CLH Report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Aclonifen**

EC Number: **277-704-1**

CAS Number: **74070-46-5**

Submitted by: **Germany**

Version: **November 2010**

CONTENTS

TABLES

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: Aclonifen

EC Number: 277-704-1

CAS number: 74070-46-5

Registration number (s): -

Purity: minimum 970 g/kg

Impurities: There are a number of impurities claimed as confidential by the producer

Proposed classification based on Directive 67/548/EEC criteria:

Health hazards: Xn; R40, Xi; R43

Environment: N; R50-53

Proposed classification based on GHS criteria:

Health hazards:

Carc. 2	H351
Skin Sens. 1	H317

Environment:

Aquatic acute 1	H400
Aquatic chronic 1	H410

Proposed labelling:

Directive 67/548/EEC:

Symbol: Xi, Xn, N

Risk phrases: R40-43-50/53

Safety phrases: S60-61

Regulation EC1272/2008 (GHS criteria):

Pictogram: GHS07, GHS08, GHS09

Signal word: Warning

Hazard statement codes: H317, H351, H410

Proposed specific concentration limits (if any):

Environment

Specific concentration limits based on Directive 67/548/EEC:

Concentration	Classification
C≥0.25%	N; R50-53
0.025%≤C<0.25%	N; R51-53
0.0025%≤C<0.025%	R52-53

Where C is the concentration of aclonifen in the preparation.

M-factor based on Regulation EC 1272/2008

The M-factor is determined by using the reported ErC50 value of 0.0067 mg/L obtained for the algae *Desmodesmus subspicatus* in a 96 hr static study. Consequently, an M-factor of 100 is assigned.

Proposed notes (if any):

none

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name: Benzenamine, 2-chloro-6-nitro-3-phenoxy-

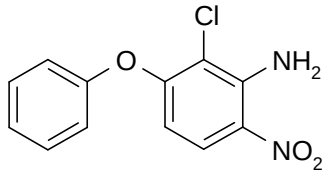
EC Name: -

CAS Number: 74070-46-5

IUPAC Name: 2-chloro-6-nitro-3-phenoxyaniline

1.2 Composition of the substance

There are a number of impurities stated as confidential by the producer.

Chemical Name:	Benzenamine, 2-chloro-6-nitro-3-phenoxy-
EC Number:	277-704-1
CAS Number:	74070-46-5
IUPAC Name:	2-chloro-6-nitro-3-phenoxyaniline
Molecular Formula:	$C_{12}H_9ClN_2O_3$
Structural Formula:	
Molecular Weight:	264.7 g/mol
Typical concentration (% w/w):	confidential information
Concentration range (% w/w):	> 970 g/kg

1.3 Physico-chemical properties

Table 1.3-1: Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 KPa	3.1	yellow powder (purity 99.4 %)	Draft Assessment Report Monograph EFSA conclusions
VII, 7.2	Melting/freezing point	3.2	81.2 °C (purity 99.6 %)	
VII, 7.3	Boiling point	3.3	not detectable	
VII, 7.4	Relative density	3.4 density	1.50 at 20 °C (purity 99.6 %)	
VII, 7.5	Vapour pressure	3.6	1.6×10^{-5} Pa at 20 °C (99.3 % purity)	
VII, 7.6	Surface tension	3.10	72.0 mN/m at 20 °C (99.4 % purity)	
VII, 7.7	Water solubility	3.8	1.4 mg/L at 20 °C pH 5, 7 and 9 (99.7 % purity)	
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	4.37	
VII, 7.9	Flash point	3.11	not relevant	
VII, 7.10	Flammability	3.13	not highly flammable (99.4 % purity)	
VII, 7.11	Explosive properties	3.14	not explosive (99.4 % purity)	
VII, 7.12	Self-ignition temperature		not detected	
VII, 7.13	Oxidising properties	3.15	no oxidising properties (99.4 % purity)	
VII, 7.14	Granulometry	3.5	not relevant	
XI, 7.15	Stability in organic solvents and identity of relevant degradation products	3.17	not detected	
XI, 7.16	Dissociation constant	3.21	not measurable, by calculation constant is -3.15	
XI, 7.17,	Viscosity	3.22	not detected	
	Auto flammability	3.12	No self ignition between room temperature and melting point (99.4 % purity)	
	Reactivity towards container material	3.18	not detected	
	Thermal stability	3.19	decomposition starts at 297 °C (99.6 % purity)	

2 MANUFACTURE AND USES

2.1 Manufacture

confidential information

2.2 Identified uses

Herbicide for pre-emergence control of annual grass and broad-leaved weed species in several dicotyledonous crops.

