) is observed. This criterion is fulfilled. Subcategory 1B is required when ≥30% responses at 1% intradermal induction dose. However, as no information is available after intradermal induction at 1%, it cannot be fully excluded that clethodim will not require subclassification in 1A. This could be considered as data not sufficient for sub-categorisation as in paragraph 3.4.2.2.1.1 of CLP and therefore requiring category 1 without subclassification.

4.6.1.5 Conclusions on classification and labelling

Clethodim should be classified with Skin Sens Cat 1: H317 according to the CLP Regulation.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

Clethodim gave a positive response in a Guinea pig maximisation test (GPMT) with 9/10 animals showing signs of sensitisation. The intradermal induction dose was 50 % clethodim. According to CLP, a substance should be classified as a skin sensitiser (category 1B) when a positive response in a GPMT test (in ≥ 30 % of the animals at > 1 % intradermal induction dose) is observed. This criterion is fulfilled. However, as no information is available following induction with < 1 % clethodim, it cannot be fully excluded that sub-classification with category 1A would be required. Therefore, clethodim meets the criteria for classification for skin sensitisation, category 1.

Comments received during public consultation

Four Member States commented during the public consultation and all agreed with the classification proposal for Skin sensitisation, category 1.

Assessment and comparison with the classification criteria

A guideline–compliant GPMT is available. In this study, a preliminary range-finding test was carried out to determine the concentration for intradermal and topical applications in the main study. During this pre-test, intradermal injection with 15 % clethodim induced no erythema or discrete erythema, whereas 25-50 % clethodim induced moderate and confluent erythema.

In the main study, guinea pigs were induced by intradermal injection with 50 % clethodim in PEG300 followed by topical induction with 62.5 % clethodim.

Following topical induction, discrete or patchy erythema was observed in 5/10 animals at 24 h and 6/10 animals at 48 h after removal of the test substance. After challenge with 50 % clethodim, skin reactions were observed in 9/10 animals at 24 h and 8/10 animals at 48 h and 0/10 control animals, with the presence of discrete or patchy erythema to moderate and confluent erythema. This increase in the numbers of animals responding, together with the increased severity of reactions, indicate a positive result. Accordingly,

clethodim is a skin sensitiser.

Classification in sub-category 1B is appropriate when ≥ 30 % of the animals produce a positive response following an intradermal dose of 1 %. However, as clethodim was not tested at an intradermal dose of less than 50 %, this cannot be assessed adequately. Therefore, RAC agrees with the DS that clethodim should be classified for **skin sensitisation, category 1 (no sub-categorisation), H317: (May cause an allergic skin reaction)**.

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

No data available.

4.6.2.2 Human information

No data available.

4.6.2.3 Summary and discussion of respiratory sensitisation

No data available.

4.6.2.4 Comparison with criteria

No data available.

4.6.2.5 Conclusions on classification and labelling

There is no need for classification for respiratory sensitisation, based on absence of data.

RAC evaluation of respiratory sensitisation
Summary of the Dossier submitter's proposal No data available; no classification. **Assessment and comparison with the classification criteria** No data available; no classification.

4.7 Repeated dose toxicity

The results of the relevant subacute and (sub)chronic toxicity studies are summarised in the following table.

Table 12: Summary table of relevant repeated dose oral toxicity studies

Duration	Species/route	Dose (mg/kg bw/day)	Results (NOAEL)	Reference
5 weeks	Rats/ oral	0, 0.26, 12.5, 65.6, 261 and 515 mg a.i./kg bw/d for males and 0, 0.29, 13.9, 70.6, 291 and 554 mg a.i./kg bw/d for females	12.5 mg a.i./kg bw/day	Eisenlord, 1986[a]
5 weeks	Rats/ oral	0, 4.87, and 597 mg a.i./kg bw/d for males and 0, 5.78, 667 mg a.i./kg bw/d for females	-	Cushman, 1987[a]
4 weeks	Mice/ oral	0, 11.9, 29.7, 74.4, 178 and 476 mg a.i./kg bw/day	29.7 mg a.i./kg bw/day	Raymond & Cox, 1986[a]
13 weeks	rats	0, 2.3, 25, 134 and 279 mg a.i./kg bw/d for males and 0, 2.8, 30, 159 and 341 mg a.i./kg bw/d for females	25 mg a.i./kg bw/day	Dougherty, 1986[a]
90 days	dogs	0, 1, 25, 75 and 125 mg/kg bw/day (nominal)[1]	21 mg a.i./kg bw/day	Daly, 1987[a]
1 year	dogs	0, 1, 75 and 300[2,3] mg/kg bw/day (nominal)	0.83 mg a.i./kg bw/day	Cox, 1988[a]
2 years	Rats/ oral	0, 5, 20, 500 and 2500 mg/kg food[4]	16 mg/kg bw/day	Dougherty, 1988[a]
78 weeks	Mice/ oral	0, 20, 200, 1000 and 2000/3000) mg/kg food[5]	24 mg/kg bw/day	Cox, 1988[a]

[1] 0, 0.83, 21, 62 and 104 mg a.i./kg bw/d after correction for purity of the test substance.
[2] 200 mg/kg bw/day during week 1-7, increased to 300 mg/kg bw/day because clinical pathology data on day 31 did not reveal any changes in alkaline phosphatase levels;
[3] equal to 0, 0.83, 62 and 250 mg a.i./kg bw/d after correction for purity
[4] equal to 0, 0.15, 0.57, 16 and 86 mg/kg bw/day in males and 0, 0.20, 0.72, 21 and 113 mg/kg bw/day in females. See section 4.10.
[5] no calculations were made for the actual intake of test substance. Based on a default value for conversion of mg/kg food to mg/kg bw/d and correction for the purity of the test substance, the following intakes were calculated: 2.4, 24, 119 and 238/357 mg/kg bw/day for both males and females. See section 4.10.
[a] as summarized in the DAR 2005, B6, toxicology and metabolism

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Reference	:	Eisenlord, 1986	exposure	:	35 days, diet
Type of study	:	5-week oral toxicity study (pilot)	dose	:	0, 5, 200, 1000, 4000 and 8000 mg/kg food (nominal)[1]
year of execution	:	1985-1986	vehicle	:	Acetone
test substance	:	RE-45601 tech. (Clethodim), Lot no. SX-1653, purity 83.4%	GLP statement	:	Yes
Route	:	Oral	guideline	:	predominantly in accordance with OECD 407 (1995)
species	:	rat, Sprague-Dawley, Crl:CD (SD)BR	acceptability	:	acceptable as range-finding study
group size	:	10/sex/dose	**NOAEL**	:	12.5 mg a.i/kg bw/day

[1]equal to 0, 0.26, 12.5, 65.6, 261 and 515 mg a.i./kg bw/d for males and 0, 0.29, 13.9, 70.6, 291 and 554 mg a.i./kg bw/d for females

The study generally complied with OECD 407. However, animals were dosed for 5 weeks, the weight of epididymes, thymus, spleen and heart was not determined, neither was the blood clotting potential measured. Functional observations were not performed. Histopathology on bone marrow was not performed. The formulation at the 5 mg/kg level was not homogenous and not stable.

Moreover, bone marrow was not investigated histopathologically and the weight of epididymes, thymus, spleen and heart was not determined. Functional observations were not performed. In the 1-year study in dogs (Cox, 1988), only a marginal effect on bone marrow was noted in the absence of red blood cell effects. It is therefore considered suitable to establish a NOAEL in the present study. However, in the absence of bone marrow histopathology, the observed haematological effects are considered adverse effects. The study is acceptable as range-finding study for a semichronic study.
No mortality was observed upon dietary exposure of rats to 0, 0.26, 12.5, 65.6, 261 and 515 mg a.i./kg bw/d for males and 0, 0.29, 13.9, 70.6, 291 and 554 mg a.i./kg bw/d for females of clethodim (purity 83.4%). Reduced stool was seen in 2 females at 554 mg a.i /kg in the first few days of the study, possibly a result of reduced food consumption. Body weight gain was significantly reduced in males at 261 and 515 mg a.i./kg bw/d (89 and 72% when compared to controls) and females at 291 and 554 mg a.i./kg bw/d (75 and 56% of controls). Food consumption was significantly reduced in males and females at 261/291 and 515/554 mg a.i./kg bw/d, possibly as a result of palatability problems. Haematology showed significantly increased platelet counts in males at 12.5 mg a.i./kg bw/d or higher, with no dose-related trend, and these deviations could therefore be incidental. The toxicological significance of the increase in platelet count is unclear in the absence of histopathological information on bone marrow. Erythrocytes were significantly decreased in females at 0.29, 70.6 and 554 mg a.i./kg bw/d. Haemoglobin was significantly decreased at 65.6, 261, and 515 mg a.i./kg bw/d in males and at 0.29, 70.6 and 554 mg a.i./kg bw/d in females. Haematocrit was significantly decreased at 261, and 515 mg a.i./kg bw/d in males. Changes in red blood cell parameters were only slight (93-96%) when compared to control values. No significant deviations in any red blood cell parameters were noted in males at 0.26 mg a.i./kg bw/d and in males and females at 12.5/13.9 mg a.i./kg bw/d. The effects at 0.29 mg a.i./kg bw/d in females were caused by a low value in one female. In absence of histopathological examination of bone marrow the toxicological significance of the effect at 0.29 mg a.i./kg bw/d in females was unclear. Thus, the haematological changes point to a mild normochromic normocytic anaemia at 70.6 mg a.i./kg bw/d or higher. Clinical chemistry indicated significantly increased uric acid values in females at 291 and 554 mg a.i./kg bw/d and significantly increased cholesterol values in males at 515 mg a.i./kg bw/d (168% of controls). These clinical chemistry deviations point to functional perturbations in the liver (cholestasis). Absolute liver weight was significantly increased at 65.6 mg a.i./kg bw/d and higher in males, with a dose-related trend, and at 554 mg a.i./kg bw/d in females. Relative liver weight was significantly increased at 261/291 and 515/554 mg a.i./kg bw/d in males and females, with a dose-related trend. Changes in relative brain, testes and kidney weights at 515/554 mg a.i./kg bw/d were also noted and attributed to decreased terminal body weights. Microscopy revealed compound-related centrilobular hypertrophy of the liver in males at 65.6, 261, and 515 mg a.i./kg bw/d and in females at 291 and 554 mg a.i./kg bw/, correlating with the observed liver weight changes. The NOAEL in this study is 12.5 mg/kg bw/d based on dose dependent decreases of hemoglobin (HGB) at 65.6 mg/kg bw/d and higher in both sexes, decreases in hematocrit (HCT) in males at 65.6 mg/kg bw/d and higher, and increased liver weights accompanied by increased liver pathology (centrilobular hypotrophy in males at 65.6 mg/kg bw/d and higher.

Table 13 observations for 5-week oral toxicity test

Dose (mg/kg food)	**0**		**5**		**200**		**1000**		**4000**		**8000**		**dr**
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
Mortality	none												
Clinical signs - reduced stool												2/10	

Dose (mg/kg food)	0		5		200		1000		4000		8000		dr
	m	f	m	f	m	f	m	f	m	f	m	f	
Body weight gain									dc	dc	dc	dc	m/f
Food consumption									dc	dc	dc	dc	m/f
Ophthalmo-scopy	no treatment-related findings												
Haematology													
- Platelet count			i		ic		ic		ic		ic		m
- RBC				dc				dc	d		d	dc	
- HGB				dc			dc	dc	dc	d	dc	dc	m/f
- HCT									dc		dc		m
Clin. Chemistry													
- cholesterol									i		ic	i	m
- uric acid										ic		ic	
Urinalysis													
- Urine volume									ic		i		
Organ weights													
- liver							ic^{a}		$ic^{a,r}$		$ic^{a,r}$	$ic^{a,r}$	m
- brain											ic^{r}	ic^{r}	
- kidneys											ic^{r}	ic^{r}	
Pathology													
macroscopy	no treatment-related findings												
microscopy liver:													
- centrilobular hypertrophy	0/10	0/10	0/10	0/10	0/10	0/10	3/10	0/10	6/10	1/10	8/10	4/10	m/f

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative

Reference	:	Cushman, 1987	exposure	:	5 weeks, diet
Type of study	:	5-week oral toxicity study	dose	:	0, 1200 mg process neutrals RE-45601/kg food and 6800 mg RE-45601/kg food (nominal)[1]
year of execution	:	1986	vehicle	:	Acetone
test substance	:	RE-45601 (clethodim), Lot no. SX-1718, purity 96.2% and Process Neutrals of RE-45601, Lot no. SX-1717, containing 3.3% RE-45601	GLP statement	:	Yes
route	:	Oral	guideline	:	-
species	:	rat, Sprague-Dawley, Crl:CD (SD)BR	acceptability	:	Acceptable
group size	:	10/sex/dose	**NOAEL**	:	-

[1]equal to 0, 4.87 or 597 mg/kg bw/d RE-45601 for males and 0, 5.78 or 667 mg/kg bw/d RE-45601 for females

The study was designed to investigate whether the observed toxicity in studies performed with low purity RE-45601 (84.3% purity) could be ascribed to the impurities or Process Neutrals. High purity RE-45601 (96.2%; 6800 mg/kg food) and Process Neutrals of RE-45601 (containing 3.3% RE-45601; 1200 mg/kg food) were administered in the diet to groups of 10 rats of each sex for five weeks. The levels were selected to approximate the levels of 8000 mg/kg RE-45601 (83.4% pure)

in the 5-week rat study (5.3.1-02). A limited amount of organs, including the target organs, were investigated macroscopically/microscopically.
No mortality was observed on dietary exposure of rats to high purity RE-45601 or process neutrals of RE-45601. Mean body weights in males and females were significantly lower during week 2 through week 5 leading to significantly lower total body weight gains in both genders at 597/667 mg/kg bw/d (male/female). Absolute food consumption values were statistically significantly decreased in males in each week of the study and in females in weeks 1, 3, and 5, but relative food consumption was significantly decreased only in males during the first week of the study, suggesting that the diet was initially not palatable to males. Deviations in red blood cell parameters were observed in males (significantly reduced red blood cell counts, haemoglobin and haematocrit) and in females (significantly reduced red blood cell counts and haemoglobin), pointing to a normochromic normocytic anaemia. Total protein and albumin were significantly increased in males, which could reflect reduced hydration, but since the deviations were within historical reference ranges, their relationship to treatment was considered uncertain. Absolute and relative liver weights were significantly increased in males (112% and 134% of male controls, respectively) and relative liver weights were significantly increased in females (124% of female controls). The decreased absolute adrenal weights and the increased relative kidney and brain weights in both sexes, and the increased relative testes weights in males were attributed to lower terminal body weights. There were no treatment-related gross changes at necropsy. Histopathology revealed centrilobular hypertrophy in all males and 8 females.
Mean body weights were significantly lower in males in week 5 only and total body weight gains were also significantly lower in males 4.87 mg/kg bw/d, but no significant differences in mean body weight or total body weight gain were noted in females at 5.78 or 667 mg/kg bw/d. Absolute food consumption was significantly less than controls in males during weeks 1, 3, 4, and 5, while no significant deviations in relative food consumption were noted in males; absolute and relative food consumption was similar to that of controls in females. There was a very slight reduction in red blood cell counts and haemoglobin and haematocrit values in males and females, albeit not significantly in statistical terms. Alkaline phosphatase was significantly decreased in females; the value was, however, well within historical control values and was, therefore, not considered to be treatment-related. Absolute liver weight was significantly increased in females (110% of controls) and the relative liver weight was significantly increased in males and females (107 and 110% of controls, respectively). Histopathology revealed centrilobular hypertrophy in 6 males and 3 females.
The results observed with high purity RE-45601 are consistent with those seen in the 5-week feeding study with RE-45601 technical (83.4%) indicating that the active ingredient caused the changes in body weight gain, red blood cell parameters and in the liver; however, the results observed with the process neutrals indicate that the impurities also made a minor contribution to these effects.

Table 14 observations for 5-week oral toxicity test

Dose (mg/kg food)	**Control 0**		**Process neutrals 1200**		**RE-45601 6800**		**dr**
	m	**f**	**m**	**f**	**m**	**f**	
Mortality	none						
Clinical signs	no treatment-related findings						
Body weight gain			dc		dc	dc	
Food consumption			dc[a]		dc[a]	dc[a]	
Ophthalmoscopy	no treatment-related findings						
Haematology - RBC			d	d	dc	dc	

Dose (mg/kg food)	Control 0		Process neutrals 1200		RE-45601 6800		dr
	m	f	m	f	m	f	
- HGB			d	d	dc	dc	
- HCT			d	d	dc	d	
Clin. Chemistry							
- total protein					ic		
- albumin					ic		
- alk. phosphatase				dc			
Urinalysis	not performed						
Organ weights							
- liver			ic^{r}	$ic^{a,r}$	$ic^{a,r}$	i^{a}, ic^{r}	
- adrenals					dc^{a}	dc^{a}	
- kidneys					ic^{r}	ic^{r}	
- testes					ic^{r}		
Pathology							
macroscopy	no treatment-related findings						
microscopy liver:							
- centrilobular hypertrophy	0/10	0/10	6/10	3/10	10/10	8/10	

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative

Reference	:	Raymond & Cox, 1986	exposure	:	28 days, diet
Type of study	:	28-day oral toxicity study	dose	:	0, 100, 250, 625, 1500 and 4000 mg/kg food (nominal)[1]
year of execution	:	1986	vehicle	:	Acetone
test substance	:	RE-45601 tech. (Clethodim), Lot no. SX-1688, purity 83.3%	GLP statement	:	Yes
route	:	Oral	guideline	:	in accordance with OECD 407 (1995)
species	:	mouse, CD-1 (ICR-derived)	acceptability	:	acceptable as range-finding study
group size	:	10/sex/dose	**NOAEL**	:	29.7 mg a.i./kg bw/day

[1]equivalent to 0, 11.9, 29.7, 74.4, 178 and 476 mg a.i./kg bw/day for males and females (corrected for purity of the test substance)

The study generally complied with OECD 407. However, no clinical biochemistry and no functional observations were performed; also blood clotting potential was not determined and the weight of thymus, spleen and heart was not determined. Histopathology on bone marrow was not performed. The study is considered acceptable as a range-finding study. No clinical biochemistry and no bone marrow histopathology were performed. In the 1-year study in dogs (Cox, 1988), only a marginal effect on bone marrow was noted in the absence of red blood cell effects. It is therefore considered suitable to establish a NOAEL in the present study. However, in the absence of bone marrow histopathology, the observed haematological effects are considered adverse effects.
No mortality or treatment-related clinical signs were observed upon dietary exposure of mice to 11.9, 29.7, 74.4, 178 and 476 mg a.i./kg bw/day of clethodim (purity 83.3%). Body weight gain and food consumption were similar at all dose levels. Red blood cell counts were significantly decreased at 178 and 476 mg a.i./kg bw/day in males and at 178 mg a.i./kg bw/day in females. Haemoglobin was significantly decreased at 74.4, 178 and 476 mg a.i./kg bw/day in males and at 178 mg a.i./kg bw/day in females. Haematocrit was significantly decreased at 476 mg a.i./kg bw/day in males. The observed changes in red blood cell parameters in males and females were only slight (92-96% of control values). The changes point to a mild normocytic normochromic anaemia at 74.4

mg a.i./kg bw/day and higher. Absolute and relative liver with gallbladder weights were significantly increased at 178 mg a.i./kg bw/day in males (113% when compared to controls for both absolute and relative liver weight) and at 476 mg a.i./kg bw/day in males (142% when compared to controls for both absolute and relative liver weight) and females (116% and 123% when compared to controls for absolute and relative liver weight, respectively). Histopathological evaluations demonstrated an increased incidence (10/10 for males and 8/10 for females) and severity of hypertrophy of centrilobular hepatocytes in males and females at 476 mg a.i./kg bw/day, which was considered to be the microscopic correlate of the higher liver weights. The changes observed point to effects in the liver at 178 mg a.i./kg bw/day and higher. The NOAEL is set at 29.7 mg a.i./kg bw/day, based on changes in red blood cell parameters in males at 74.4 mg a.i./kg bw/day and higher.