2.3 Uses advised against

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

According to table 3.1 of Annex VI (index no 612-120-00-6), aclonifen is classified as

Hazard class:

Aquatic Acute 1

Aquatic Chronic 1

Hazard Statement:

H400

H410

According to table 3.2 of Annex VI (index no 612-120-00-6), aclonifen is classified as

Classification:

N; R50-53

Risk phrases: R50/53

Safety phrases: S60-61

3.2 Self classification(s)

Not relevant for this dossier.

4 ENVIRONMENTAL FATE PROPERTIES

The environmental fate properties assessment for aclonifen is based on the Draft Assessment Report and Proposed Decision of Germany prepared in the context of the possible inclusion of aclonifen in Annex I of Council Directive 91/414/EEC (DAR August 2006 + Final addendum June 2008, RMS Germany).

4.1 Degradation

4.1.1 Stability

Hydrolysis

- Godward, P.J. et al., 1991, Document No.: R007157

Under sterile aqueous conditions, at temperatures of 22 °C, 50 °C and 70 °C, aclonifen was found to be hydrolytically stable at pH 5, 7 and 9. The study was performed according to OECD 111 (1981) and BBA 55 (1980) with [^{14}C]-labelled aclonifen dissolved in sterile buffers at a nominal concentration of approximately 1 mg/L (actual concentrations pH 5, 0.91 mg/L; pH 7, 0.88 mg/L; pH 9, 0.76 mg/L).

Photolysis in water

- Oddy, A. et al., 2003, Document No.: C031518

Photolysis in buffered solution at pH 7 takes place to a certain, but not high extent. The half-life for the decline of aclonifen in the irradiated experiment was calculated to be equivalent to 197 days natural summer sunlight (European Union at latitude 50°N) according to first order kinetics.

- Offizorz, P., 1993, Document No.: R007202

The quantum yield of direct photolysis of aclonifen in aqueous solution was determined to be 5.19×10^{-6}.

Based on this quantum yield ABIWAS 2.0 calculations for middle Europe (55 ° North) result in DT_{50} values of 9 days (May, Minimum) to 1040 days (December, Maximum).

Photolysis in soil

- van Dijk, A. and Burri, R., 1994, Document No.: R007084

The photolytic degradation of [U-14C-aniline]-labelled aclonifen was studied following application to a loamy sand soil under artificial sunlight for a period of 30 days. The artificial sunlight was provided by a xenon arc lamp with filters to cut off any radiation below 290 nm. The samples were incubated at 22 ºC under a 12 hour light/12 hour dark cycle (irradiated samples) or in the dark (non-irradiated samples).

The presence of light slightly enhanced the degradation rate of aclonifen on soil surfaces. The DT_{50} value for aclonifen assuming first order kinetics under irradiated conditions was 75.3 days. No degradation of aclonifen was observed in samples incubated in the dark.

Photo-oxidative degradation in air

- Maurer, T., 2000, Document No.: C010366

Based on AOP version 1.88 the half-life of aclonifen in the atmosphere was calculated as being in the range of 0.84 to 1.26 days dependent upon the mean aerial OH concentration chosen for the calculation, 0.5 x 10^6 cm^{-3} averaged over a 24 hours or 1.5 x 10^6 cm^{-3} averaged over 12 hours, respectively. It can be concluded that aclonifen will be readily degraded in the air due to its fast reaction with photolytically generated hydroxyl radicals.

Recalculation using AOP version 1.91 yields the same results.

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

No data available.

4.1.2.2 Screening tests

Readily biodegradability

- Voigt, H., 1990, Document No.: R003640

The ready biodegradability of aclonifen was determined according to the Sturm test (OECD guideline 301B). Aclonifen of purity 91.3 % was incubated in the test medium, inoculated with activated sludge (from municipal purification plant at Hildesheim), at concentrations of 5 and 10 mg/L. The released carbon dioxide was monitored for a period of 28 days and quantified by precipitation as $BaCO_3$ followed by back titration of $Ba(OH)_2$ with 0.05 M HCl. A parallel experiment was performed using sodium acetate to validate the test results.

The results, expressed as a percentage of the maximum theoretical CO2 production, for both aclonifen and the reference substance (sodium acetate) are shown in Table 4.1-1. Aclonifen was found to be not readily biodegradable within 28 days.