Table 15 observations for 28-day oral toxicity test

Dose (mg/kg food)	**0**		**100**		**250**		**625**		**1500**		**4000**		**dr**
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
Mortality	none												
Clinical signs	no treatment-related findings												
Body weight gain	no treatment-related findings												
Food consumption	no treatment-related findings												
Ophthalmo-scopy	not performed												
Haematology													
- RBC									dc	dc	dc		m/f
- HGB							dc		dc	dc	dc		m/f
- HCT											dc		m
Clinical chemistry	not performed												
Organ weights													
- liver incl. gall bladder									ic[a,r]		ic[a,r]	ic[a,r]	m
Pathology													
macroscopy	no treatment-related findings												
microscopy													
liver:													
- centrilobular hypertrophy	4/10	0/10	0/10	0/10	3/10	0/10	2/10	0/10	4/10	1/10	10/10	8/10	m/f

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative

Reference	:	Dougherty, 1986	exposure	:	13 weeks, diet, 6 weeks recovery
Type of study	:	13-week oral toxicity study	dose	:	0, 50, 500, 2500 and 5000 mg/kg food (nominal)[1]
year of execution	:	1986	vehicle	:	Acetone
test substance	:	RE-45601 tech. (Clethodim), Lot no. SX-1688, purity ca. 83.3%	GLP statement	:	Yes
route	:	Oral	guideline	:	predominantly in accordance with OECD 408 (1998)
species	:	rat, Sprague-Dawley, Crl:CD (SD)BR	acceptability	:	Acceptable
group size	:	12/sex/dose	**NOAEL**	:	25 mg a.i./kg bw/day

[1]equal to 0, 2.3, 25, 134 and 279 mg a.i./kg bw/d for males and 0, 2.8, 30, 159 and 341 mg a.i./kg bw/d for females

The study was generally in compliance with OECD 408. However, sensory reactivity and functional observations were not performed. Also the weight of epididymides, thymus, spleen, heart and uterus was not determined, neither was the blood clotting potential measured. Additional recovery groups (12/sex/dose; 6 weeks) were used for the control, and the two highest dose groups.
No treatment-related mortality or clinical signs were observed upon dietary exposure of rats to 2.3, 25, 134 and 279 mg a.i./kg bw/d for males and 2.8, 30, 159 and 341 mg a.i./kg bw/d for females of clethodim (purity 83.3%). Body weight gain was significantly reduced in males at 134 mg a.i./kg bw/d (90% of control) and in both sexes at 279/341 mg a.i./kg bw/d (82 and 76% of control for males and females, respectively). During recovery phase, significantly higher weight gains were recorded for males at 279 mg a.i./kg bw/d. Food consumption was significantly reduced in males and females during treatment at 279/341 mg a.i./kg bw/d. No effects on food consumption were seen in the recovery phase. For haematology, reticulocyte count was significantly increased in males at 134 mg a.i./kg bw/d. Non-statistically significant increases in reticulocyte count were noted at 2.3, 25, 279 mg a.i./kg bw/d (126-135% of controls). No historical control data were available in the study report, however, an increase of approximately 30% is, in general, not considered toxicologically relevant. No treatment-related changes in urinalysis parameters were noted. Clinical chemistry showed significantly higher cholesterol, total protein and globulin values at 279 mg a.i./kg bw/d in males (131%, 105% and 109% of control values, respectively), which could be related to perturbations in liver function (cholestasis). The reversibility of these changes was not assessed. Absolute liver weight was significantly increased for females at 341 mg a.i./kg bw/d (114% of control) Relative liver weight was significantly increased in both sexes at 2500 and 5000 mg/kg food, with a dose-related trend (ranging from 112% to 128%). The significantly increased relative kidney and brain weights in both sexes at 5000 mg/kg food were attributed to significantly reduced terminal body weights. Following the recovery phase, absolute liver weights were significantly higher in females at 341 mg a.i./kg bw/d, and relative liver weights were significantly higher in females at 159 and 341 mg a.i./kg bw/d. There were no treatment-related macroscopic findings. Microscopy showed an increased incidence of centrilobular hypertrophy of the liver in males and females at 159 and 341 mg a.i./kg bw/d, which was the microscopic correlate of the liver weight changes. These changes were not present at the end of the recovery period. The NOAEL is established at 25 mg a.i./kg bw/day, based on body weight changes and centrilobular hypertrophy in the liver were observed at doses of 159 mg a.i./kg bw/d and above.

Table 16 observations for 13-week oral toxicity test

Dose (mg/kg food)	**0**		**50**		**500**		**2500**		**5000**		**dr**
Main group	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
Mortality	No treatment-related findings										
Clinical signs	No treatment-related findings										

Dose (mg/kg food)	0		50		500		2500		5000		dr
Main group	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
Body weight gain					d		dc		dc	dc	m
Food consumption									dc	dc	
Ophthalmo-scopy	No treatment-related findings										
Haematology											
- Reticulocyte			i		i		ic		i		
Clin. Chemistry											
- cholesterol									ic		
- total protein									ic		
- globulin									ic		
Urinalysis	No treatment-related findings										
Organ weights											
- brain									ic^r	ic^r	
- liver							ic^r	ic^r	ic^r	$ic^{a,r}$	m/f
- kidneys									ic^r	ic^r	
Pathology											
macroscopy	No treatment-related findings										
microscopy											
liver:											
- centrilobular hypertrophy	0/12	0/12	0/12	0/12	0/12	0/12	8/12	2/12	10/12	7/12	m/f

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative

Table 17 observations after 6-week recovery period

Dose (mg/kg food)	0		50		500		2500		5000		dr
Recovery group	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
Mortality	None										
Clinical signs	No treatment-related findings										
Body weight gain									ic		
Food consumption	No treatment-related findings										
Ophthalmo-scopy	Not performed										
Haematology	Not performed										
Clin. Chemistry	Not performed										
Urinalysis	Not performed										
Organ weights											
- liver			-	-	-	-		$ic^{a,r}$		ic^r	f
Pathology											

macroscopy	No treatment-related findings	
microscopy	No treatment-related findings	

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative
- no data available/not performed

Reference	:	Daly, 1987	exposure	:	90 days, gelatine capsule
Type of study	:	90-day oral toxicity study	dose	:	0, 1, 25, 75 and 125 mg/kg bw/day (nominal)[1]
year of execution	:	1985/86	vehicle	:	None
test substance	:	RE-45601 tech. (clethodim), Lot no. SX-1688, purity 83.3%	GLP statement	:	No
route	:	Oral	guideline	:	in accordance with OECD 409 (1998)
species	:	dog, Beagle	acceptability	:	acceptable
group size	:	4/sex/dose	**NOAEL**	:	21 mg a.i./kg bw/day

[1] 0, 0.83, 21, 62 and 104 mg a.i./kg bw/d after correction for purity of the test substance.

The study was generally in accordance with OECD 409. However, the weight of epididymides, thymus, spleen and uterus was not determined. Histopathology on bone marrow was not performed. For haematology and clinical chemistry blood was taken before the start of the test and on day 35, 55 and 91. It should be noted that bone marrow was not investigated histopathologically. In the 1-year study in dogs (Cox, 1988), only a marginal effect on bone marrow was noted in the absence of red blood cells effects. Therefore, it is considered suitable to establish a NOAEL in the present study, in the absence of bone marrow histopathology. Although no GLP statement was present, the study is considered acceptable.

No mortality was observed upon on exposure of dogs to 1, 25, 75 or 125 mg/kg bw/day of clethodim (purity 83.3%) via gelatine capsule. No treatment-related clinical signs or ocular abnormalities were observed. No treatment-related findings for body weight gain or food consumption were seen. White blood cells were significantly increased in males at 75 and 125 mg/kg bw/d at day 35 of exposure. Mean corpuscular haemoglobin was significantly increased in females at 125 mg/kg bw/d at day 91 of exposure. Activated partial thromboplastin time was significantly decreased in females at 75 and 125 mg/kg bw/d at day 35 of exposure. Since all these haematological deviations were only seen at one point in time, they were not regarded to be of toxicological significance. In the course of the study, mean alkaline phosphatase (ALP) activity progressively increased in males and females at 125 mg/kg bw/d, whereas it progressively decreased in respective control animals (in females at 125 mg/kg bw/d, these differences from control were statistically significant throughout the study). Similarly, mean cholesterol level in females at 125 mg/kg bw/d progressively increased, whereas it remained unchanged in control females; these differences from control were statistically significant after 1 and 2 months. Females at 75 mg/kg bw/d showed significantly increased cholesterol levels after 1 and 2 months as well, but since these values were very similar to those at pre-test, the relationship to treatment was considered uncertain. Globulin was significantly increased in males at 125 mg/kg bw/d at day 91 of exposure and correspondingly the albumin/globulin ratio was significantly decreased at 125 mg/kg bw/d at day 91 of exposure. Chloride was statistically significantly decreased in females at 75 and 125 mg/kg bw/d at day 35 of the study. Since this change was only seen at one time point and was very slight (97-98% of controls), the decrease in chloride was considered of no toxicological relevance. The deviations in ALP, cholesterol and globulin at 125 mg/kg bw/d point to perturbations in liver functions. Absolute liver weight was increased at 75 and 125 mg/kg bw/d in males (116 and 134% of controls) and females (115 and 130% of controls), the differences from control being statistically significant at 125 mg/kg/d only. Relative liver weight was increased at 75 and 125 mg/kg bw/d in

both males (112 and 127% of controls) and females (106 and 119%); these deviations were not significant in statistical terms. No macroscopic effects were observed. Histopathology showed vesiculation/vacuolation in the cytoplasm of centrilobular hepatocytes in all males at all levels including the control group and in all treated females and 3 control females, but increased in severity at 125 mg/kg bw/d, which was attributed to treatment. Based on changes in liver weight at 75 and 125 mg/kg bw/d, the NOAEL is set at 25 mg/kg bw/d (equal to 21 mg a.i./kg bw/d).

Table 18 observations for 90-day oral toxicity test

Dose (mg/kg bw/day)	**0**		**1**		**25**		**75**		**125**		**dr**
Main group	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
Mortality	None										
Clinical signs	No treatment-related findings										
Body weight gain	No treatment-related findings										
Food consumption	No treatment-related findings										
Ophthalmoscopy	No treatment-related findings										
Haematology											
- WBC							ic[1]		ic[1]		
- MCH										ic[2]	
- APTT								dc[1]		dc[1]	
Clin. Chemistry											
- alkaline phos.									i	ic	
- cholesterol								ic		ic	
- globulin									ic[2]		
- A/G ratio									dc[2]		
- chloride								dc[1]		dc[1]	
Urinalysis	No treatment-related findings										
Organ weights											
- liver							i[a]	i[a]	ic[a], i[r]	ic[a], i[r]	m/f
Pathology											
macroscopy	No treatment-related findings										
microscopy											
liver:											
- centrilobular vesicules/vacuoles	4/4	3/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative
[1] on day 35
[2] on day 91

Reference	:	Cox, 1988	exposure	:	1 year, gelatine capsule
Type of study	:	1-year oral toxicity study	dose	:	0, 1, 75 and 300[1,2] mg/kg bw/day (nominal)
year of execution	:	1987/88	vehicle	:	None
test substance	:	RE-45601 tech., Lot no. SX-1688, purity 83.3%	GLP statement	:	Yes
route	:	Oral	guideline	:	in accordance with OECD 452 (1981)
species	:	dog, Beagle	acceptability	:	Acceptable
group size	:	6/sex/dose	**NOAEL**	:	0.83 mg a.i./kg bw/d

[1] 200 mg/kg bw/day during week 1-7, increased to 300 mg/kg bw/day because clinical pathology data on day 31 did not reveal any changes in alkaline phosphatase levels

[2] equal to 0, 0.83, 62 and 250 mg a.i./kg bw/d after correction for purity

The study was generally in accordance with OECD 452. However, ornithine decarboxylase was not determined. For haematology and clinical chemistry blood was taken before the test and on day 31, 90, 180, 270 and 360.
No mortality was observed upon exposure of dogs to 1, 75 or 300 mg/kg bw /d of clethodim (purity 83.3%) via gelatine capsule. There were no treatment-related clinical signs. No treatment-related changes in body weight gain or food consumption were seen. The ophthalmoscopic changes observed were not treatment-related. Erythrocyte count was statistically significantly decreased in males at 300 mg/kg bw/d on days 270 and 360 and in females at 300 mg/kg bw/d on days 180, 270 and 360. Haemoglobin and haematocrit were statistically significantly decreased in females at 300 mg/kg bw/d on days 180, 270 and 360. These deviations point to a normocytic normochromic anaemia in females at 300 mg/kg bw/d in the second half of the study. Platelet count was statistically significantly increased in both sexes at 300 mg/kg bw/d during the whole exposure period. Prothrombin time was statistically significantly decreased in all treated males at day 90. Since effects at other sampling times were not present, the effect is considered to be of no toxicological significance. The white blood cell count was statistically significantly increased in females at 300 mg/kg bw/d on days 90, 180, 270 and 360 and in females at 75 mg/kg bw/d at day 90 only. Segmented neutrophils were significantly higher in females at 300 mg/kg bw/d on days 31, 90 and 270. The albumin/globulin ratio was decreased in females at 300 mg/kg bw/d at day 270 and 360. The glucose level was significantly decreased in males at 300 mg/kg bw/d on day 270, in females at 300 mg/kg bw/d on days 180 and 360, and in females at 75 mg/kg bw/d at day 360. Alkaline phosphatase was significantly increased from day 90 onwards at 300 mg/kg bw/d in both sexes. ALT was statistically significantly increased at 300 mg/kg bw/d in both sexes from day 180 onwards. Cholesterol was statistically significantly increased at 300 mg/kg bw/d in males at day 360 only and in females throughout the study. Triglycerides were significantly increased in both sexes at 300 mg/kg bw/d at day 360. The clinical biochemistry deviations point to perturbations in liver function at 300 mg/kg bw/d; the increased ALT values suggest liver injury. Urinalysis showed no treatment-related findings. Absolute and relative thyroid/parathyroid weight was significantly increased in males at 300 mg/kg bw/d (183 and 200% of controls, respectively), but there was no microscopic correlate. Absolute and relative liver weight was significantly increased in both sexes at 300 mg/kg bw/d (156 and 160% of controls for males, respectively, and 170 and 168% of controls for females, respectively), and in females at 75 mg/kg bw/d (134 and 158% of controls, respectively). In males at 75 mg/kg bw/d absolute liver weight was increased (127%) and relative liver weight was statistically significantly increased (116%). Macroscopic examinations revealed a dark liver in 4 males and 4 females at 300 mg/kg bw/d and an enlarged liver in 2 males and 2 females at 300 mg/kg bw/d. Histopathology showed centrilobular to midzonal hepatocellular hypertrophy in 5/6 males and 4/6 females at 300 mg/kg bw/d. Increased pigmentation of the liver was observed in one male at 75 mg/kg bw/d and all animals at 300 mg/kg bw/d; the pigment was negative for bile, iron, and lipofuscin and its nature was not identified. Hyperplasia of the sternum marrow was observed in one male and one female at 75 mg/kg bw/d and all animals at 300 mg/kg bw/d, probably a response to anaemia and an explanation for the increases in peripheral leukocytes and platelets at 300 mg/kg bw/d. The study identified the liver and red blood cells as potential targets of the test substance. Based on the changes in clinical chemistry and liver weight, the NOAEL is set at 1 mg/kg bw/d (equal to 0.83 mg a.i./kg bw/d).

Table 19 observations for 1-year oral toxicity test

Dose (mg/kg bw/d)	0		1		75		300		dr
	m	f	m	f	m	f	m	f	
Mortality	None								
Clinical signs	No treatment-related findings								
Body weight gain	No treatment-related findings								
Food consumption	No treatment-related findings								
Ophthalmoscopy	No treatment-related findings								
Haematology									
- RBC							dc[1]	dc[2]	
- HCB								dc[2]	
- HCT								dc[2]	
- MCH								ic[3]	
- platelet count							ic	ic	
- PT			dc[4]		dc[4]		dc[4]		
- WBC						ic[4]	ic[3]	ic[5]	f
- Segmented neutrophils								ic	
Clin. Chemistry									
- A/G ratio								dc[6]	f
- glucose						dc[6]	dc[7]	dc[2]	f
- alk. phosphatase							ic[5]	ic[5]	
- cholesterol						i[3]	ic[6]	ic	
- triglycerides							ic[8]	ic[8]	
- ALT						dc[3]	ic[2]	ic[2]	
Urinalysis	No treatment-related findings								
Organ weights									
- thyroid/parathyr.						i[a]	ic[a,r]		
- liver						i[a], ic[r]	ic[r]	ic[a,r]	ic[a,r]	m/f
Pathology									
macroscopy									
- liver, dark	0/6	0/6	0/6	0/6	0/6	0/6	4/6	4/6	
- liver, enlarged	0/6	0/6	0/6	0/6	0/6	0/6	2/6	2/6	
microscopy									
liver:									
- hypertrophy	0/6	0/6	0/6	0/6	0/6	0/6	5/6	4/6	
- incr. pigment	0/6	0/6	0/6	0/6	1/6	0/6	6/6	6/6	m
sternum marrow:									
- hyperplasia	0/6	0/6	0/6	0/6	1/6	1/6	6/6	6/6	m/f

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative
[1] on day 270 and 360
[2] on day 180, 270 and 360
[3] on day 180
[4] on day 90
[5] on day 90 till 360
[6] on day 360
[7] on day 270
[8] only measured on day 360

Table 20 Critical for the NOAEL in both the 90 day and 1 year dog studies are the terminal liver weights. Absolute and relative (to body weight) liver weights are given in the table.

Absolute and relative liver weights at the end of the study in 90 day and 1 year oral studies with clethodim in the dog.				
Dose[1] (mg/kg bw/day)	males		females	
	Absolute (g)	Relative (%)	Absolute (g)	Relative (%)
90 day study (4/sex/dose)				
0	294	2.7	255	2.8
1	287	2.6	240	2.6
25	304	2.8	270	2.9
75	339	3.0	293	3.0
125	393*	3.4	331*	3.4
1 year study (6/sex/dose)				
0	258	2.5	208	2.4
1	259	2.7	209	2.4
75	317	2.9*	279*	3.3*
300	390*	4.0*	354*	4.2*

[1] doses not corrected for purity.

4.7.1.2 Repeated dose toxicity: inhalation

No data available.