Table 4.1-1: Ready biodegradability expressed as percentage of maximum theoretical CO_2 production

Time (days)	Aclonifen (5 mg/L)	Aclonifen (10 mg/L)	Sodium acetate (20 mg/L)
7	9 %	4 %	70 %
16	15 %	0 %	70 %
28	22 %	0 %	74 %

4.1.2.3 Simulation tests

Biodegradation in water/sediment systems

- Lowden, P. et al., 2000, Document No.: C009991

The behaviour of [^{14}C]-labelled aclonifen, uniformly labelled in the aniline ring, was investigated in two contrasting water/sediment systems, characterised as a sandy silt loam (Manningtree system) and a clay loam (Ongar system), over a period of 180 days according to the guidelines EU (= EEC) 95/36/EC, Section 7.2.1.3.2, (1995) and SETAC 1.1 (1995).

The results of the aerobic incubation are summarised in Table 4.1-2.

Table 4.1-2: Degradation of aclonifen in aerobic water/sediment system

Substance	Water / sediment system	T (^{o}C)	pH water	pH sed.	oc[1)] (%)	DT_{50} water (d)	DT_{50} sed. (d)	DT_{50} whole system (d)
[^{14}C]-labelled aclonifen	I Manning-tree	20	6.7	6.8	5.7	3.2	92	11.2
	II Ongar	20	7.5	8.4	3.8	5.6	No decline	17.3

[1)] organic carbon content of sediment

Aclonifen was metabolised in both sediment water systems at a moderate rate with DT_{50} values of 11.2 days and 17.3 days. Aclonifen steadily partitioned to the sediment and degraded. None of the metabolites observed reached 5 % AR in any of the phases. Mineralization was negligible in both systems (max CO_2 = 2.07 % AR) and unextractable residue in the sediment amounted up to 65.6 - 76.5 % AR at the end of the experiments (180 d).

Biodegradation in soil

The rate of degradation of aclonifen was investigated in three laboratory the studies in a total of nine soils according to guideline BBA IV, 4-1; BBA Merkblatt 36, EU (= EEC) 95/36/EC, Section 7.1.1.2, (1995) and SETAC 1.1, (1995). Degradation under dark aerobic conditions at 10 °C was also investigated in a study with two soils. The experiments are summarised in Table 4.1-3.

Table 4.1-3: Degradation of aclonifen in aerobic laboratory studies

Soil type/site	oc[1)] (%)	pH	T ^{o}C / % MWHC	DT_{50} /DT_{90} (d)	DT_{50} (d) 20 °C pF2/10kPa	Reference
Aldhams House (94/8/2) silty sand	1.1	6.7	20 °C / 60 % FC	134 / 443	93.6	Schanné, C. (1994), Document No.: R007085
Shelley Field (94/9/2) silty loam	1.9	7.0	20 °C / 60 % FC	73 / 242	51.0	
Westleton (94/10/2) silty loam	1.5	6.8	20 °C / 60 % FC	95 / 315	66.4	
Westleton (94/10/2) silty sand	1.5	6.8	20 °C / 30 % FC	>> 118 d		

sandy loam Arable	1.48[2)]	7.3	22 °C / 40 % MWHC	32/ 107	29.5	Schlueter, H., 1983, Document No.: R003641
sandy loam Standard soil 2.3	0.92[2)]	6.6	22 °C / 40 % MWHC	78/ 259	72.6	
loamy sand (Speyer 2.2 A)	2.64	6.0	22 °C / 40 % MWHC	93/309	83.7	Anonymous, 1982, Document No: R003643
loamy sand (Speyer 2.2 B)	2.64	6.0	22 °C / 40 % MWHC	76/ 254	68.7	
sandy loam (Speyer 2.3)	1.06	7.0	22 °C / 40 % MWHC	53/ 177	41.9	
loamy sand Westleton	6.8	6.8	10 °C / 50 % MWHC	222/ 740	86.5	England et al., 1988, Document No.: R007107
clay loam Stockland	7.2	7.2	10 °C / 50 % MWHC	218/ 723	61.8	

[1)] organic carbon, [2)] om (organic matter) value

In aerobic laboratory soil degradation studies the overall geometric mean DT_{50} value of aclonifen at 20 °C and pF2 is 62.3 days (SFO, range 41.9 – 93.6 days; n = 10).

Practically the totality of the extracted radioactivity consisted in parent compound with only very minor metabolites detected. Mineralisation was negligible or very low (CO_2: 0.7 – 5.2 % AR). Unextracted soil residue increase continuously up to 40.9 – 57.6 % AR at the end of the studies.

Two field dissipation studies are available in North Europe (1 study in Germany, 4 sites) and Southern Europe (1 study in Spain and France, 1 site each). First order half lives between 57 d – 195 d were observed in these trials. The results are summarised in Table 4.1-4.

Table 4.1-4: Results of field dissipation studies of aclonifen

Soil type	**Location**	**pH**	**Depth (cm)**	**DT_{50} (d) actual, SFO**	**DT_{90}(d) actual**	**Reference**
silty loam	Goch-Nierswalde, Germany	5.9	0 – 10	61	202	Hoenzelaers, R. and Schulz, J., 1994, Document No.: R007356 and Stratmann, A., 1994, Document No.: R007355
silty loam	Meißner-Vockerode, Germany	6.4	0 – 10	119	395	
sandy loam	Schwichteler, Germany	6.3	0 – 30	195	649	
sandy loam	Niederkirchen, Germany	7.3	0 – 30	13 / 57[1]	182	
clay loam (cropped with sunflower)	Almacelles, Spain	7.8	0 – 30	51/ 108[1]	357	Duncan, P. et al., 2003, Document No.: C032811

sandy silt loam (cropped with sunflower)	Cruas, France (Southern EU)	8.2	0 – 30	31	104	

[1] recalculated SFO DT_{50} (DT_{50} (FOMC) = DT_{90}/3.32)

4.1.3 Summary and discussion of persistence

Biodegradation in water

Aclonifen was found to be not readily biodegradable in the available study.

In water/sediment systems aclonifen was metabolised at a moderate rate with DT_{50} values of 11.2 days and 17.3 days.

Biodegradation in soil

In aerobic laboratory soil degradation studies the overall geometric mean DT_{50} value of aclonifen is 62.3 days (SFO, 20 °C, pF2). In field dissipation studies DT_{50} values of aclonifen between 57 d – 195 days (SFO) were observed.

Based on the findings from the screening test on ready biodegradability, water/sediment simulation test and soil aclonifen appears to be susceptible for primary degradation and not ultimate mineralisation. Considering the results of the test on ready biodegradability and levels of mineralisation in the simulation study, aclonifen is considered not readily biodegradable (a degradation of >70% degradation within 28 days) for purposes of classification and labeling.

4.2 Environmental distribution

Not relevant for this dossier.

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

Aclonifen has a log Kow of 4.37 (pH 5-6, distilled water).

4.3.1.2 Measured bioaccumulation data

In a first study [^{14}C]-aclonifen accumulated in rainbow trout with a total radioactive residue (TRR) bioconcentration factor (BCF) of 2896 L/kg ww for whole fish. Maximum BCF was reached after 16 days and then declined throughout the remaining exposure period. Based on the fitted uptake and depuration rate constants, the kinetic BCF is 2248 L/kg ww. When exposure ceased, the residues depurated with a half-life of 2.0 days. At the end of the 20 day depuration period, residues declined to a level of 1.0 % in total fish tissues, relative to those residues at the end of the uptake phase. The bioconcentration factors determined from this 28 day exposure study (considered as key study)

were higher than those reported from a previous second study in which rainbow trout had been exposed continuously to [^{14}C]-aclonifen for 8 days (Maximum BCF: 1645 – 1742 L/kg ww). This lower BCF's were likely to be due to the shorter exposure duration and so the steady state was not reached. These results are only considered as additional information.

The studies are summarised in Table 4.3-1.

Table 4.3-1: Results of aquatic bioconcentration measurements

guideline/ test method	exposure	log Kow	Initial conc. [µg/L]	Steady state BCF [L/kg ww]	Kinetic BCF	Depuration time CT50(d)	Depuration time CT95(d)	Remarks	reference
OECD 305 & 305E	28 d, flow - trough	4.37	26.9 (real) 30(nom)	2896	2248	2.0	8.8	Whole fish based on TRR	Wyness, L.E. (1995), Document No.: R007430
OECD 305 & 305E	8 d, flow - trough	4.37	4.24 (real) 6 (nom) 37.7 (real) 60(nom)	1742[1)] 1645[1)]	1275 1326	0.77 0.89	3.32 3.85	Whole fish based on TRR [2)]	Wyness, L.E. (1995), Document No.: C034500

[1)] BCFmax, because steady state was not reached since only 8 days exposure was applied

[2)] Majority of the total radioactive residues (TRR) in water and fish are chromatographic analysed as parent substance (aclonifen)

4.3.2 Terrestrial bioaccumulation

No data available.