4.7.1.3 Repeated dose toxicity: dermal

Reference	:	Hedgecock, 1987	exposure	:	4 weeks, 5 days/week, 6 hours/day, dermal (approx. 8% of body area)
Type of study	:	4-week dermal toxicity study	dose	:	0, 10, 100 and 1000 mg/kg bw/d [1]
year of execution	:	1987	vehicle	:	0.7% carboxymethyl cellulose and 1.0% TWEEN 80 (w/w) in distilled water
test substance	:	RE-45601 tech. (clethodim), Lot no. SX-1688, purity 83.2%	GLP statement	:	yes
route	:	Dermal	guideline	:	in accordance with OECD 410 (1981)
species	:	rat, Sprague-Dawley, Crl:CD BR	acceptability	:	Acceptable
group size	:	6/sex/dose	**NOAEL**	:	local: <8.3 mg a.i./kg bw/d systemic: 83 mg a.i./kg bw/d

[1] 0, 8.3, 83, 832 mg a.i./kg bw/d after correction for purity of the test substance

In an OECD 410 study, no mortality was observed upon dermal exposure of rats to 0, 10, 100 or 1000 mg/kg bw/d of clethodim (purity 83.2%). After correction for purity of the test substance the corresponding doses are 0, 8.3, 83, 832 mg a.i./kg bw/d. A treatment-related anogenital discharge with corresponding staining of anogenital fur was noted in both sexes in the highest dose group. Irritation of the exposed skin was dose-dependently increased in incidence and severity during the 4-week exposure period. Body weight gain in males at 1000 mg/kg bw per day was significantly decreased (65% of the control). Relative food consumption in males at 1000 mg/kg bw per day was significantly increased only on day 21. There were no significant changes in haematology parameters. Clinical biochemistry revealed significantly decreased plasma chloride levels in males and females at 1000 mg/kg bw per day and significantly increased plasma triglyceride levels in females at 100 and 1000 mg/kg bw per day. The absolute and relative liver weight was increased in females at 1000 mg/kg bw (120 and 122% of controls, respectively). The increased relative weight of kidneys and testes in males at 1000 mg/kg bw per day (113% of controls) were attributed to lower terminal body weights. Macroscopic and microscopic examinations revealed no treatment-related findings. Based on decreased body weights and increased liver weights, the NOAEL for systemic effects was set at 100 mg/kg bw per day (83 mg a.i./kg bw/d). The NOAEL for local effects was established at < 10 mg/kg bw per day (<8.3 mg a.i./kg bw/d).

Table 21 observations for 4-week dermal toxicity test

Dose % in vehicle	**0**		**10**		**100**		**1000**		**dr**
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
Mortality	None								
Clinical signs									
- anogenital discharge	0/6	0/6	0/6	0/6	0/6	0/6	6/6	2/6	
- skin irritation			i[1]	i[1]	i[1]	i[1]	i[1]	i[1]	
Body weight gain							dc		
Food consumption	No treatment-related findings								
Haematology	No treatment-related findings								
Clin. Chemistry									
- Chloride							dc	dc	
- Triglycerides						ic	dc	ic	
Organ weights									
- kidneys							ic[r]	i	
- liver								ic[a,r]	
- testes							ic[r]		
Pathology									
macroscopy	No treatment-related findings								
microscopy	No treatment-related findings								

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative
[1] a dose-related increase in oedema and erythema is observed; the number of animals affected increases during the study

4.7.1.4 Repeated dose toxicity: other routes

No data available.

4.7.1.5 Human information

No data available.

4.7.1.6 Other relevant information

No data available.

4.7.1.7 Summary and discussion of repeated dose toxicity

Dietary exposure of mice to 0, 11.9, 29.7, 74.4, 178 and 476 mg a.i./kg bw/day of clethodim (purity 83.4%, equivalent to) for 4 weeks resulted in changes in haematology parameters indicative of mild anaemia (decreased red blood cell count, haemoglobin, haematocrit) at 74.4 mg a.i./kg bw/day and higher. Liver weight was increased and centrilobular hypertrophy was observed at 178 mg a.i./kg bw/day and higher. A NOAEL of 29.7 mg a.i./kg bw/day was established.

Dietary exposure of rats to 0, 0.26, 12.5, 65.6, 261 and 515 mg a.i./kg bw/day for males and 0, 0.29, 13.9, 70.6, 291 and 554 mg a.i./kg bw/day for females of clethodim (purity 83.3%, equal to) for 5 weeks showed apparent dose-related changes in haematological parameters (decreased red blood cell count, haemoglobin, haematocrit) at 0.26 mg a.i./kg bw/day and above, indicative of mild normocytic normochromic anaemia. Increased cholesterol and uric acid were observed from 261 and 291 mg a.i./kg bw/day onwards for males and females, respectively. Liver weights were significantly increased and centrilobular hypertrophy was observed at 65.6/70.6 mg a.i./kg bw/day and above in males and females. The haematological changes point to a mild normochromic normocytic anaemia at 65.6 mg a.i./kg bw/day or higher. The NOAEL in this study is 12.5 mg/kg bw/d based on dose dependent decreases of HGB at 65.6 mg/kg bw/d and higher in both sexes, decreases in HCT in males at 65.6 mg/kg bw/d and higher, and increased liver weights accompanied by increased liver pathology (centrilobular hypotrophy in males at 65.6 mg/kg bw/d and higher. The results observed with high purity RE-45601 (96.2%) are consistent with those seen in the 5-week feeding study with RE-45601 technical (83.4%) indicating that the active ingredient caused the changes in body weight gain, red blood cell parameters and in the liver; however, the results observed with the process neutrals indicate that the impurities also made a minor contribution to these effects.

Dietary exposure of rats to 0, 2.3, 25, 134 and 279 mg a.i./kg bw/day for males and 0, 2.8, 30, 159 and 341 mg a.i./kg bw/day for females of clethodim (purity 83.3%) for 13 weeks caused an increased reticulocyte count in males at all dose levels; an increase of approximately 30% is, in general, not considered toxicologically relevant. Cholesterol, total protein and globulin were significantly increased at 5000 mg/kg food in males (equal to 279 mg a.i./kg bw/day) and females (equal to 341 mg a.i./kg bw/day), indicative of liver effects. Liver weight was increased significantly at doses of 134/159 mg a.i./kg bw/day and above in males and females. Concomitantly, centrilobular hypertrophy was noted. Except for the increased liver weight in females at 341 mg a.i./kg bw/day effects were reversible. The NOAEL is established at 25 mg a.i./kg bw/day, based on body weight changes and centrilobular hypertrophy in the liver were observed at doses of 134 mg a.i./kg bw/day and above.

Three month exposure of dogs to 0, 1, 25, 75 or 125 mg/kg bw/day of clethodim (purity 83.3%) via gelatine capsule (equal to 0, 0.83, 21, 62 and 104 mg a.i./kg bw/day) resulted in changes in biochemical parameters indicative of liver effects. Correspondingly, increased liver weight and an increase in centrilobular vesicules/vacuoles were observed at 75 mg/kg bw/day (equal to 62 mg a.i./kg bw/day) and above. The NOAEL was established at 25 mg/kg bw/day (equal to 21 mg a.i./kg bw/d).

Exposure of dogs during 1 year to 0, 1, 75 or 300 mg/kg bw /d of clethodim technical via gelatine capsule (equal to 0, 0.83, 62 and 250 mg a.i./kg bw/d) resulted in decreased erythrocyte count at 300 mg/kg bw/d. In females also haemoglobin and haematocrit were significantly decreased at 300 mg/kg bw/d, which pointed to normocytic normochromic anaemia in females. Platelet count was significantly increased in both sexes at 300 mg/kg bw/d. White blood cell count was significantly increased from day 90 onwards and segmented neutrophils were significantly increased at several sampling times in females at 300 mg/kg bw/d. Deviations in biochemical parameters, such as a decrease in albumin/globulin ratios and glucose level, and an increase in alkaline phosphatase, alanine aminotransferase, cholesterol and triglycerides point to perturbations in liver function at 300 mg/kg bw/d. Thyroid/parathyroid weight was significantly increased, but no microscopic correlate was noted. Liver weights were increased at 75 and 300 mg/kg bw/d in both sexes (116-160%). Darkening and enlargement of the liver were noted at 300 mg/kg bw/d. Centrilobular to midzonal hepatocellular hypertrophy and increased, unidentified pigmentation was observed at 300 mg/kg bw/d. Hyperplasia of the sternum marrow in one male and one female at 75 mg/kg bw/d and all animals at 300 mg/kg bw/d is considered to be a response to anaemia and explains the increases in

peripheral leukocytes and platelets observed at 300 mg/kg bw/d. The NOAEL is set at 1 mg/kg bw/d (equal to 0.83 mg a.i./kg bw/d).

In conclusion, in all rodent studies with oral exposure and in the 1-year dog study changes haematological parameters were observed indicating anaemia. In the 1-year dog study anaemia was confirmed by hyperplasia of the sternum marrow. However, in most of the rodent studies with oral exposure bone marrow was not investigated histopathologically. Only in the 90-day rat study histology of bone maarow (femur, sternum) was performed. No effects on bone marrow were seen in this study. In the absence of bone marrow histopathology, observed haematological effects and centrilobular hypertrophy in the liver were considered adverse effects.

Dermal exposure of rats to 0, 10, 100 or 1000 mg/kg bw/d of clethodim (purity 83.3%, equal to 0, 8.3, 83 and 832 mg a.i./kg bw/day) for 4 weeks resulted in treatment-related anogenital discharge (only at the top dose) and a dose-dependent skin irritation in both sexes. Body weight gain in males was decreased at the top dose. No changes in haematological parameters were observed. Plasma chloride levels were decreased at 832 mg a.i./kg bw/d in both sexes and triglyceride levels were increased in females at 83 and 832 mg a.i./kg bw/d. Liver weight was increased in females at 832 mg a.i./kg bw/d. No abnormalities were found upon macroscopic and microscopic examination. The NOAEL for systemic effects was 83 mg a.i./kg bw/d. The NOAEL for local effects was established at <8.3 mg a.i./kg bw/d.

4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

This paragraph is considered irrelevant seen the repeal of Directive 67/548/EEC with effect from 1 June 2015.

4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

This paragraph is considered irrelevant seen the repeal of Directive 67/548/EEC with effect from 1 June 2015.

4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

This paragraph is considered irrelevant seen the repeal of Directive 67/548/EEC with effect from 1 June 2015.

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

Dietary exposure of mice to clethodim for 4 weeks resulted in changes in haematology parameters indicative of anaemia (decreased red blood cell count, haemoglobin, haematocrit) at 74.4 mg a.i./kg bw/day and higher. Liver weight was increased and centrilobular hypertrophy was observed at 178 mg a.i./kg bw/day and higher. A NOAEL of 29.7 mg a.i./kg bw/day was established. Dietary exposure of rats to clethodim for 13 weeks caused body weight changes and centrilobular

hypertrophy in the liver at doses of 134 mg/kg bw/d and above. The NOAEL is established at 25 mg/kg bw/d. Three month exposure of dogs to clethodim resulted in changes in biochemical parameters indicative of liver effects. Correspondingly, increased liver weight and an increase in centrilobular vesicules/vacuoles were observed at 250 mg a.i./kg bw/d and above. The NOAEL was established at 21 mg a.i./kg bw/d. Exposure of dogs during 1 year to clethodim resulted in changes in haematology parameters at 62 mg a.i./kg bw/d. Liver weights were increased at 62 and 250 mg a.i./kg bw/d in both sexes.

Dermal exposure of rats to clethodim for 4 weeks resulted in treatment-related anogenital discharge (only at the top dose) and a dose-dependent skin irritation in both sexes. Plasma chloride levels were decreased at 832 mg/kg bw/d in both sexes and triglyceride levels were increased in females at 83 and 832 mg/kg bw/d. Liver weight was increased in females at 832 mg/kg bw/d. No abnormalities were found upon macroscopic and microscopic examination. The NOAEL for systemic effects was 83 mg/kg bw/d.

In conclusion, in some rodent studies with oral exposure and in the 1-year dog study changes in haematological parameters and liver weight were observed at the doses < 100 mg a.i./kg bw/day.

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

Oral

The cut-off values for STOT RE category 2 are $10 < C \leq 100$ mg/kg bw/d in the CLP Regulation (for a study duration of 90 days). Toxic effects have been observed in several rodent and dog studies in the range between 10 and 100 mg/kg bw/d (or extrapolated according to Haber's rule for study duration other than 90 days) (see following evidence). However, these effects are not severe enough for STOT RE category 2 classification.

The effects in the 5 week oral study in rats (reference) at the cut-off value for STOT RE 2 of 240 mg/kg bw/day were limited to effects on body weight gain, food consumption, changes in haematological parameters, some changes in clinical chemistry and urinanalysis, an increase in male liver weight and liver centrilobular hypertrophy (mainly males) using the effects observed at 4000 ppm (261 mg a.i./kg bw/d). The changes in red blood cell values were slight (93-96%) and do not fulfil the criteria. The liver effects are limited and probably adaptive. The remaining effects were observed in only one sex and not always significant. This study does not fulfil the criteria for STOT RE.

In another study, dietary exposure of rats to 0, 2.3, 25, 134 and 279 mg a.i./kg bw/day for males and 0, 2.8, 30, 159 and 341 mg a.i./kg bw/day for females of clethodim (purity 83.3%) for 13 weeks caused an increased reticulocyte count in males at all dose levels; an increase of approximately 30% is, in general, not considered toxicologically relevant. Cholesterol, total protein and globulin were significantly increased at 5000 mg/kg food in males (equal to 279 mg a.i./kg bw/day) and females (equal to 341 mg a.i./kg bw/day), indicative of liver effects. Liver weight was increased significantly at doses of 134/159 mg a.i./kg bw/day and above in males and females. Concomitantly, centrilobular hypertrophy was noted. Except for the increased liver weight in females at 341 mg a.i./kg bw/day effects were reversible. The NOAEL is established at 25 mg a.i./kg bw/day, based on body weight changes and centrilobular hypertrophy in the liver were observed at doses of 134 mg a.i./kg bw/day and above. Effects on haematology parameters and on liver weight are small (<10% for haematology parameters and <20% for liver) and have been observed at values above cut-off value of 100 mg//kg bw/d. Therefore, this study does not fulfil the criteria for STOT RE.

Dietary exposure of mice to 0, 11.9, 29.7, 74.4, 178 and 476 mg a.i./kg bw/day of clethodim (purity 83.4%, equivalent to) for 4 weeks resulted in changes in haematology parameters indicative of anaemia (decreased red blood cell count, haemoglobin, haematocrit) at 74.4 mg a.i./kg bw/day and higher. However, the effects were only slight (92-96%) and therefore do not fulfil the cut-off of 20% for classification based on reduction of haemoglobin. Absolute and relative liver with gallbladder weights were significantly increased at 178 mg a.i./kg bw/day in males (113% when compared to controls for both absolute and relative liver weight) and at 476 mg a.i./kg bw/day in males (142% when compared to controls for both absolute and relative liver weight) and females (116% and 123% when compared to controls for absolute and relative liver weight, respectively). Effects on on liver weight are small (<20%) for both males and females at 178 mg a.i./kg bw/day. Histopathological evaluations demonstrated an increased incidence (10/10 for males and 8/10 for females) and severity of hypertrophy of centrilobular hepatocytes in males and females at 476 mg a.i./kg bw/day, which was considered to be the microscopic correlate of the higher liver weights. These effects have been observed at values above cut-off value of 300 mg//kg bw/d. Therefore, this study does not fulfil the criteria for STOT RE.

Three month exposure of dogs to 0, 1, 25, 75 or 125 mg/kg bw/day of clethodim (purity 83.3%) via gelatine capsule (equal to 0, 0.83, 21, 62 and 104 mg a.i./kg bw/day) resulted in changes in biochemical parameters indicative of liver effects. Absolute liver weight was increased at 75 and 125 mg/kg bw/d in males (116 and 134% of controls) and females (115 and 130% of controls), the differences from control being statistically significant at 125 mg/kg/d only. Histopathology showed vesiculation/vacuolation in the cytoplasm of centrilobular hepatocytes in all males at all levels including the control group and in all treated females and 3 control females, but increased in severity at 125 mg/kg bw/d, which was attributed to treatment. This study does not fulfil the criteria for STOT RE.

Exposure of dogs during 1 year to 0, 1, 75 or 300 mg/kg bw /d of clethodim technical via gelatine capsule (equal to 0, 0.83, 62 and 250 mg a.i./kg bw/d) resulted in decreased erythrocyte count at 300 mg/kg bw/d. In females also haemoglobin and haematocrit were significantly decreased at 300 mg/kg bw/d, which pointed to normocytic normochromic anaemia in females. Platelet count was significantly increased in both sexes at 300 mg/kg bw/d. White blood cell count was significantly increased from day 90 onwards and segmented neutrophils were significantly increased at several sampling times in females at 300 mg/kg bw/d. Deviations in biochemical parameters, such as a decrease in albumin/globulin ratios and glucose level, and an increase in alkaline phosphatase, alanine aminotransferase, cholesterol and triglycerides point to perturbations in liver function at 300 mg/kg bw/d. Thyroid/parathyroid weight was significantly increased, but no microscopic correlate was noted. Liver weights were increased at 75 and 300 mg/kg bw/d in both sexes (116-160%). Darkening and enlargement of the liver were noted at 300 mg/kg bw/d. Centrilobular to midzonal hepatocellular hypertrophy and increased, unidentified pigmentation was observed at 300 mg/kg bw/d. Hyperplasia of the sternum marrow in one male and one female at 75 mg/kg bw/d and all animals at 300 mg/kg bw/d is considered to be a response to anaemia and explains the increases in peripheral leukocytes and platelets observed at 300 mg/kg bw/d. The study identified the liver and red blood cells as potential targets of the test substance. These effects were observed at 300 mg/kg bw/d, higher than the cut-off value of 100 mg/kg bw/d. This study does not fulfil the criteria for STOT RE.

In a 2-year chronic toxicity and carcinogenicity study in rats, administration of clethodim (dietary administration of 0, 0.15, 0.57, 16 and 86 mg/kg bw/day in males and 0, 0.20, 0.72, 21 and 113 mg/kg bw/day in females) resulted in a decrease in body weight gain and food consumption at 86 mg/kg bw/day. Food intake, calculated relative to body weight, was slightly greater at 86 in males and 113 mg/kg bw/day in females respectively, than in other groups. There were no treatment-

related deviations in clinical pathology parameters. At interim sacrifice after one year, increased liver weights and slight to mild centrilobular hypertrophy were noted in rats of each sex fed 86 and 113 mg/kg bw/day for males and females, respectively. Increased liver weights seen in females at 21 mg/kg bw/day were not correlated with any microscopically discernible change. At terminal sacrifice, liver weights of females at 113 mg/kg bw/day were increased; males had no significant increase in liver weight, and no treatment-related centrilobular hypertrophy was seen in animals of either sex. Females treated at 113 mg/kg bw/day had a slightly greater (12%) incidence of binucleated cells in the liver than the controls (2%), but the effect was of uncertain toxicological significance. This study does not fulfil the criteria for STOT RE because effects were observed only at dose levels above the cut-off of 12.5 mg/kg bw/day.

In a 78-week carcinogenicity study in mice, administration of clethodim (dietary administration of 0, 2.4, 24, 119 and 238/357 mg/kg bw/day for both males and females) resulted in an increased mortality rate at 238/357 mg/kg bw/day; the predominant cause of death was an increased incidence and severity of systemic amyloidossis. Body weights and food consumption were not affected by treatment, with the exception of a slight decrease in body weight gain in high dose females (92% of controls). Red blood cell count was statistically significantly decreased in males at 238/357 mg/kg bw/day in week 27 and 79 and in females at 238/357 mg/kg bw/day in week 27. Haemoglobin and haematocrit was statistically significantly decreased in males at 238/357 mg/kg bw/day in week 27. These red blood cell deviations are consistent with a mild normochromic normocytic anaemia, as noted in mice and in other species in subacute and semichronic toxicity studies, and were considered to be related to treatment and toxicologically significant. After 52 weeks of treatment, increased liver weights and centrilobular hypertrophy of the liver were observed in males at 119 mg/kg bw/day and in males and females at 357 mg/kg bw/day. Increased pigment, described as morphologically compatible with haemosiderin and bile, was noted in males at 357 mg/kg bw/day. After 78 weeks of treatment, the hepatic changes included increased liver weights in females and males at 357 mg/kg bw/day (112-114% of controls), centrilobular hypertrophy and increased pigment in both males and females at 119 and 357 mg/kg bw/day and bile-duct hyperplasia in males at > 119 mg/kg bw/day. An increased incidence of multifocal, amphophilic alveolar lung macrophages was also observed in animals of each sex treated at > 119 mg/kg bw/day. These effects were observed at the doses higher than the cut-off value of 16.6 mg/kg bw/d after correction for duration. This study does not fulfil the criteria for STOT RE.

Dermal

The cut-off values for STOT RE category 2 are $60 < C \leq 600$ mg/kg bw/d in the CLP Regulation (for a study duration of 28 days). Dermal exposure of rats to 0, 8.3, 83 and 832 mg a.i./kg bw/day of clethodim for 4 weeks resulted in treatment-related anogenital discharge at the top dose. Body weight gain in males was decreased at the top dose. No changes in haematological parameters were observed. Plasma chloride levels were decreased at 832 mg a.i./kg bw/d in both sexes and triglyceride levels were increased in females at 83 and 832 mg a.i./kg bw/d. Liver weight was increased in females at 832 mg a.i./kg bw/d. No abnormalities were found upon macroscopic and microscopic examination. The LOAEL for systemic effects was 832 mg a.i./kg bw/d. These effects have been observed at values above cut-off value of 600 mg//kg bw/d. This study does not fulfil the criteria for STOT RE.

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

Based on all rodent and dog studies, clethodim does not need to be classified for STOT RE according to CLP.

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

Summary of the Dossier submitter's proposal

Studies of repeated exposure in rats, mice and dogs are available, of which those summarised below are included in the summary of the Dossier submitter.

Dietary exposure of mice to clethodim for 4 weeks resulted in changes to haematology parameters indicative of anaemia (decreased red blood cell count, haemoglobin and haematocrit) at doses ≥ 74.4 mg/kg bw/day. Liver weight was increased and centrilobular hypertrophy was observed at ≥ 178 mg/kg bw/day.

Dietary exposure of rats to clethodim for 13 weeks caused body weight changes and centrilobular hypertrophy in the liver at doses ≥ 134 mg/kg bw/day.

Treatment of dogs for 3 months with oral capsules containing clethodim resulted in changes to biochemical parameters indicative of liver effects. Increased liver weight and an increase in centrilobular vesicles/vacuoles were observed at ≥ 250 mg/kg bw/day. In a comparable 1-year study, changes in haematology parameters were seen at 62 mg/kg bw/day. Liver weights were increased at 62 and 250 mg/kg bw/day in both males and females.

Dermal exposure of rats to clethodim for 4 weeks resulted in treatment-related anogenital discharge at 832 mg/kg bw/day and dose-dependent skin irritation in both males and females. Plasma chloride levels were decreased at 832 mg/kg bw/day and triglyceride levels were increased in females at 83 and 832 mg/kg bw/day. Liver weight was also found to be increased in females only at 832 mg/kg bw/day. There were no macroscopic or microscopic abnormalities.

In conclusion, in some studies involving oral exposure in rodents and in an oral study in dogs (1 year duration), changes in haematological parameters and liver weight were observed at doses < 100 mg/kg bw/day. However, the effects observed at doses less than this cut-off dose level for classification with STOT-RE 2 were not sufficiently severe for classification. Therefore, no classification for STOT-RE was proposed for clethodim.

Comments received during public consultation

Two MS were in general agreement with the proposal for toxicological hazards.

Assessment and comparison with the classification criteria

Clethodim has been tested for repeated dose toxicity by the oral route in mice, rats and dogs and in one dermal study in rats. A summary of findings at doses relevant for classification is provided below.

<u>35-Day dietary study in rats</u>
Guidance values for classification with STOT-RE 1: C ≤ 26 mg/kg bw/day, STOT-RE 2: 26 < C ≥ 260 mg/kg bw/day

Clethodim was administered to male and female rats at doses of 0, 4.87/5.78 and 597/667 mg/kg bw/day (males/females).

Deviations in red blood cell parameters were noted in males and females (including reduced red blood cell count and haemoglobin). Absolute and relative liver weights were increased in males (12 % and 34 % increase, respectively) and relative liver weights were increased in females (24 % increase in comparison to controls). Centrilobular liver

hypertrophy was seen in 10/10 males and 8/10 females (versus 0 in controls). These effects all occurred at a dose higher than the guidance value for classification with STOT RE 2.

Some mild changes to blood parameters were observed in males and females dosed with ~ 5 mg/kg bw/day, however these were not statistically significant. Relative liver weight was increased in males and females (7 % and 10 % of controls respectively). Histopathology revealed an increased incidence of centrilobular hypertrophy of the liver in 6/10 males and 3/10 females (versus 0 in controls).

There were some effects to red blood cell parameters and to the liver, occurring mainly at a dose above the guidance level for STOT-RE 2. Similar effects, occurring at much milder severity occurred at the low dose which was within the guidance range for classification with STOT-RE 1. However, these effects were not considered severe enough for classification with STOT-RE 1.

28-Day dietary study in mice (i.e. cited as Raymond and Cox 1986 in the CLH report)
Guidance values for classification with STOT-RE 2: 30 < C ≤ 300 mg/kg bw/day

Clethodim was administered to male and female mice at doses of 0, 11.9, 29.7, 74.4, 178 and 476 mg/kg bw/day. There was a marginal reduction in red blood cell parameters at doses ≥ 74.4 mg/kg bw/day in males and at 178 mg/kg bw/day in females (< 10 % when compared to controls). Absolute and relative liver weights were increased in males only at 178 mg/kg bw/day (13 % increase compared to controls) but there were no histopathological correlates at this dose.

The effects observed in this study are not considered severe enough to support classification with STOT-RE, category 2.

35-Day dietary study in rats
Guidance values for classification with STOT-RE 2: 26 < C ≤ 260 mg/kg bw/day

Clethodim was administered to male and female rats at doses of 0, 0.22/0.29, 12.5/13.9, 65.6/70.6, 261/291 and 515/554 mg/kg bw/day (males/females). Some changes to haematological parameters were noted in this study. These were a reduction in red blood cells in females – but in the absence of a dose response, a reduction in haemoglobin in males at doses ≥ 65.6 mg/kg bw/day and in females, again in the absence of a dose response and a reduction in haematocrit in males only at 261 mg/kg bw/day. These effects were slight in nature (< 10 % difference to controls).

The effects observed in this study are not considered severe enough to warrant classification for STOT-RE, category 2.

90-Day dietary study in rats
Guidance values for classification with STOT-RE 2: 10 < C ≤ 100 mg/kg bw/day

Clethodim was administered to male and females rats at doses of 0, 2.3/2.8, 25/30, 134/159 and 279/341 mg/kg bw/day (males/females). There were no effects observed at doses relevant for classification.

90-Day capsule study in dogs
Guidance values for classification with STOT-RE 2: 10 < C ≤ 100 mg/kg bw/day (based on figures for rats without further extrapolation)

Clethodim was administered to male and female dogs in gelatine capsules at doses of 0, 0.83, 21, 62 and 104 mg/kg bw/day. At doses of ≥ 104 mg/kg bw/day there were effects

to indicate perturbations in liver function. These were characterised by deviations in alkaline phosphatase, cholesterol and globulin levels in males and females. At 104 mg/kg absolute liver weight was statistically significantly increased in males and females [34 % and 30 % increase compared to controls (respectively)]. Histopathology revealed an increase in severity of centrilobular vesiculation/vacuolation of the liver at 104 mg/kg bw/day.

The effects observed in this study occurred only at the cut-off level for classification and were not considered severe enough for classification with STOT-RE, category 2.

1-Year capsule study in dogs
Guidance values for classification with STOT-RE 2: 2.5 < C ≤ 25 mg/kg bw/day [based on the guidance values for a 90 day rat study, extrapolated using Haber's rule (x0.25)]

Clethodim was administered to male and female dogs in gelatine capsules at doses of 0, 0.83, 62 and 250 (increased from 104 mg/kg bw/day after week 7) mg/kg bw/day. There were no adverse effects at doses < 62 mg/kg bw/day.

2-Year carcinogenicity study in rats
Guidance values for classification with STOT-RE 2: 1.2 < C ≤ 12 mg/kg bw/day

There were no adverse effects at doses relevant for classification.

28-Day dermal study in rats
Guidance values for classification with STOT-RE 2: 20 < C ≤ 200 mg/kg bw/day

Clethodim was administered to the skin of male and female rats, at doses of 0, 8.3, 83, and 832 mg/kg bw/day. There were no adverse effects at doses relevant for classification.

Conclusion
Clethodim has been tested by the oral route in mice, rats and dogs and dermally in rats. Effects were observed in blood cell parameters and also in the liver, occasionally at doses relevant for classification. However, the effects were not consistent and generally mild and therefore it is **not considered appropriate to classify for specific target organ toxicity following repeated dosing**.

4.9 Germ cell mutagenicity (Mutagenicity)

Table 22: Summary table of relevant in vitro and in vivo mutagenicity studies

Method	Results	Remarks	Reference
OECD TG 471 like protocol	negative	Ames test	Machado, 1986[a]
OECD TG 471 like protocol	negative	Ames test	Machado, 1986[a]
OECD TG 476 like protocol	negative	Gene mutation in CHO Chinese hamster ovary cells	Lehn, 1990[a]
OECD TG 473 like protocol	Positive (-S9) Negative (+S9)	Chromosome aberrations in CHO Chinese hamster ovary cells	Putman, 1986[a]
OECD TG 473 like protocol	negative	Chromosome aberrations CHO Chinese hamster ovary cells	Putman, 1986[a]
OECD TG 475 like protocol	negative	Chromosome aberrations in rat bone marrow cells	Putman, 1987[a]
OECD TG 468 like protocol	negative	in vivo UDS assay in the liver	Steinmetz, Mirsalis, 1986[a]

[a] as summarized in the DAR 2005, B6, toxicology and metabolism

4.9.1 Non-human information

4.9.1.1 In vitro data

Type of study: Ames test, plate incorporation method

Indicator cells	Endpoint	Res. - act.	Res. +act.	Activation		Dose range	Reference
				Tissue	Inducer		
B: *S. typh.* TA 98 TA 100 TA 1535 TA 1537	. point mut. point mut. point mut. point mut.	 - - - -	 - - - -	rat liver	Arochlor 1254	0.1, 0.3, 1, 3.3 and 10 mg/plate [1,2)] Vehicle: DMSO Negative and positive controls included	Machado, 1986
1) Dose levels were based on previous studies. 2) Slight toxicity observed at 10 mg/plate in the tester strains TA100 and TA1537 Test substance: RE-45601 Technical (Clethodim technical); Purity 83%, batch SX-1688, dark amber liquid No independent repeat test GLP statement: yes According to OECD 471: no, see acceptability According to 40 CFR 158.135, Pesticide Assessment Guideline No.84-2: yes							

The study does not fulfil the requirements of the more recent OECD 471 guideline of 1997, since the *Escherichia coli* strain WP_2uvrA was not included in the present study and no independent repeat test was performed. However, the study is considered acceptable. It is concluded that clethodim did not induce point mutations in *S. Typhimurium*.

Type of study: Ames test, plate incorporation method, with independent repeat assay

Indicator cells	Endpoint	Res. - act.	Res. +act.	Activation		Dose range	Reference
				Tissue	Inducer		
B: *S. typh.* TA 98 TA 100 TA 1535 TA 1537 B: *E. coli* WP_2uvrA	. point mut. point mut. point mut. point mut. . point mut.	 +[3)] - - - -	 - - - - -	rat liver	Arochlor 1254	0.1, 0.3, 1, 3.3 and 10 mg/plate [1,2)] Vehicle: DMSO Negative and positive controls included	Machado, 1986
1) Dose levels were based on a dose-range finding study with levels of 0.003-10 mg/plate. Slight toxicity was observed at 10 mg/plate. 2) Slight toxicity observed at 10 mg/plate in the tester strains TA100 (with S9-mix) 3) In the absence of metabolic activation, the test item induced an up to 2.0-fold increases in the number of revertant colonies compared to the solvent controls in tester strain TA98. This increase was considered not relevant since the increase was not seen in the first experiment. Test substance: RE-45601 Technical (Clethodim technical); Purity 83.3%, batch SX-1688, amber liquid GLP statement: yes According to OECD 471: no, see acceptability According to 40 CFR 158.135, Pesticide Assessment Guideline No.84-2: yes							

The study fulfils the requirements of OECD 471. It is concluded that clethodim did not induce point mutations in *S. Typhimurium*.

Type of study: mammalian cells *in vitro*, gene mutation test, with independent repeat assay

Indicator cells	Endpoint	Res. –act.	Res. +act.	Activation		Dose range	Reference
				Tissue	Inducer		
CHO Chinese hamster ovary cells	gene mutations (HGPRT)	- [4]	-	rat liver	Arochlor 1254	Without metabolic activation: first exp.: 100, 200, 300, 400 and 500 µg/ml [1, 2] Second exp. :100, 200, 300, 400 and 450 µg/ml Third exp.: 100, 200, 300, 400, 450 and 500 µg/ml [3] With metabolic activation: First and second exp.: 100, 200, 300, 400, 450 and 500 µg/ml [2] Vehicle: DMSO Negative and positive controls included	Lehn, 1990
1 Dose levels were based on a dose range finding study in which levels of 25 to 500 µg/ml were tested. The test substance was tested up to its limit of solubility. Toxicity was only observed at the highest dose level of 500 µg/ml in the absence of metabolic activation. 2 Test substance precipitated in the exposure medium at 500 µg/ml 3 In experiment 1 and 2 severe toxicity observed at 500 µg/ml and no toxicity in experiment 3. 4 100 µg/ml (duplo), 200 µg/ml (duplo) and 500 µg/ml (single) showed statistically increases. This was due to extreme low mutant frequencies of the vehicle controls, so even one negative control showed a statistically increase. The increases were not-dose related and did not exceed the range, which is typical of vehicle control variations. So only one increase of one duplicate culture in the highest dose group was evaluated as biologically significant. Two additional experiments were performed, in which no biologically relevant increases were observed. Test substance: Select (Clethodim technical), batch 10195-36, purity 92.7%, CAS 99129-21-2, brown oily liquid GLP statement: yes According to OECD 476: no, see acceptability							

The study does not fulfil the requirements of the more recent OECD 476 guideline of 1997, such as

cytotoxicity criteria and number of dose levels tested. However, the study is considered acceptable. It is concluded that clethodim did not induce gene mutations in mammalian cells.

Type of study: mammalian cells *in vitro*, cytogenetic assay, with independent repeat assay

Indicator cells	Endpoint	Res. -act.	Res. +act.	Activation		Dose range	Reference
				Tissue	Inducer		
Chinese hamster ovary (CHO) cells	chromosome aberration	+	-	rat liver	Arochlor 1254	First exp.: 0.03, 0.1, 0.3 and 1 µl/ml (-S9, 10 h); 0.03, 0.1, 0.3 and 1 µl/ml (+S9, 2 h + 8 h) Second exp.: 0.6, 0.8, 1.0 and 1.2 µl/ml (-S9, 10 h); 0.6, 0.8, 1.0 and 1.2 µl/ml (+S9, 2 h + 8 h) Solvent: DMSO Negative and positive controls included	Putman, 1986
No cytotoxicity observed in the toxicity test up to and including 1 µl/ml. Precipitation was observed at dose levels of 0.6 µl/ml and above. A significant increase in the frequency of structural chromosome aberrations per cell was observed in the first experiment at 1 µl/ml and in the second experiment at 1 and 1.2 µl/ml in the absence of S9-mix. Test substance: Chevron RE-45601 Technical (Clethodim technical); batch SX-1688, brown viscous liquid, purity 83.3% GLP statement: yes According to OECD 473: no, see acceptability According to 40 CFR 158.135, Pesticide Assessment Guideline No.84-2: yes							

The study does not fulfil the requirements of the more recent OECD 473 guideline of 1997, concerning the different treatment and fixation times. However, the study is considered acceptable. The test substance induced chromosome aberrations in Chinese hamster ovary (CHO) cells in the absence of an exogenous source of metabolic activation, but not in the absence of metabolic activation.

Type of study: mammalian cells *in vitro*, cytogenetic assay, with independent repeat assay

Indicator cells	Endpoint	Res. -act.	Res. +act.	Activation		Dose range	Reference
				Tissue	Inducer		
Chinese hamster ovary (CHO) cells	chromosome aberration	-	-	rat liver	Arochlor 1254	First exp.: 0.03, 0.1, 0.3 and 1 µl/ml (-S9, 10 h); 0.03, 0.1, 0.3 and 1 µl/ml (+S9, 2 h + 8 h) Second exp.: 0.6, 0.8, 1.0 and 1.2 µl/ml (-S9, 10 h); 0.6, 0.8, 1.0 and 1.2 µl/ml (+S9, 2 h + 8 h) Solvent: DMSO Negative and positive controls included	Putman, 1986
No cytotoxicity observed in the toxicity test up to and including 1 µl/ml. Precipitation was observed at dose levels of 0.3 µl/ml and above. A significant increase in the frequency of structural chromosome aberrations per cell was only observed in the first experiment at 0.1 µl/ml in the presence of S9-mix compared to the solvent control, but not when compared to the untreated control. The statistically significance was due to an unusually low background rate and was not considered to be biologically significant.							

Indicator cells	Endpoint	Res. -act.	Res. +act.	Activation		Dose range	Reference
				Tissue	Inducer		
Test substance: Purified Chevron RE-45601 (Clethodim technical); purity 96.1%, batch SX-1718, amber liquid GLP statement: yes According to OECD 473: no, see acceptability According to 40 CFR 158.135, Pesticide Assessment Guideline No.84-2: yes							

The study does not fulfil the requirements of the more recent OECD 473 guideline of 1997, concerning the different treatment and fixation times. However, the study is considered acceptable. It is concluded that the test substance did not induce chromosome aberrations in Chinese hamster ovary (CHO).

4.9.1.2 In vivo data

Type of study: mammalian bone marrow cells *in vivo*, cytogenetic assay

Indicator cells	Endpoint	Result	Dose range	Reference
Rat, bone marrow, Sprague-Dawley 5/sex/dose (vehicle control, positive control, 2 lowest treatment groups) 20/sex/dose (highest treatment group)	bone marrow cells, chromosomal aberrations	-[1]	0.15, 0.5 and 1.5 g/kg bw[2], once by gavage, sacrifice at 12, 24 and 48 hours after dosing. Positive control included (24 hrs sacrifice only). Vehicle: CMC/Tween-80	Putman, 1987
[1.] Slides of 5 animals/sex were examined (50 metaphases per slide). [2] In the dose-range finding study, the test item was lethal to some animals at levels of 1.2 g/kg and above. Test substance: RE-45601 technical (Clethodim technical), batch SX-1688, amber liquid, purity 83.3% GLP statement: yes According to OECD 475: no, see acceptability According to 40 CFR 158.135, Pesticide Assessment Guideline No.84-2: yes				

The study does not fulfil the requirements of the more recent OECD 475 guideline of 1997, since only 50 cells are analysed instead of the prescribed 100 cells. However, the study is considered acceptable. It is concluded that clethodim did not induce chromosomal aberrations in bone marrow cells of male and female Sprague-Dawley rats.

Type of study: mammalian cells *in vivo*, unscheduled DNA synthesis

Indicator cells	Endpoint	Result	Dose range	Reference
Mouse hepatocytes, male B6C3F1 3/male/dose (vehicle control, positive control, 2 lowest treatment groups) 5/male/dose (highest treatment group, 16 hours treatment) [2]	Unscheduled DNA synthesis	- [3]	100, 1000 and 5000 mg/kg bw [1] once, sacrifice at 2and 16 hours after dosing. Positive control included (16 hrs sacrifice only). Vehicle: CMC/Tween-80 (16 hrs sacrifice only).	Steinmetz, Mirsalis, 1986

Indicator cells	Endpoint	Result	Dose range	Reference
1 Dose levels were based on a dose range finding study in which the maximum level of 5000 mg/kg bw was tested and 1 out of three animal was found dead at 5000 mg/kg bw and the other two had distended stomachs. 2 2 male animals were used at the vehicle control group and at the highest dose group of 5000 mg/kg bw at the 16 hrs sacrifice period. 3 3 slides per animal and 50 cells per slide were counted. Test substance: Chevron RE-45601 technical (Clethodim technical), batch SX-1688, purity 83.3%, amber liquid GLP statement: yes According to OECD 486: no, see acceptability According to 40 CFR 158.135, Pesticide Assessment Guideline No.84-4: yes				

The study fulfils the requirements of OECD 471. It is concluded that clethodim did not induce UDS in hepatocytes isolated ex vivo and Clethodim had no genotoxic activity in this test system.

4.9.2 Human information

No data available.

4.9.3 Other relevant information

No data available.

4.9.4 Summary and discussion of mutagenicity

Positive results have been reported in one chromosome aberration *in vitro* test with CHO cells. Two Ames tests, except for tester strain TA 98, are negative. Two *in vivo* studies showed negative for chromosomal aberrations and UDS in rodents. The equivocal results of some of the *in vitro* tests, were not confirmed by *in vivo* studies. Therefore, clethodim is considered to be non-genotoxic.

4.9.5 Comparison with criteria

The classification for mutagenicity is based on the total weight of evidence available, with positive results in somatic cell mutagenicity tests *in vivo*. As the *in vivo* chromosomal aberrations and UDS tests in rodents are negative, it seems no need for classification for mutagenicity. Clethodim does not fullfill the CLP criteria for classification for mutagenicity.

4.9.6 Conclusions on classification and labelling

Clethodim is considered to be non-genotoxic. There is therefore no need to classify clethodim for mutagenicity.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

A positive result was found without metabolic activation in a CHO cell chromosome aberration test. Bacterial mutagenicity tests and a CHO gene mutation test gave negative results. Both a rat bone marrow chromosomal aberration study and a mouse liver UDS test gave negative results.

Following a weight-of-evidence approach, clethodim was not considered genotoxic as the results of the *in vivo* studies in rodents were negative. Therefore, clethodim was considered non-genotoxic and does not meet the criteria for classification for

mutagenicity.

Comments received during public consultation

Two MS were in general agreement with the proposal for toxicological hazards.

Assessment and comparison with the classification criteria

The potential mutagenicity of clethodim has been studied *in vitro* in both bacteria and mammalian cells, and *in vivo* in a rat bone marrow chromosomal aberration test and a mouse liver UDS assay. All these tests were generally consistent with the relevant OECD guideline and all were considered acceptable by the Dossier Submitter.

Two bacterial mutagenicity studies gave clear negative results both in the presence and absence of metabolic activation. Investigations included both *S.typhimurium* and *E.coli* tester strains. Similarly, clethodim produced negative results in a hprt gene mutation test in Chinese hamster ovary cells. In all these studies, the top dose tested was limited by the toxicity of the test substance.

In contrast, in a Chinese hamster ovary cell chromosome aberration test, a reproducible increase in the frequency of structural aberrations was found in the absence of exogenous metabolic activation following a 10 h exposure period. In a second study, performed by the same laboratory according to a similar protocol, no clear increase in structural aberrations was observed, with or without exogenous metabolic activation. No explanation was available for the contrasting results seen in these studies; the overall conclusion is that clethodim may be clastogenic in cultured mammalian cells, without exogenous metabolic activation.

In a follow-up *in vivo* study, oral administration of clethodim (150-1500 mg/kg) to male and female rats produced no increase in bone marrow cell chromosome aberrations. Sacrifice times of 12, 24 and 48 h were assessed. Although 50 cells per sample were scored rather than the 100 cells recommended by the more recent OECD test guideline, this negative result is considered reliable. Further reassurance of a lack of genotoxic activity is provided by a negative result in a mouse liver UDS test. Hepatocytes were harvested in this test at 2 and 16 h following oral treatment of mice with 100, 1000 and 5000 mg/kg clethodim. There was no increase in UDS.

Overall, in spite of the isolated positive result in one of two *in vitro* chromosome aberration studies, it can be concluded reliably that clethodim lacks mutagenic potential. The positive *in vitro* result (-S9 only) was not reproduced in a second study, nor was an increase in chromosome aberrations found in a follow-up *in vivo* study. Therefore RAC agrees with the DS that **no classification is required for germ cell mutagenicity**.

4.10 Carcinogenicity

Table 23: Summary table of relevant carcinogenicity studies

Method	Results (mg/kg bw/day)	Remarks	Reference
OECD guideline 453	NOAEL=16, rats	No increase in tumor incidence	Dougherty, 1988[a]
OECD guideline 451	NOAEL=24, mice	No increase in tumor incidence	Cox, 1988[a]

[a] as summarized in the DAR 2005, B6, toxicology and metabolism

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

Characteristics

reference	:	Dougherty, 1988	exposure	:	Two years, diet
type of study	:	combined chronic toxicity and carcinogenicity study	doses	:	0, 5, 20, 500 and 2500 mg/kg food[1]
year of execution	:	1985-1988	vehicle	:	Acetone and diet
test substance	:	RE-45601 Technical (Clethodim), SD-1688, purity 83%	GLP statement	:	Yes
route	:	Oral	guideline	:	OECD guideline 453
species	:	Rat, Sprague-Dawley, Crl:CD	acceptability	:	Acceptable
group size	:	65/sex/dose	**NOAEL**	:	16 mg/kg bw/day

[1] equal to 0, 0.15, 0.57, 16 and 86 mg/kg bw/day in males and 0, 0.20, 0.72, 21 and 113 mg/kg bw/day in females.

The study was performed in accordance with OECD 453. The mortality rate was highest among males at 86 mg/kg bw/day (67%), but not significantly different from that of male controls (53%). Clinical signs most frequently reported were decreased motor activity, malocclusion, weakness, ano-genital discharge, reduced stools, exophthalmia, ocular red discharge, nasal discharge, broken teeth, alopecia, malocclusion, stained fur and scabs. The incidence of these clinical signs, which are not uncommon in chronic rat studies, did not distinguish treated animals from controls. No treatment-related changes in the incidence of ocular findings were observed. Body-weight gain and food consumption were significantly decreased in animals of each sex during the first year of treatment with 86 and 113 mg/kg bw/day for males and females, respectively. Food intake, calculated relative to body weight, was slightly greater at 86 in males and 113 mg/kg bw/day in females respectively, than in other groups.
There were no treatment-related deviations in clinical pathology parameters. At interim sacrifice after one year, increased liver weights and slight to mild centrilobular hypertrophy were noted in rats of each sex fed 86 and 113 mg/kg bw/day for males and females, respectively. Increased liver weights seen in females at 21 mg/kg bw/day were not correlated with any microscopically discernible change. At terminal sacrifice, liver weights of females at 113 mg/kg bw/day were increased; males had no significant increase in liver weight, and no treatment-related centrilobular hypertrophy was seen in animals of either sex. Females treated at 113 mg/kg bw/day had a slightly greater (12%) incidence of binucleated cells in the liver than the controls (2%), but the effect was of uncertain toxicological significance. Clethodim technical at dietary levels up to 86 in males and 113 mg/kg bw/day in females showed no evidence of carcinogenic potential. The NOAEL was 16 mg/kg bw per day, on the basis of decreased body-weight gain, decreased food intake, increased liver weight and associated centrilobular hypertrophy at 86 mg/kg bw/day.

Table 24 observations for combined chronic toxicity and carcinogenicity study

Dose (mg/kg food)	**0**		**5**		**20**		**500**		**2500**		**dr**
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**F**	
Survival	37/65	39/65	37/65	40/65	34/65	37/65	37/65	32/65	28/65	36/65	
Clinical signs	No treatment-related findings										
Body weight (gain)									dc	dc	
Food consumption									dc	dc	
Ophthalmoscopy	No treatment-related findings										

Dose (mg/kg food)	**0**		**5**		**20**		**500**		**2500**		**dr**
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**F**	
Haematology	No treatment-related findings										
Haematology	No treatment-related findings										
Urinalysis	No treatment-related findings										
Clinical chemistry	No treatment-related findings										
Organ weights											
Interim sacrifice											
- liver								i^{a}, ic^{b}	i^{a}, ic^{r}	$ic^{a,b}$	
Terminal sacrifice											
- liver										i^{a}, ic^{r}	
Pathology											
Macroscopy											
Interim sacrifice:	No treatment-related findings										
Terminal sacrifice: (including interim deaths)	No treatment-related findings										
Microscopy (including interim deaths) *neoplastic lesions*	No treatment-related findings										
microscopy *non-neoplastic lesions*											
Interim sacrifice											
Liver:											
- centrilobular hyperthr.	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	1/10	3/10	
All animals	No treatment-related findings										

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative
b organ/brain weight ratio
[1] at 6 months only.
[2] at 2 years only.
[3] at 1 and 2 years only.
[4] at 3 months only.

reference	:	Cox, 1988	exposure	:	78-weeks, diet
type of study	:	carcinogenicity study	doses	:	0, 20, 200, 1000 and 2000/3000) mg/kg food[1]
year of execution	:	1986-1988	Vehicle	:	Acetone and diet
test substance	:	Chevron RE-45601 Technical (Clethodim), SX-1688, purity 83.3%	GLP statement	:	Yes
route	:	Oral	Guideline	:	OECD guideline 451
species	:	Mouse, Crl:CD-1 (ICR)BR	Acceptability	:	Acceptable
group size	:	60/sex/dose	**NOAEL**	:	24 mg/kg bw/day Not oncogenic

[1] no calculations were made for the actual intake of test substance. Based on a default value for conversion of mg/kg food to mg/kg bw/d and correction for the purity of the test substance, the following intakes were calculated: 2.4, 24, 119 and 238/357 mg/kg bw/day for both males and females.

The study was performed in accordance with OECD 451. Treatment for 78 weeks with the test substance at 238/357 mg/kg bw/day significantly reduced the survival rate; the predominant cause of death at this dose was an increased incidence and severity of systemic amyloidosis. The observed clinical signs did not distinguish treated animals from controls. Body weights and food consumption were not affected by treatment, with the exception of a slight decrease in body weight gain in high dose females (92% of controls). Red blood cell count was statistically significantly decreased in

males at 238/357 mg/kg bw/day in week 27 and 79 and in females at 238/357 mg/kg bw/day in week 27. Haemoglobin and haematocrit was statistically significantly decreased in males at 238/357 mg/kg bw/day in week 27. These red blood cell deviations are consistent with a mild normochromic normocytic anaemia, as noted in mice and in other species in subacute and semichronic toxicity studies, and were considered to be related to treatment and toxicologically significant. After 52 weeks of treatment, increased liver weights and centrilobular hypertrophy of the liver were observed in males at 119 mg/kg bw/day and in males and females at 357 mg/kg bw/day. Increased pigment, described as morphologically compatible with haemosiderin and bile, was noted in males at 357 mg/kg bw/day. After 78 weeks of treatment, the hepatic changes included increased liver weights in females and males at 357 mg/kg bw/day (112-114% of controls), centrilobular hypertrophy and increased pigment in both males and females at 119 and 357 mg/kg bw/day and bile-duct hyperplasia in males at > 119 mg/kg bw/day. An increased incidence of multifocal, amphophilic alveolar lung macrophages was also observed in animals of each sex treated at > 119 mg/kg bw/day. The NOAEL was set at 24 mg/kg bw per day, on the basis of hepatic changes, notably centrilobular hypertrophy, increased pigment and bile-duct hyperplasia, and an increased incidence of alveolar macrophages in the lungs of mice treated at 119 mg/kg bw/day and above. There was no evidence that clethodim has carcinogenic potential.

Table 25 observations for 78-week carcinogenicity study

Dose (mg/kg food)	**0**		**20**		**200**		**1000**		**2000/3000**		**dr**
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
Survival (n=50) after 78 weeks	29 (58%)	33 (66%)	33 (66%)	42 (84%)	30 (60%)	40 (80%)	25 (50%)	29 (58%)	16* (32%)	24* (48%)	
Clinical signs	No treatment-related findings										
Body weight (gain)										d	
Food consumption	No treatment-related findings										
Haematology											
- RBC									dc^1	dc^2	
- haemoglobin									dc^2		
- haematocrit									dc^2		
Organ weights											
Interim sacrifice											
- liver							i^a, ic^r		$ic^{a,r}$	i^a, ic^r	
Terminal sacrifice											
- liver									$i^{a,r}$	i^a, ic^r	
Pathology											
macroscopy	No treatment-related findings										
microscopy	No treatment-related findings										
neoplastic lesions											
microscopy											
non-neoplastic lesions											
Interim sacrifice											
liver:											
- centrilobular hypertrophy	0/10	1/10	1/10	2/10	1/10	2/10	8/10	1/10	10/10	9/10	m
- increased pigment	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	5/10	0/10	

Dose (mg/kg food)	0		20		200		1000		2000/3000		dr
	m	f	m	f	m	f	m	f	m	f	
Terminal sacrifice liver:											
- centrilobular hypertrophy	1/28	0/32	1/31	0/41	1/30	0/39	10/24	4/29	16/16	10/22	m,f
- hyperplasia bile duct	0/28	1/32	0/31	0/41	1/30	0/39	4/24	0/29	5/16	2/22	m
- increased pigment	0/28	2/32	0/31	1/41	0/30	4/39	7/24	5/29	11/16	8/22	m,f
lung:											
- foci of amphophilic alveolar macrophages	0/28	0/32	0/31	0/41	1/30	0/39	5/24	3/29	8/16	13/22	m,f

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative
* statistically significant different from control, $p \leq 0.05$
[1] statistically significant in week 27 and 79
[2] statistically significant in week 27

4.10.1.2 Carcinogenicity: inhalation

No data available.

4.10.1.3 Carcinogenicity: dermal

No data available.

4.10.2 Human information

No data available.

4.10.3 Other relevant information

No data available.

4.10.4 Summary and discussion of carcinogenicity

In a 2-year chronic toxicity and carcinogenicity study in rats, administration of clethodim (dietary administration of 0, 0.15, 0.57, 16 and 86 mg/kg bw/day in males and 0, 0.20, 0.72, 21 and 113 mg/kg bw/day in females) resulted in a decrease in body weight gain and food consumption at 86 mg/kg bw/day. The mortality rate in the study was rather high (53-67%) over the dose groups, without a dose-response. There was no evidence that clethodim has carcinogenic potential in rats.

In a 78-week carcinogenicity study in mice, administration of clethodim (dietary administration of 0, 2.4, 24, 119 and 238/357 mg/kg bw/day for both males and females) resulted in an increased mortality rate at 238/357 mg/kg bw/day; the predominant cause of death was an increased incidence and severity of systemic amyloidossis. There was no evidence that clethodim has carcinogenic potential in mice.

4.10.5 Comparison with criteria

Classification for carcinogenicity should be on the basis of evidence of increases in tumor formation obtained from animal studies or epidemiology. There are no human data available. Two studies in

rats and mice showed no evidence of carcinogenic activity of clethodim. Overall, there is no evidence of an increase in tumor formation due to exposure to clethodim.

4.10.6 Conclusions on classification and labelling

There is no need to classify clethodim for carcinogenicity.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

In a two-year rat chronic toxicity and carcinogenicity study, clethodim was administered in the diet at doses of 0, 0.15/0.20, 0.57/0.72, 16/21 and 86/113 mg/kg bw/day (males/females). There was no evidence of carcinogenicity in this study.

In a 78-week carcinogenicity study in mice, animals were fed clethodim in the diet at doses of 0, 2.4, 24, 119 and 238/357 mg/kg bw/day. There was no evidence of carcinogenicity in this study.

Classification for carcinogenicity should be on the basis of evidence of increases in tumour formation obtained from animal studies or epidemiology.

There were no human studies available and two studies, one in mice and one in rats showed no evidence of carcinogenic activity of clethodim. Therefore, there is no evidence of an increase in tumour formation following exposure to clethodim. No classification was proposed for carcinogenicity.

Comments received during public consultation

Two MS were in general agreement with the proposed classifications for toxicological hazards.

Assessment and comparison with the classification criteria

The carcinogenic potential of clethodim has been assessed in two well-performed studies, one in mice and one in rats. The results of these studies showed no evidence of carcinogenic activity. Therefore, in the view of RAC **clethodim should not be classified for carcinogenicity**.

4.11 Toxicity for reproduction

Table 26: Summary table of relevant reproductive toxicity studies

Method	Results	Remarks	Reference
OECD 416	NOAEL, rats > 133.7 mg a.i./kg bw/day	No effects on fertility and development were observed at the highest tested concentration of 133.7 mg a.i./kg bw/day	Tellone, 1987[a]
OECD 414	NOAEL, rats 83.3 mg a.i./kg bw/day	Maternal toxicity effects were associated with foetotoxic changes at the same dose levels.	Schreuder, 1987[a]
OECD 414	NOAEL, rabbits 250 mg a.i./kg bw/day	no malformations and no developmental changes that could be attributed to treatment were noted for foetuses of females treated up to 250 mg a.i./kg bw/day.	Dearlove, 1987[a]

[a] as summarized in the DAR 2005, B6, toxicology and metabolism

4.11.1 Effects on fertility

4.11.1.1 Non-human information

reference	:	Tellone, 1987	exposure	:	Diet continuously throughout the study period
type of study	:	2-generation reproduction study	doses	:	0, 5, 20, 500 and 2500 mg/kg food[1]
year of execution	:	1986-1987	vehicle	:	None
test substance	:	Clethodim Technical (RE-45601), batch no. SX-1688, purity 83.2%	GLP statement	:	Yes
route	:	Oral	guideline	:	EPA 40 CFR 158.135, No. 83-4. OECD 416
species	:	Rat, Sprague Dawley Crl:COBS/CD®(SD)	acceptability	:	Acceptable
group size	:	30/sex/dose	**NOAEL**par	:	26.7 mg a.i./kg bw/day
			NOAELdev	:	≥133.7 mg a.i./kg bw/day
			NOAEL reproductive effects	:	≥133.7 mg a.i./kg bw/day

[1] Equal to 0, <1, 1, 32 and 160.5 mg/kg bw/day (mean intake over all weeks, both sexes F_0 generation) or 0, <1, 1, 34, and 181.5 mg/kg bw/day (mean intake over all weeks, both sexes F_1 generation). After correction for the purity, the values for the actual intake of the active ingredient were 0, <0.8, 0.8, 26.7 and 133.7 mg a.i./kg bw/day (F_0 generation, sexes combined) and 0, < 0.8, 0.8, 28.3, and 151.2 mg a.i./kg bw/day (F_1 generation, sexes combined).

The study was performed in accordance with the OECD 416. The only adverse effect on parental animals was a decrease in body weights and food consumption among males and females of the F_0 and F_1 generation receiving high dose levels of clethodim (purity 83.2%). Effects on body weights were particularly noted in males of both generations, while female body weights were also reduced but only in the F_1 generation. In the high dose group decreased food consumption values were noted among males and females of the F_0 and F_1 generation. For F_1 generation males this was seen during many intervals while for females it was only seen a few days during gestation. There were no changes detected between parental animals of the treated and control groups in mating indices, pregnancy rates, male fertility, oestrus cycle, macroscopic findings, microscopic findings and organ weights.

No treatment-related changes were detected in litter size, pup weights, sex ratio or litter survival of the F_0 and F_1 offspring. An increase of stillborn pups was noted in F_1 litters (14 stillborn pups in 7 litters). However, this difference most probably was due to a low control value (2 stillborn pups in 2 litters) because in the control group of the F_2 generation the number of stillborn pups was 7 in 5 litters and in a previous 2-generation reproduction study the number of stillborn pups was 9 in 6 litters. Based on the data presented in this study, the NOAEL for parental toxicity was 500 mg/kg food (equivalent to 26.7 mg a.i./kg bw/day). The NOAEL for reproductive toxicity as well as for developmental toxicity was considered to exceed 2500 mg/kg food (equivalent to 133.7 mg a.i./kg bw/day).

Table 27 observations for 2-generation reproduction study

Dose (mg/kg food)	**0**		**5**		**20**		**500**		**2500**		**dr**
	m	**f**	**m**	**f**	**m**	**f**	**m**	**f**	**m**	**f**	
F0 animals											
Mortality	No treatment-related mortality										
Clinical signs	No treatment-related findings										
Body weight									dc		
Body weight gain	No treatment-related findings										
Food consumption									dc*	dc	
Mating/fertility/gestation	No treatment-related findings										
Oestrus cycle	No treatment-related findings										
Fertility/fecundity	No treatment-related findings										
Organ weight	No treatment-related findings										
Pathology											
macroscopy	No treatment-related findings										
microscopy	No treatment-related findings										
F1 pups											
Litter size	No treatment-related findings										
Stillborn									I[b]		
Survival index	No treatment-related findings										
Sex ratio	No treatment-related findings										
Body weight	No treatment-related findings										
Pathology											
macroscopy	No treatment-related findings										
F1 animals											
Mortality	No treatment-related mortality										
Clinical signs	No treatment-related findings										
Body weight (gain)									dc	dc	
Food consumption									dc	dc	
Organ weight	No treatment-related findings										

Dose (mg/kg food)	0		5		20		500		2500		dr
	m	f	m	f	m	f	m	f	m	f	
Mating/fertility/gestation	No treatment-related findings										
Pathology											
macroscopy	No treatment-related findings										
microscopy	No treatment-related findings										
F2 pups											
Litter size	No treatment-related findings										
Survival index	No treatment-related findings										
Sex ratio	No treatment-related findings										
Body weight	No treatment-related findings										
Pathology											
macroscopy	No treatment-related findings										

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/r absolute/relative organ weight
* occasionally, not during the same period when reduced bodyweights occurred.
b within historical control values. No similar effects noted in F_2 generation

4.11.1.2 Human information

No data available.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

reference	:	Schreuder, 1987	exposure	:	Days 6-15 of gestation, gavage (10 ml/kg)
type of study	:	teratogenicity study	doses	:	0, 10, 100, 350 and 700 mg/kg bw/day[1]
year of execution	:	1986	vehicle	:	Aqueous carboxy methyl cellulose/ Tween 80
test substance	:	Clethodim Technical (RE-45601), batch no. SX-1688, purity 83.3%	GLP statement	:	Yes
route	:	Oral	guideline	:	EPA/FIFRA Pesticide Assessment Guideline, Subdivision F (Oct. 1982)
species	:	Rat Crl: CD®(COBS)	acceptability	:	acceptable
group size	:	25 females/dose	**NOAEL**mat	:	83.3 mg a.i./kg bw/day
			NOAELdev	:	83.3 mg a.i./kg bw/day
			teratogenic effects	:	≥ 583 mg a.i./kg bw/day

[1] equal to 0, 8.3, 83.3, 292 and 583 mg a.i./kg bw/day after correction for purity.

The study was performed in accordance with OECD 414. Mean body weight during the treatment period of gestation (i.e. days 6-15) were comparable between the control and the treated groups at doses of 10 and 350 mg/kg bw/day. On day 20 of gestation, mean body weights were comparable between the control and treated groups of 10 and 100 mg/kg bw/day and statistically significantly lower than control in groups of 350 and 700 mg/kg bw/day. Mean weight gains for the Day 6-20 interval using corrected Day 20 weights were lower than control in groups of 350 and 700 mg/kg bw/day; however, these differences from control were not statistically significant. These results

suggest that maternal toxicity was seen in the 350 and 700 mg/kg bw/day dose levels. No mortality occurred in the control group or in groups treated at the 10, 100 or 350 mg/kg bw/day dose levels. At 700 mg/kg bw/day maternal toxicity was evident as indicated by a 20% increase of mortality, decreased body weights and food consumption and higher incidence of clinical signs, i.e. excessive salivation, excessive lacrimation, poor condition, red/mucoid nasal discharge, alopecia and staining of the ano-genital area. The gravid uterus weight was also noted as decreased in this group. With the exception of excessive lacrimation and poor condition similar maternal effects, but less in severity, were noted at 350 mg/kg bw/d. None of the treated groups revealed any adverse effects in pathology. The slightly increased incidence of excessive lacrimation at 100 mg/kg bw/day was without dose-relation. No adverse effects of treatment at the 10 or 100 mg/kg bw/day dose levels were evident from maternal parameters (body weight and weight change data, food consumption data, physical observations, uterine implantation data or gross postmortem observations) or fetal parameters (body weights and sex distribution). No external malformations were seen in the control group (353 fetuses, 25 litters), 10 (351 fetuses, 25 litters) and 350 mg/kg bw/day (350 fetuses, 25 litters). The incidence of fetuses with external malformations in 100 and 700 mg/kg bw/day were 0.3% (1/329 fetuses) and 3.6% (8/221 fetuses), respectively. The incidence of litters containing fetuses with external malformations in 100 and 700 mg/kg bw/day were 4.2% (1/24 litters) and 33.3% (6/18 litters), respectively. The incidence of external malformations both on a per fetus and per litter basis for the group of 100 mg/kg bw/day did not differ statistically from control; however, in the group of 700 mg/kg bw/day, these incidences were statistically significantly increased from control. Dose levels of 350 and 700 mg/kg bw/day were considered to be foetotoxic, based on the increased post-implantation loss (high dose only), decreased foetal weights and associated retardation of skeletal ossification. Incomplete ossification was particularly seen in sacral and caudal vertebral elements and in the 5^{th} and 6^{th} sternebrae. Increased incidences of tail defects (absence of tail, short tail or filamentous tail) were observed among foetuses of the 700 mg/kg bw/d dose group. In the 700 mg/kg bw/d dose group, seven fetuses, representing six litters, had tail malformations. Some of these fetuses with tail defects also had other external malformations (i.e. imperforate anus, edema). Many of these same fetuses had visceral and/or skeletal malformations. Tail defects have been identified as malformations in rat fetuses that are frequently seen in association with maternal toxicity. These tail defects were attributed to the severe signs of maternal toxicity and considered not to reflect a teratogenic effect of the test substance.

Table 28 observations for teratogenicity study

Dose (mg/kg bw/day)	**0**	**10**	**100**	**350**	**700**	**dr**
Maternal effects						
Mortality	0/25	0/25	0/25	0/25	5/25	
Clinical signs						
-excessive salivation				+	++	
-excessive lacrimation			+		+	
-poor condition					+	
-red/mucoid nasal discharge				+	++	
-alopecia				+	++	
-staining ano-genital area				+	++	
Pregnant animals	25	25	24	25	24	
Body weight (gain)				d	dc	dr
day 15	284±20	284±19	280±17	273±18	266±16*	
day 20	362±26	362±26	357±19	337±36*	332±18**	
day 6-15	47±8	47±9	45±10	40±14	28±15**	

Dose (mg/kg bw/day)	0	10	100	350	700	dr
day 15-20	70±10	69±11	69±8	58±20*	58±13**	
net BW	280.7±20.1	281.9±19.3	280.8±17.2	263.5±27.7*	271.5±13.9	
net BWG	34.7±10.5	36.9±11.0	37.2±12.9	24.5±21.2	27.8±9.3	
Gravid uterus weight				d	dc	dr
Food consumption				dc[b]	dc[e]	dr
Pathology						
macroscopy	No treatment-related findings					
Litter response						
Live foetuses	353	351	329	350	221	
Litter Size	14.1	14.0	13.7	14.0	12.3	
Foetal weight				dc	dc	dr
Post implantation loss					i	
Sex ratio	No treatment-related findings					
Examination of the foetuses						
External observations						
-tail defects						
absence (%)	0	0	0	0	3	
short (%),	0	0	0	0	2	
filamentous (%)	0	0	0	0	2	
Skeletal findings						
-unossified vertebral elements (sacral, caudal)				i	i	
-unossified 5th/6th sternebrae				i	i	
Visceral findings	No treatment-related findings					

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
b/e gestation day 7 / gestation days 7,8,9,10

reference	:	Dearlove, 1987	exposure	:	Days 7-19 of gestation, gavage (5 ml/kg)
type of study	:	teratogenicity study	doses	:	0, 25, 100 and 300 mg/kg bw/day[1]
year of execution	:	1986	vehicle	:	Aqueous carboxy methyl cellulose/ Tween 80
test substance	:	Clethodim Technical (RE-45601), batch no. SX-1688, purity 83.3%	GLP statement	:	Yes
route	:	Oral	guideline	:	EPA/FIFRA 40 CFR 158.135 Pesticide Assessment Guideline, Subdivision F (Nov. 1983). No 83-3. OECD 414
species	:	Rabbit Hra: (NZW)SPF	acceptability	:	acceptable
group size	:	19-20 females/dose	**NOAEL**mat	:	20.8 mg a.i./kg bw/day
			NOAELdev	:	≥250 mg a.i./kg bw/day
			teratogenic effects	:	≥250 mg a.i./kg bw/day

[1] equal to 0, 20.8, 83.3 and 250 mg a.i./kg bw/day after correction for purity.

Another rabbit study was also performed in accordance with OECD414. On gestation day 22 one female at 100 mg/kg bw/d died prematurely and on gestation day 17 one female of at 25 mg/kg bw/d aborted. These incidences were in the absence of a dose response considered not to have a relationship with treatment. Signs of maternal toxicity were noted in females treated at 100 or 300 mg/kg bw/day and comprised clinical signs (red substance in the pan and dried faeces) and decreased body weight, food consumption and gravid uterus weight values. Only the gravid uterus weight was not statistically significant when compared to controls. When comparing treated does with those of the control group, no treatment-related effects were noted in the number of pregnancies, the number of live foetuses, the litter size and post-implantation loss. No malformations and no developmental changes that could be attributed to treatment were noted for foetuses of females treated up to 300 mg/kg bw/day (equal to 250 mg a.i./kg bw/day).

Table 29 observations for teratogenicity study

Dose (mg/kg bw/day)	**0**	**25**	**100**	**300**	**dr**
Maternal effects					
Mortality	0/19	0/20	1/20[a]	0/20	
Aborted	0/19	1/20[b]	0/20	0/20	
Clinical signs					
-red substance in pan				+	
-dried faeces			(+)	+	
Pregnant animals[c]	19	18(17)	17(16)	17	
Body weight (gain)			d	dc	dr
Gravid uterus weight				d	
Food consumption			d(c)	dc	dr
Pathology					
macroscopy	No treatment-related findings				
Litter response					
Live foetuses	138	114	117	111	
Litter Size	7.3	6.8	7.3	6.5	
Foetal weight	No treatment-related findings				
Post implantation loss	No treatment-related findings				

Dose (mg/kg bw/day)	0	25	100	300	dr
Sex ratio	No treatment-related findings				
Examination of the foetuses					
External observations	No treatment-related findings				
Skeletal findings	No treatment-related findings				
Visceral findings	No treatment-related findings				

dr dose related
dc/ic statistically significantly decreased/increased compared to the controls
d/i decreased/increased, but not statistically significantly compared to the controls
a/b gestation day 17 / gestation day 22
c between brackets: used for foetal evaluations

4.11.2.2 Human information

No data available.

4.11.3 Other relevant information

No data available.

4.11.4 Summary and discussion of reproductive toxicity

In an oral 2-generation reproduction study in rats (0, 5, 20, 500 and 2500 mg/kg food), a decrease in body weights and food consumption was noted among males and females of the F_0 and F_1 generation at 2500 mg/kg food. There were no changes detected between parental animals of the treated and control groups in mating indices, pregnancy rates, male fertility, oestrus cycle, macroscopic findings, microscopic findings and organ weights.
No treatment-related changes were detected in litter size, pup weights, sex ratio or litter survival of the F_0 and F_1 offspring.
In a teratogenicity study in rats (0, 8.3, 83.3, 292, 583 mg a.i./kg bw/d), maternal toxicity was observed at 292 and 583 mg a.i./kg bw/d, indicated by.an increase of mortality, decreased body weights and food consumption, a higher incidence of clinical signs and decreased gravid uterus weight. An increased post-implantation loss (high dose only), decreased foetal weights and associated retardation of skeletal ossification were observed at 292 and 583 mg a.i./kg bw/d.
In a teratogenicity study in rabbits (0, 20.8, 83.3 and 250 mg a.i./kg bw/day), maternal effects on clinical signs and decreased body weight, food consumption and gravid uterus weight were observed at 83.3 and 250 mg a.i./kg bw/day. No malformations and no developmental changes that could be attributed to treatment were noted for foetuses of females treated up to 250 mg a.i./kg bw/day.

4.11.5 Comparison with criteria

Classification for reproductive toxicity is based on effects that have the potential to interfere with sexual function and fertility as well as the development of the offspring. No reproductive effects or effects on reproductive organs were observed in the 2-generation study and in the available repeated dose studies.

In the rat developmental study, clear foetal effects were observed at the highest dose including reduced litter size, post implantation loss, reduced foetal weight, increase in tail defects and reduced

ossification in the presence of marked maternal toxicity including 20% mortality. The foetal effects are considered to be secondary to the maternal toxicity according to the CLP criteria as there is maternal mortality greater than 10% (criteria chapter 3.7.2.4.4). At the dose of 350 mg/kg bw/day, the foetal effects were limited to reduced foetal weight and reduced ossification. The dams at this dose levels showed maternal toxicity in the form of reduced body weight and body weight gain and clinical effects. The limited foetal toxicity is of limited severity and considered to be secondary to the maternal toxicity.

No developmental effects were observed in the developmental study in rabbits.

4.11.6 Conclusions on classification and labelling

There is no need to classify clethodim for reproductive toxicity.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

In a 2-generation reproduction study, clethodim was administered to rats via the diet. A decrease in body-weight and reduced food consumption was noted in animals of the F_0 and F_1 generation at the top-dose only. There were no changes detected between parental animals of the treated and control groups in mating indices, pregnancy rates, male fertility, oestrous cycle, macroscopic findings, microscopic findings and organ weights. There were no treatment-related changes detected in litter size, pup weights, sex ratio or litter survival of the F_0 and F_1 offspring.

Classification for reproductive toxicity is based on effects that have the potential to interfere with sexual function and fertility as well as the development of the offspring. No such effects were observed in a two-generation study or in the repeated dose studies available.

In a teratogenicity study in rats, maternal toxicity was observed at the 2 highest doses, indicated by an increase of mortality, decreased body weights and food consumption, a higher incidence of clinical signs and decreased gravid uterus weight. Decreased litter size, increased post-implantation loss and tail defects were evident at the high dose only, and decreased foetal weights and associated retardation of skeletal ossification were observed at the top 2 doses. The foetal effects were considered by the Dossier submitter to be secondary to the maternal toxicity according to the CLP criteria as there is maternal mortality greater than 10% (criteria chapter 3.7.2.4.4) at the top dose. At the second highest dose, the foetal effects were limited to reduced foetal weight and reduced ossification. The dams at this dose levels showed maternal toxicity in the form of reduced body weight and body weight gain and clinical effects. The limited foetal toxicity was of limited severity and considered to be secondary to the maternal toxicity.

In a teratogenicity study in rabbits, maternal effects such as clinical signs and decreased body weight, food consumption and gravid uterus weight were observed at the 2 highest doses. No malformations and no developmental changes that could be attributed to treatment were found.

No classification for developmental toxicity was proposed.

Comments received during public consultation

Two MS were in general agreement with the proposal for toxicological hazards.

Assessment and comparison with the classification criteria

Fertility and reproductive function

Data are available from a 2-generation reproductive toxicity study in rats. It was performed to contemporary guideline standards (including OECD 416). Rats were administered clethodim (83% purity) at dietary levels of 0, 5, 20, 500 and 2500 ppm: equivalent to doses of approx. 0, <0.8, 0.8, 26.7 and 133.7 mg/kg clethodim (F0 animals) and 0, <0.8, 0.8, 28.3 and 151.2mg/kg clethodim (F1 animals).

As indicated in the Dossier Submitter's proposal, there were no indications of an effect on sexual function or fertility. At the highest dose, the only adverse effects on parental animals were a decrease in body weight and food consumption. Unfortunately, the figures were not presented by the Dossier Submitter, but the effects do not appear to have been marked. An increase of stillborn pups was noted in F1 litters at the top dose (14 stillborn pups across 7 litters, contrasting with 2 stillborn pups in 2 litters in controls). In the F2 generation, the control incidence of stillborn pups was 7 in 5 litters. No data were provided by the Dossier Submitter for the other dose groups. However, a historical value of 9 stillborn pups from 6 litters was cited from one control group in a different 2-generation study performed earlier by the same laboratory, but in isolation this information is not particularly informative. Although no details of the numbers of stillborn pups in the other dose groups were provided by the Dossier Submitter in either the CLH report or the accompanying Draft Assessment Report (DAR), it seems most likely that the apparent increased incidence of F1 stillborn pups at the top dose was an incidental finding, prominent because of the low control incidence in this phase of the study.

Additional information provided by the Dossier Submitter confirmed this assessment (see BD*).*

Developmental toxicity

Clethodim has been assessed for developmental toxicity in rats and rabbits. The studies were performed in the 1980s and met contemporary guidelines.

Study in rats

Rats were administered clethodim (83% pure) by gavage on days 6-15 of gestation. Increased mortality was observed in dams at the top dose of clethodim (583 mg a.i./kg). The death rate was 5/25 (versus 0 in all other treatment and control groups), i.e. 20 %. At this dose, clinical signs included excessive salivation, red/mucoid nasal discharge, alopecia and staining of the anogenital area. Mean maternal body weight gain was reduced over the periods of gestation days 6-15 and 15-20. Gravid uterus weight was also statistically significantly reduced (no data presented).

At this dose there was a clear effect on foetuses: an increase in the incidence of external malformations in 8/221 foetuses, with tail defects noted in 7/221 foetuses (3.2 %) across 6 litters (versus 0 in control animals). Mean foetal weight in this group was statistically significantly reduced compared to controls. Incomplete ossification was observed in the sacral and caudal vertebral elements and in the 5^{th} and 6^{th} sternebrae, however these findings were not statistically significant. Increased post-implantation loss was also observed, but again in the absence of any statistical significance. Although the number of live foetuses born (221; mean 12.3) was significantly less than controls (353; mean 14.1), this was not reported to be statistically significant.

At the second highest dose of 292 mg a.i./kg bw/day, no mortality was observed. There

was a small effect on maternal body weight gain compared to controls (less than 10%) together with excessive salivation, red/mucoid nasal discharge, alopecia and staining of the anogenital area. Foetal weight was statistically significantly reduced (no data provided). Similarly to the foetuses of the top dose group, there was incomplete ossification present (in the absence of statistical significance). No external malformations were observed and there were no effects on post-implantation loss, the number of live foetuses or on litter size. There were no other toxicologically significant findings at any other doses in this study.

Table: Rat developmental toxicity study - data presented by the Dossier Submitter

Dose (mg a.i./kg/day)	**0**	**8.3**	**83.3**	**292**	**583**
Maternal effects					
Mortality	0/25	0/25	0/25	0/25	5/25 (20%)
Pregnant animals	25	25	24	25	24
Body weight (g)					
Day 15	284+/-20	284+/-19	280+/-17	273+/-18	266+/-16*
Day 20	362+/-26	362+/-26	357+/-19	337+/-36*	332+/-18**
Days 6-15	47+/-8	47+/-9	45+/-10	40+/-14	28+/-15**
Days 15-20	70+/-10	69+/-11	69+/-8	58+/-20*	58+/-13**
Net Body weight	281+/-20	282+/-19	281+/-17	263.5+/-27*	271.5+/-14
Net Body weight gain	35+/-10.5	37+/-11	37+/-13	24.5+/-21	28+/-9
Foetal effects					
Live foetuses	353	351	329	350	221
Litter size	14.1	14.0	13.7	14.0	12.3
Total external malformations (number of foetuses)	0	0	1	0	8
Tail defects (%)					
- absence	0	0	0	0	3
- short	0	0	0	0	2
- filamentous	0	0	0	0	2

Statistical significance denoted by * and **

Net body weight and body with gain values rounded to nearest gram

Aside from the effect on foetal weight, all the adverse effects on foetuses seen in this study were observed at a maternally lethal dose (causing 20% mortalities). In isolation, the effect on foetal weight appears most likely to have been related to maternal toxicity and is not viewed as evidence of developmental toxicity. Therefore, this study did not show a clear developmental effect of clethodim.

<u>Study in rabbits</u>

Rabbits were administered clethodim by gavage on days 7-19 of gestation. There was one premature death in the mid-dose treatment group (83.3 mg/kg bw/day) and one at the low-dose (20.8 mg/kg bw/day). In the absence of any dose-response relationship, these effects are not considered to be treatment-related. There were some signs of maternal toxicity in the mid- and top-dose groups, including reduced body weight-gain, reduced food consumption and a decrease in gravid uterus weight (top-dose only) (data not presented by the Dossier Submitter).

There were no treatment-related effects on the number of pregnancies, the number of live foetuses, litter size and post-implantation loss. No malformations or developmental changes that could be attributable to treatment were observed at any dose level.

Comparison with criteria
RAC shares the view of the Dossier Submitter that no classification is justified for reproductive toxicity.

There was no indication of an adverse effect on fertility or reproductive function in a 2-generation reproductive study in rats and no developmental effects were seen in this species in the absence of maternal toxicity. No developmental effects were seen in rabbits.

According to Annex I, section 3.7.2.4.4 of the CLP Regulation, an increase in the incidence of maternal mortality of > 10 % is considered excessive and data for that dose level should not normally be considered for further evaluation. Therefore, in the rat study, the adverse effects in the foetuses of the top-dose group (583 mg a.i./kg) are not considered relevant for the classification given the increase in mortality of 20 %.

The remaining effects observed in the rat developmental toxicity study occurred at the second highest dose (292 mg a.i./kg). These included a statistically significant reduction in foetal weight and a non-significant incidence of incomplete ossification. This mild foeto-toxicity is considered to have been related to maternal toxicity (6 % reduction in body weight and some clinical signs including increased salivation and red mucoid nasal discharge) and is therefore not considered as a developmental effect. **Accordingly, no classification is proposed for toxicity to reproduction.**

Supplemental information - In depth analyses by RAC

Developmental Toxicity
One aspect of the data, on which RAC felt unable to make an independent assessment of, related to the number of stillborn pups in the high dose F1 group. In order to confirm that this was not a treatment-related effect but a consequence of the low number of stillborn pups in the F1 control groups, the DS provided the following tabulated information.

F0/1	Group I	Group II	Group III	Group IV	Group V
dams pregnant and surviving delivery	22	25	23	24	28
surviving dams with stillborn pups	2	5	4	4	7
% dams with stillborn pups	9	20	17	17	25
Pups delivered	298	308	286	285	367
Stillborn	2	5	5	7	14
Stillborn/litter	0.09	0.20	0.22	0.29	0.50
% stillborn	0.7	1.6	1.7	2.5	3,8
F1/2					
dams pregnant and surviving delivery	21	23	29	27	25

surviving dams with stillborn pups	5	5	6	8	6
% dams with stillborn pups	24	22	21	30	24
Pups delivered	264	254	371	344	321
Stillborn	7	6	7	11	10
Stillborn/litter	0.33	0.26	0.24	0.41	0.40
% stillborn	2.7	2.4	1.9	3.2	3.1

Rats were administered clethodim (83% purity) at dietary levels of 0, 5, 20, 500 and 2500 ppm: equivalent to doses of approx. 0, <0.8, 0.8, 26.7 and 133.7 mg/kg clethodim (F0 animals) and 0, <0.8, 0.8, 28.3 and 151.2 mg/kg clethodim (F1 animals).

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

No data available.

4.12.1.2 Immunotoxicity

No data available.

4.12.1.3 Specific investigations: other studies

No data available.

4.12.1.4 Human information

No data available.

4.12.2 Summary and discussion

4.12.3 Comparison with criteria

4.12.4 Conclusions on classification and labelling

RAC evaluation of aspiration toxicity
No classification was proposed for this endpoint (not evaluated).

5 ENVIRONMENTAL HAZARD ASSESSMENT

The environmental hazards of clethodim were assessed in the Draft Assessment Report and its addenda prepared in the context of the possible inclusion of clethodim in Annex I of Council Directive 91/414/EEC. The DAR is publicly available via the EFSA web site (http://dar.efsa.europa.eu/dar-web/provision). The summaries included in this proposal are copied from the DAR (and its addenda and assessment reports when these contain updated information). For an overview of the hazard property being evaluated, all reliable information relating to that property has been summarised in a table. Detailed information is included for the key studies used to derive the classification. For more details the reader is referred to the DAR and its addenda.

5.1 Degradation

Table 30: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Biodegradation	readily biodegradable	OECD 301D	Dengler D., 2002
Simulation test	DT50 = 23 d; DT90 = 77 d	BBA IV, 5-1	Heintze A., 1998

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5.1.1 Stability

No valid study is available for hydrolysis.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

5.1.2.2 Screening tests

Reference	:	Dengler D., 2002	GLP statement	:	Yes
Type of study	:	Ready biodegradability (Closed bottle test)	Guideline	:	OECD 301 D
Year of execution	:	2001	Acceptability	:	Acceptable
Test substance	:	Clethodim technical, batch 10773, 94.6% pure			

The ready biodegradability of clethodim was studied in a closed bottle test according to OECD 301 D, and in compliance with GLP. Test solutions containing clethodim technical (94.6% pure, *2* mg/L, added in acetone, final conc. 0.2% v/v, which was allowed to evaporate) and inoculum prepared from effluent from a municipal sewage treatment plant (0.1 mL/L) were kept in completely full, closed bottles in the dark at for 28 days at 20 ± 2°C. Duplicate flasks for the inoculum blank controls (inoculum, no test substance), the reference substance (sodium benzoate, 2 mg/L) and the toxicity control (clethodim, 1 mg/L and sodium benzoate, 1mg/L) were included. Oxygen concentrations were determined in duplicate flasks using an oxygen electrode on day 0, 7, 14, 21 and 28 days. The pass level for the reference substance (60% ThOD) was reached within 7 days. Clethodim was readily biodegradable in this test (56% and ≥100% biodegradation after 7 and

14 days respectively). No inhibitory effects of the test substance were observed (>25% degradation within 14 days). Clethodim was readily biodegradable in a closed bottle test.

5.1.2.3 Simulation tests

Reference	:	Heintze A., 1998 (IIA 7.2.1.3.2/02)	GLP statement	:	Yes
Type of study	:	Aerobic water sediment	Guideline	:	BBA IV, 5-1 (1990)
Year of execution	:	1989	Acceptability	:	Acceptable (additional information requested)
Test substance	:	[Ring-4,6-^{14}C] clethodim, S.A. 56 mCi/mMole, radiochemical purity 97.4%.			

Water/sediment studies were conducted in one system according to BBA IV, 5-1 (1990) guidelines, in compliance with GLP. The fate of clethodim in a water-sediment system was investigated under aerobic conditions at 20°C in the dark. Samples of untreated pond water (~500 mL, ~6 cm overlying on sediment) from Bauschlott, Germany, and associated wet loamy silt sediment (~130 g dry weight, ~2.5 cm thick) were placed in 1 L cylindrical flasks and equilibrated prior to treatment for about 56 days at 20°C in the dark under aerobic conditions (aeration four times for 45 minutes each day). Water and sediment were characterised (water: organic carbon 5.6 mg/L; sediment: % sand/silt/clay, 15/74/12, organic carbon, 3.99%). Following equilibration, [ring-4,6-14C]-clethodim (radiochemical purity 97.4%) was added in acetone (130 µL) to the flasks at 0.077 mg a.s./L (equivalent to a surface application of 48 g a.s./ha). Treated flasks were incubated in a closed gas flow system at 20°C in the dark under aerobic conditions (aeration with CO_2–free air four times for 45 minutes each day) for up to 196 days. Volatile organics were trapped in Tenax, and CO_2 in two solid phase traps (NaOH pellets).

The pH, dissolved O_2 and redox potential of water and sediment were measured throughout equilibration and incubation. The time course of the parameter values indicated that the systems had reached an equilibrium at the end of the acclimatisation period. During aerobic incubation, dissolved O_2 (2-3 mg/L) and redox potential of the water (≥+100 mV) were indicative of aerobic conditions, whereas the redox potential of the sediment (≤-145 mV) was negative throughout. The pH in the water ranged between 7.5 and 8.3.

Duplicate flask were analysed after 0, 0.25, 1, 2, 7, 14, 28, 61 and 103 days, and single flasks after 121 and 196 days. Sediment and water were separated by decanting. Sediment was extracted 3X with methanol, followed by 3X with 0.01M $CaSO_4$. Methanol extracts containing >5% AR were evaporated and fractionated by GPC. The main fraction (containing 95% of the RA chromatographed) was concentrated and analysed by RP HPLC. Clethodim and metabolites were extracted from the water using Envicarb cartridges, eluted with organic solvent and analysed by RP HPLC. Fractions in sediment and water extracts, containing compounds that were poorly separated by HPLC, were collected and analysed by TLC. Compound identification was achieved by comparison to reference standards. Tenax was extracted with acetone. $^{14}CO_2$ in solid phase NaOH traps was released by acidification and trapped in LSC cocktail. Radioactivity in extracts, trapping liquids and water was quantified by LSC. Non-extracted radioactivity in sediment was quantified by combustion LSC. The recovery of clethodim during the above extraction procedure was determined by analysis of water and concentrated sediment extract fortified with clethodim and found to be 96-98% (not clear whether recovery was based on LSC or on LSC and HPLC).

In a pond water-sediment system treated with [ring-2,4-14C]-clethodim at 0.077 mg/L, and incubated at 20°C in the dark, the radioactivity level in the water decreased from 96.4% AR on day 0 to 24.5% AR on day 103 and 12.2% AR on day 196. The amount of radioactivity partitioning into

the sediment increased to 61.4% and 63.3% AR after 103 and 196 days, respectively. The unextractable fraction in the sediment increased to 22.0% and 32.5% AR after 103 and 196 days, respectively. CO_2 was a major degradation product (14.2% and 18.3% AR after 103 and 196 days, respectively). Metabolites, that were identified at levels >5% AR in water and/or sediment were clethodim sulfoxide (max. 32.4 / 1.2% AR in water / sediment), clethodim imine (max. 0.0 / 27.3% AR in water / sediment), clethodim imine sulfoxide (max. 6.2 / 15.5% AR in water / sediment) and clethodim oxazole (max. 7.7 / 0.0% AR in water / sediment). Metabolites, that were identified at levels <5% AR in water and sediment were clethodim imine sulfone and clethodim sulfone.Volatile organics were insignificant (0.0% AR). It is concluded that clethodim degraded with $DT50_{system}$ and $DT90_{system}$ values of 23 and 77 days, respectively.

5.1.3 Summary and discussion of degradation

No valid study is available for hydrolysis.

The substance is demonstrated to be readily biodegradable in a 301D closed bottle test, The fate of [ring-2,4-14C]-Clethodim in a system of pond water and associated loamy silt sediment (pH 7.8, 3.99% oc) was investigated under aerobic conditions at 20°C in the dark. Clethodim degraded with DT50 and DT90 values of 23 and 77 days, respectively.

In view of the ready biodegradability data clethodim is considered rapidly degradable for classification and labelling purposes.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

The adsorption and desorption behaviour of [^{14}C]-clethodim (radiochemical purity 99.8%) on soil was determined using the batch equilibrium method according to OECD Guideline No. 106. The soils used were Speyer 2.2 (sandy loam, soil I), Mechtildshausen (loam, soil II), Mussig (clay loam, soil III) and Bretagne 1 (silt loam, soil IV). In the preliminary/screening test, the adsorption behaviour of [^{14}C]-clethodim on soil at a test concentration of 0.20 mg/L was tested using a soil (dry weight) to aqueous phase ratio of 1/1 (10 g/10 mL) for all four soils. Initially, the adsorption test was performed using non-sterilised soil samples and intervals up to 48 hours of adsorption. However, rapid degradation of the test item was observed in the supernatants. Therefore, in order to minimise degradation, γ-irradiated soil was used and shorter intervals were selected. Despite these precautionary measures, degradation of the test item was still observed. The suspensions were incubated in sealed Teflon centrifuge tubes on a shaker at about 150 strokes per minute, in the dark, at 20 °C. After 2, 5 and 24 hours of agitation, aliquots of the aqueous phase were measured by LSC, and after 24 hours the radioactivity was additionally characterised by HPLC analysis. No adsorption of the test item (or its degradates) on the surface of the test vials was found in the control samples.
The results of the preliminary/screening test showed that it was necessary to analyse the supernatants and soil extracts in order to take the degradation of clethodim into account for the calculation of the adsorption coefficients.
Adsorption and desorption isotherms were determined in an advanced test at five concentrations (0.195, 0.049, 0.020, 0.005 and 0.002 mg/L) covering two orders of magnitude in all four soils. A soil/solution ratio of 1/1 and an agitation time of 2 hours were used. The desorption isotherms were calculated from the values obtained after 2 hours of desorption.
A mean adsorption K_{FOC} of 23 (individual values depending on soil pH) and a mean desorption K_{FOC} of 28 were obtained. The calculated $K_{FOC,des}$ values were little higher than those obtained for the adsorption

isotherms, indicating a partial irreversible sorption process. The 1/n values of between 0.97 and 1.05 for the adsorption show a linear adsorption process for all soils studied. A small part of radioactivity could not be extracted with organic solvents and therefore, remained bound to the soil.
The higher adsorption of [14C]-clethodim to soils I and IV correlated with the acidic pH of these soils (5.80 and 5.97) whereas the rather low adsorption to soils II and III correlated with their slightly basic pH (7.26 and 7.20). Radioactivity in the control samples was entirely recovered for all concentrations. The mass balance was performed for all four soils at the highest concentration of the test item used in the advanced test (0.195 mg/L). The recovery of the radioactivity was 93.7%, 96.6%, 95.6% and 93.2% for soils I, II, III and IV, respectively. In the supernatant, amounts of 49.3%, 93.5%, 90.4% and 51.8% of the radioactivity applied were detected, respectively. Extractions with acetonitrile/water (4/1; v/v) recovered 42.1%, 1.9%, 2.4% and 39.1% for soils I, II, III and IV, respectively. Amounts of 2.3%, 1.2%, 2.7% and 2.3% of the radioactivity applied remained non-extracted in the corresponding soils.

The Koc and Kd values at different pH are as follows:
Koc : 3-5 L/kg (pH 7.2); 40-43 L/kg (pH 5.9)
Kd : 0.064-0.124 (pH 7.2); 0.8-0.989 (pH 5.9).

5.2.2 Volatilisation

Clethodim is not volatile (VP = 2.08 x 10^{-6} at 20°C and 4.92 x 10^{-6} at 25°C Pa and Henry's Law Constant = 1.4 x 10^{-7} Pa.m^3.mol^{-1} at 20°C).

5.2.3 Distribution modelling

5.3 Aquatic Bioaccumulation

Table 31: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
Screening criteria	Potential B		
bioconcentration fish test	Not B	Bluegill sunfish	Forbis 1987b

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5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

The log Kow of clethodim is 4.2, which is higher than that of cut-off value of 4, indicating that the substance has a bioaccumulation potential.

5.3.1.2 Measured bioaccumulation data

Reference	:	Forbis A.D. (1987b)	GLP statement	:	yes
type of study	:	Bioconcentration in fish	guideline	:	FIFRA 72-6 and 165-4
year of execution	:	1987	acceptability	:	acceptable
test substance	:	[Allyl-2 ^{14}C]-RE-45601, radiochemical purity 98%, sp. act. 3.73x10^6 dpm/mg; [Cyclohexene-1-one-4,6-^{14}C]-RE-45601, radiochemical purity 98%, sp. act. 3.43x10^6 dpm/mg			

Bluegill sunfish (*Lepomis macrochirus*) were exposed to [Allyl-2 ^{14}C] and [Ring-4-^{14}C]-clethodim (radiochemical purity 98% for both labels) for 28 days in a flow-through system, followed by 14 days of depuration (Section B.9.2.2.3, DAR, 2005). Nominal concentrations were 0.05 mg a.s./L for both labels, plus control. The mean measured radioactivity concentrations in the water during exposure were 0.064 and 0.065 mg a.s. eq./L (standard deviation 0.0053 and 0.0047 mg a.s. eq./L) for the allyl- and ring-label, respectively. Taking into consideration the mean percentage of parent compound determined in water samples during the uptake phase (39% and 57%), the mean measured concentrations of clethodim in the water during exposure were 0.025 and 0.037 mg a.s./L for allyl- and ring-label respectively. Water quality parameters were: temperature (21°C), dissolved oxygen (6.3-9.0 mg/L) and pH (8.0-8.4). Water and at least six fish were sampled at day 0.17, 1, 3, 7, 14, 21 and 28 and at day 1, 3, 7, 10 and 14 during exposure and depuration, respectively. Total radioactive residues in water, three whole fish, and fillets and viscera from three more fish, were determined at all sampling times. Extraction and metabolite identification was performed on samples of water, whole fish, fillet and viscera taken at day 21 and 28. The tissue samples were extracted using chloroform-methanol and methanol-water, leaving 9-38%, 20-77% and 7-28% of the initial Total Radioactivity Residues (TRR) in post-extracted solids of whole fish, fillet and viscera, respectively. Subsequent extraction with methanol/1N HCl (2:1 v:v) released <5% of the 14C, but reflux in 6N HCl solubilised >80% of the ^{14}C. Water samples were extracted using dichloromethane, diethyl ether and diethyl ether-ethanol. The extracts were analysed by reversed phase HPLC with confirmation by normal phase TLC. Compound identity was based on co-chromatography with reference standards.

A steady-state situation for ^{14}C concentration in whole fish was reached within 3 days of exposure for both labels. For the allyl- and ring-label, respectively, the CT50 (whole fish) was 4.9 and 0.23 days, and the CT90 16 and 0.76 days (determined by the BIOFAC modelling programme). After 14 days in uncontaminated water, 72% and >70% of the mean plateau radioactivity was cleared from whole fish from the [Allyl-2-^{14}C]-clethodim and [Ring-4-^{14}C]-clethodim exposure group, respectively. The steady-state biological concentration factor (BCF) for whole fish based on radioactivity measurements was calculated to be 2.1 and 2.1 L/kg wet weight for [Allyl-2-^{14}C]- and [Ring-4-^{14}C]-clethodim, respectively. Lipid content was not determined. Therefore, the BCF could not be normalised to the standard lipid content of 5%.

5.3.2 Summary and discussion of aquatic bioaccumulation

The log Kow of clethodim is 4.2, higher than the cut-off value of 4, indicating a bioaccumulation potential. However, one BCF value of 2.1 L/kg wet weight was determined in the experimental bioconcentration fish test, indicating that the substance does not bioconcentrate.

5.4 Aquatic toxicity

Table 32: Summary of relevant information on aquatic toxicity

Method	Results L(E)C50 (a.s. mg/L)	Remarks	Reference

OECD 203	96h-LC50= 25	Rainbow trout	DAR, 2005
OECD 203	96h-LC50> 33	bluegill sunfish	DAR, 2005
OECD 204	21 day NOEC = 3.9	Rainbow trout	DAR, 2005
OECD 202	48h-EC50> 100	Daphnia	DAR, 2005
OECD 211	21 day NOEC = 49	Daphnia	DAR, 2005
OECD 201	72h-EC50> 12, NOEC=12	algae	DAR, 2005
OECD 201	72h-EC50 = 56, NOEC=48	algae	DAR, 2005
OECD 201	72h-EC50 = 118, NOEC=66	algae	DAR, 2005
USEPA FIFRA 123-2	14d- NOEC (frond count) = 0.37 7d-EC10 (growth rate) = 0.37	duckweed	DAR, 2005

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

A static rainbow trout toxicity test was performed with five nominal concentrations of 10, 18, 32, 56, and 100 mg/l, plus control in accordance with OECD 203 (Swigert JP. 1986 a, Section B.9.2.1.1, DAR, 2005). Actual concentrations were on day 0: 79, 47 and 31%, on day 2: 81, 62 and 26% and on day 4: 73, 59 and 42% at nominal concentration 10, 32 and 100 mg/L, respectively. Undissolved test substance (film at all concentrations and drops at the highest three concentrations) was observed throughout the test period. The 96h LC50 was 25 a.s mg/l (95% confidence interval 18-33 mg/l), which was based on the mean measured concentrations.

A static bluegill sunfish toxicity test was performed with five nominal concentrations of 10, 18, 32, 56, and 100 mg/l, plus water control in accordance with OECD 203 (Swigert JP. 1986 a, Section B.9.2.1.1, DAR, 2005). Actual concentrations were on day 0: 88, 41 and 34%, on day 2: 79, 66 and 27% and on day 4: 97, 84 and 37% at nominal concentration 10, 32 and 100 mg/L, respectively. Undissolved test substance (film at all concentrations and drops at the highest three concentrations) was observed throughout the test period. The mean measured concentration at 56 mg/L was calculated from the mean of the recoveries at 32 and 100 mg/L. The 96h LC50 was >33 a.s mg/l.

5.4.1.2 Long-term toxicity to fish

reference	:	Heintze A. (1997a)	GLP statement	:	yes
type of study	:	Chronic toxicity study in rainbow trout	guideline	:	OECD 204
year of execution	:	1997	acceptability	:	acceptable
test substance	:	Clethodim technical, batch 05/Lot 70855, chemical purity 95.2%			

DAR 2005, B9, Ecotoxicity

A prolonged toxicity flow-through study was undertaken with rainbow trout (*Oncorhynchus mykiss*) in accordance with OECD 204. Ten fish per replicate (one replicate per concentration) were exposed to clethodim (95.2% pure) at nominal concentrations of 0.50, 1.1, 2.4, 5.3, 12, 26 and 57 mg a.s./L plus control and solvent control. Mean measured concentrations were 0.41, 0.79, 1.9, 3.9, 9.0, 17 and 40 mg a.s./L, representing 71 to 86% of nominal. Water quality parameters were: temperature (15.5-16.9°C), dissolved oxygen (≥70% of saturation) and pH (7.0 to 7.8). The total duration of the exposure period was 21 days. Endpoints were: mortality, growth and symptoms. Survival was not affected at 9.0 mg a.s./L and below when compared to the pooled control group, but was reduced by 20% and 100% at 17 and 40 mg a.s./L respectively. Symptoms including effects on swimming behaviour, movement and maintenance of equilibrium over periods longer than 48

hours were observed at 9.0 mg a.s./L and above. Weight and length gain were reduced at 17 mg a.s./L. The NOEC and LOEC for survival and growth were 9.0 and 17 mg a.s./L, respectively. The NOEC and LOEC for symptoms were 3.9 and 9.0 mg a.s./l, respectively. The overall NOEC was 3.9 mg a.s./L.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

A static Daphnia toxicity test was performed in accordance with OECD 202 (Forbis AD. 1986 a, Section B.9.2.1.1, DAR, 2005). Actual concentrations were 93-110% and 88-98% of nominal at t=0 and t=48h respectively. The reported 48-hours EC50 was >100 a.s mg/l expressed as nominal concentration.

5.4.2.2 Long-term toxicity to aquatic invertebrates

reference	:	Knoch M. (1995b)	GLP statement	:	yes
type of study	:	Chronic toxicity study in *Daphnia magna*	guideline	:	OECD 202
year of execution	:	1995	acceptability	:	acceptable
test substance	:	Clethodim technical, batch 40716, chemical purity 92.4%			

DAR 2005, B9, Ecotoxicity

The chronic toxicity of clethodim (chemical purity 92.4%) to *Daphnia magna* was assessed in a 21-day semi-static study. First instar daphnids (<24 hours old, 40 per treatment, 5 per replicate) were used to initiate the study. The nominal concentrations were 0.80, 2.3, 6.3, 18, 49 and 139 mg a.s./L plus control. The mean measured concentrations, which were determined only at nominal concentrations 0.80, 6.3 and 49 mg a.s./L, were 0.95, 7.0 and 55 mg a.s./L, representing 111 to 119% of nominal. Water quality parameters were: temperature (18.1-20.9°C), dissolved oxygen (≥89% of saturation) and pH (7.2 to 8.8). Mortality was 100% at 139 mg a.s./L, but survival was not affected at any other concentration when compared to the control group. A delay in time to first brood was not observed at any of the tested concentrations. Reproductive success, as measured by the mean no. of live young per adult per reproduction day, was not significantly reduced in any of the tested concentrations when compared to the control group. Dead offspring were found in low numbers in all groups during the study, although there appeared to be a treatment related increase (maximum 1.3% dead offspring at 49 mg a.s./L). The NOEC for parental survival was identified as 49 mg a.s./L. The NOEC for reproduction was also 49 mg a.s./L. Based on the absence of significant reproductive effects, the LOEC was identified as 139 mg a.s./L.

5.4.3 Algae and aquatic plants

An algae toxicity test with *Selenastrum capricornutum* was performed in accordance with OECD 201 (Dengler D. 1995, Section B.9.2.1.1, DAR, 2005). Actual concentrations were on day 0: 87, 96, 116, 125 and 145% and on day 5: 56, 72, 96, 128 and 143% at nominal concentration 0.5, 1.0, 2.0, 4.0 and 8.0 mg a.s./L, respectively. A 72h-EC50 for growth rate of >12 a.s mg/l (based on measured concentration) was calculated. The NOEC for growth rate was estimated to be 12 a.s mg/l.

Another algae toxicity test with *Scenedesmus subspicatus* was performed in accordance with OECD 201 (Forbis AD and Wirth Blasberg, 1990, section B.9.2.1.1, DAR, 2005). Analytical confirmation of actual test concentrations was only provided for the lowest test concentration of 34.6 mg/L in an exposed vessel without algae. Actual concentrations were 87-89% of the nominal concentration. A

72h-EC50 for growth rate of 56 a.s mg/l (95% confidence interval 29-109 mg/l) was calculated. The NOEC for growth rate was estimated to be 48 a.s mg/l .

An algae toxicity test with diatom *Navicula pellucilosa* was performed in accordance with OECD 201 (Scheerbaum D., 1999, Section B.9.2.1.1, DAR, 2005). Actual concentrations were 96-106% of nominal concentrations. A 72h-EC50 for growth rate of 118 a.s mg/l (95% confidence interval 113-123 mg/l) was calculated. The NOEC for growth rate was estimated to be of 66 a.s mg/l (based on measured concentration).

A toxicity test with *Lemna gibba* was performed in accordance with the USEPA FIFRA 123-2 (Rhodes JE and Hughe, 1991, Section B.9.2.1.1, DAR, 2005). *Lemna gibba* G3 used in this test is maintained in twenty-strength synthetic algal assay procedure nutrient medium (20X-AAP) in Erlenmeyer flasks under continuous illumination of approximately 4198-5813 lumens/m^2, temperature of 25 ± 2^0C and pH of 7.5 ± 0.1. To begin the definitive test, a primary stock solution of 40 mg/mL of clethodim (chemical purity 82.4%) in the solvent DMF (N,N-dimethylformamide) was prepared. Test concentrations were prepared by adding the required volume of the appropriate stock solution to 20X-AAP medium in 1000 mL: volumetric flasks to yield nominal test concentrations of 0.05, 0.10, 0.62, 1.25, 2.5, 5.0 and 10 mg a.s./L, respectively. A solvent control treatment was prepared to contain the same amount of DMF that was added to each test treatment, i.e. 0.25 mL/L. The control contained medium only. After thorough mixing, 200 mL of the control, solvent control, and each test treatment was added to each of three replicate test vessels. The pH of each treatment was measured at the beginning and the end of the test. The inoculum of L. gibba used to begin the test was taken from 7-d old stock cultures. Three plants consist of four fronds each per concentration (for a total of 12 fronds) was aseptically added to each test vessel. Fourteen-day observation period with frond counts on day 3, 5, 7, 10, 12 and 14. The data analysis is based on the measured test concentrations. The mean of the results for the day 0 and day 14 analyses for each test concentration are used. The mean frond count values at test termination for each test concentration were expressed as a percent relative to that in the solvent control. To determine the EC25 and EC50 values and associated 95% confidence limits, weighted least squares nonlinear regression of the log of test concentration against the Day 14 frond counts was performed. The NOEC was determined from an analysis of variance (ANOVA) and Dunnett's test. The level of significance was at 0.05. The measured concentrations yielded from 83% to 104% of the nominal concentrations on day 0 and from 6% to 66% on day 14. Initial and mean measured concentrations were 0.042, 0.099, 0.61, 1.2, 2.3, 5.2 and 10 mg a.s./L and 0.022, 0.053, 0.37, 0.79, 1.7, 4.0 and 8.4 mg a.s./L, respectively. Test concentrations are expressed as measured mean concentrations. Growth was increasingly reduced at initial concentrations of 1.2 mg a.s./L and above. The 14d-EC_{50} based on the mean frond count values was 1.34 mg/L and the 14d- NOEC was 0.37 mg/L. As the OECD guideline 221 prescribes an exposure time of 7 days. The 7d-EC_{50} and 7d-EC_{10} were calculated based on average specific growth rate, resulting in values of 1.27 and 0.37 mg/l, respectively. .

Another toxicity test with *Lemna gibba* was performed in accordance with the USEPA FIFRA 123-2 (Grimstead SR et al, 1991a, Section B.9.2.1.1, DAR, 2005). *Lemna gibba* G3 used in this test is maintained in 20X freshwater algal (*Selenastrum capricornutum*) medium under continuous fluorescent lighting at an intensity of approximately 600- foot-candles, temperature of 25 ± 2^0C. Th pH of water in each treatment and the controls were measured at the beginning and end of the test. The pH values ranged from 7.8 to 8.1 at the beginning of the test and ranged from 9.5 to 9.6 at the end of the test. A stock solution of clethodim (chemical purity 91.1%) dissolved in the solvent acetone was prepared. Test media were prepared by serial dilution to yield nominal test concentrations of 0.08, 0.16, 0.31, 0.63, 1.3, 2.5, 5.0 and 10 mg a.s./L. The data analysis is based on the measured test concentrations. The concentration of acetone in the solvent control and treatment

groups was ≤ 0.08 mL/L. At least three plants, each consisting of 3-7 fronds, were added to each test glass beakers. At the beginning of test, the total number of fronds in each replicate ranged from 14 to 17. Three replicates per treatment were tested under static conditions. The results were calculated based on direct counts of the number of fronds taken on Days 0, 3, 6, 9, 13 and 14. The number of fronds produced by the end of the test and the weight data were evaluated statistically using Dunnett's test, since the data appeared to be normally distributed and the variances appeared to be homogeneous. Initial and mean measured concentrations were 0.05, 0.11, 0.26, 0.48, 1.2, 2.1, 4.1 and 4.9 mg a.s./L and 0.04, 0.09, 0.21, 0.39, 1.0, 1.8, 3.7 and 4.8 mg a.s./L, respectively. An IC50 value could not be calculated from the results of this test because the production of fronds at the highest test concentration tested, 4.88 mg a.i./L, was not inhibited by 50% or more. By the end of the test, the number of fronds in the negative and solvent control replicates ranged from 207 to 300, while the number of fronds in replicates of the 4.88 mg a.i./L treatment ranged from 236 to 283. The test substance induced no significant reduction in the number and the total weight of fronds. The IC50 for clethodim was > 4.88 mg a.i/L based on the number and the total weight of fronds. Necrotic fronds were observed at initial concentrations of 4.1 and 4.9 mg a.s./L. The NOEC based on necrotic fronds was 2.1 mg a.s./L (initial measured) or 1.8 mg a.s./L (mean).

Both Lemna studies are considered valid. No explanation can be given for the difference in toxicity of these two studies. According to the guidance on the application of the CLP criteria the most sensitive (the one with the lowest L(E)C_{50} or NOEC/EC_{10}) is generally used for classification, where less than four acceptable tests are available for the same taxonomic group. Therefore the EC10 value of 0.37 mg/l will be used for the classification of clethodim.

5.4.4 Other aquatic organisms (including sediment)

No data available.

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

Acute aquatic hazard

Acute aquatic toxicity data are available for all three trophic levels. The lowest L(E)C50 value obtained in acute aquatic toxicity studies is 25 mg/L in the fish, *rainbow trout*. This value is above the classification threshold value of 1 mg/L. Clethodim does therefore not fulfil the criteria for classification as acute hazard to the aquatic environment.

Chronic aquatic hazard

Clethodim is considered rapidly degradable in the environment and does not fulfill the criterion BCF > 500. Chronic aquatic toxicity information is available for all three trophic levels. The long term toxicity NOEC/ EC10 values for fish, Daphnia, and algae are 3.9, 49, and 12 mg/l, respectively, which do not trigger the classification. However, the EC10 value for aquatic plant Lemna gibba is 0.37 mg/L, which triggers the classification. Therefore, clethodim does fulfill the criteria for classification as chronic category 3 hazard for the environment.

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

Clethodim needs to be classified as Aquatic Chronic 3, H412 for the environment according to CLP regulation.

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier submitter's proposal

Clethodim is a selective herbicide which does not have an existing harmonised classification in Annex VI to the CLP Regulation. The Dossier Submitter proposed Aquatic Chronic 3 (H412) based on rapid degradation and a chronic NOEC of 0.37 mg/L for aquatic macrophytes.

Comments received during public consultation

Three statements of support for the proposal were received, and no further information was submitted.

Assessment and comparison with the classification criteria

Degradability:

A valid hydrolysis study is unavailable. Clethodim was readily biodegradable in a closed bottle test (OECD TG 301 D), achieving 100% biodegradation after 14 days. Simulation testing in an aerobic pond water-sediment system using radio-labeled substance indicated a whole system DT_{50} of 23 days; after 103 days, mineralisation to carbon dioxide and formation of unextractable sediment residues accounted for 14.2% and 22.0% of applied radioactivity, respectively. On this basis, clethodim meets the criteria for being rapidly degradable (readily biodegradable) in the environment.

Bioaccumulation:

The log n-octanol-water partition coefficient (K_{ow}) of clethodim is 4.2, but a steady-state bioconcentration factor (BCF) of 2.1 L/kg wet weight was measured for Bluegill Sunfish (*Lepomis macrochirus*) based on radioactivity measurements. Lipid content was not determined so the BCF could not be normalised to a standard lipid content of 5%. However, as the BCF is much lower than 500 L/kg this does not affect the conclusion that clethodim does not meet the bioaccumulation criteria.

Ecotoxicity:

The lowest reliable ecotoxicity results were as follows (the key studies are highlighted in bold):

Trophic level	Species	Short-term result	Long-term result
Fish	Rainbow Trout *Oncorhynchus mykiss*	96-h LC_{50} = 25 mg/L	-
		21-d NOEC = 3.9 mg/L*	
Aquatic invertebrates	*Daphnia magna*	48-h EC_{50} >100 mg/L	21-d NOEC = 49 mg/L
Aquatic algae and plants	*Raphidocelis subcapitata*†	72-h E_rC_{50} > 12 mg/L	72-h NOEC = 12 mg/L
	Lemna gibba	**7-d E_rC_{50} = 1.27 mg/L**	**7-d E_rC_{10}= 0.37 mg/L**

* The dossier presents this value as a long-term result, but it is actually a prolonged acute result (OECD TG 204). Endpoints were mortality, growth and symptoms.

† *Selenastrum capricornutum* in the dossier.

All toxicity values are based on mean measured concentrations. The substance has a pKa of 4.47, indicating that it will be mostly ionised (unprotonated) at environmentally relevant pH.

Classification according to CLP

Acute aquatic hazard:

Acute toxicity data were available for all three trophic levels. The lowest reliable short-term aquatic toxicity result is above 1 mg/L so **no acute classification is necessary**.

Long-term aquatic hazard:

Clethodim is rapidly degradable. Although the CLH report indicated that long-term toxicity data were available for all three trophic levels, no information was actually available for fish. Aquatic macrophytes were the most sensitive group with a lowest reported 7-d E_rC_{10} of 0.37 mg/L for *Lemna gibba*. This is below the threshold value of 1 mg/L for rapidly degradable substances, leading to classification as Aquatic Chronic 3 (H412).

The surrogate approach can also be considered for fish in the absence of a chronic toxicity result. Based on the lowest acute 96-h LC_{50} of 25 mg/L, a low BCF and rapid degradability, no chronic classification would be indicated.

In summary, the proposed classification of clethodim as **Aquatic Chronic 3 (H412)** is justified.

6 OTHER INFORMATION

7 REFERENCES

European Commission. Draft Assessment Report Clethodim, prepared by The Netherlands, September 2005.

European Commission. Draft Assessment Additional Report Clethodim, prepared by The Netherlands, Addendum to Draft Assessment Report, April 2009.

European Commission. Draft Assessment Additional Report Clethodim, prepared by The Netherlands, Addendum to Draft Assessment Report, March 2010.

8 ANNEXES