4.3.3 Summary and discussion of bioaccumulation

Aclonifen has a log Kow of 4.37. The experimentally derived steady state BCF of 2896 and kinetic BCF of 2248 are above the trigger of 100 (criterion for bioaccumulating potential conform Directive 67/548/EEC) and also above the trigger of 500 (criterion for bioaccumulating potential conform Regulation EC 1272/2008) for not rapidly biodegradable substances. Based on the results of the bioconcentration study, aclonifen does significantly bioaccumulate.

4.4 Secondary poisoning

Not relevant for this dossier.

5 HUMAN HEALTH HAZARD ASSESSMENT

Aclonifen has been reviewed under Council Directive 91/414/EEC. For more detail on the studies described or mentioned below reference is made to the Draft Assessment Report, the final addendum to the DAR, and the EFSA conclusions.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Aclonifen is rapidly absorbed when applied orally to rats (approximately 80 % within 24 hours based on urinary and biliary excretion) and widely distributed. High dose levels (1000 mg/kg bw) seem to saturate and delay the absorption process and reduce the bioavailability to slightly more than 40 % based on renal excretion data. Kinetic data for whole blood indicate a terminal phase half-life of approximately 103 hours for both sexes. Plasma half-lives are shorter, 13 and 24 hours for males and females, respectively. Residues are found mainly in liver, kidneys, lung, thyroid and skin/fur. There is no evidence for accumulation. Bile excretion studies indicate a significant enterohepatic circulation of aclonifen-related material. Excretion is nearly complete within 48 hours. Renal excretion ranged from 38 % - 50 % in males and from 39 % - 65 % in females in the different studies available. Most of the remaining material is eliminated via the faeces. Aclonifen is extensively metabolised; more than 20 metabolites or intermediates have been identified. The main pathways are hydroxylation of the phenyl ring, cleavage of the ether bond, reduction of the nitro group and subsequent acetylation, methylation and phase II type conjugations with sulphate or glucuronic acid (Crosnier, A., Guittard, J., 2002, report no. A01255; Crosnier, A., Guittard, J., 2002, report no. A01256; Odin-Feurtet, M., 2002, report no. SA01338; Odin-Feurtet, M., 2002, report no. SA01123; Schlueter, H., 1983, report no. 127AA-651-02).

Dermal application in vivo (8 h exposure) indicated dermal absorption of up to 6 % for a concentrated (6 mg/cm^2) and 38 % for a diluted (0.015 mg/cm^2) preparation in male rats (Fitzpatrick, K., 2003, report no. BAG/355/032306). In vitro, rat and human skin (including stratum corneum) showed 4 % and 2 % dermal absorption with the concentrate, and 64 % and 15 % respectively, with the diluted formulation. (Cage, S., 2003, report no. BAG 362/032351) It is estimated that a dermal absorption of 2 % (concentrate) and 10 % (dilution) would be representative of the in vivo situation in humans.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Aclonifen was of very low acute oral toxicity in rodents. No deaths occurred in rats or mice. In rats, clinical signs consisted of reduced spontaneous activity and ataxia, which completely disappeared 24 hours after treatment. Yellow staining of the urine, indicative of ongoing excretion of the coloured test substance, persisted for 6 days. In mice, clinical signs occurred within 2 hours of dosing and consisted of reduced spontaneous activity, ataxia and piloerection. All clinical signs has disappeared on the fourth day after administration. Yellow staining of the urine was noted in the first hours after treatment and had disappeared 48 hours later.

Table 5.2-1: Summary of acute oral toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Remarks	Reference
OECD 401	Oral	Rat, Wistar-AF/HAN-EMD 5M+5F	5000	LD_{50} > 5000	Vehicle: aqueous 0.5% carboxy-methyl-cellulose	Heusener, A. and Weiße, G. (1981); report no 4/105/81
OECD 401	Oral	Mouse, NMRI-EMD 5M+5F	5000	LD_{50} > 5000	Vehicle: aqueous 0.5% carboxy-methyl-cellulose	Heusener, A. and Weiße, G. (1981); report no 4/105/81

5.2.2 Acute toxicity: inhalation

Aclonifen was of very low acute inhalation toxicity in rats. No deaths occurred. During the exposure period, wet fur and a decreased respiratory rate were noted. On removal from the exposure chamber additional signs of hunched posture, piloerection and yellow staining around the head and shoulders were seen in all animals. These signs were still evident one hour after exposure, with the addition of red/brown staining of the snout in three rats, but all signs had regressed by the following day in all but one animal which appeared normal on day three.

Table 5.2-2: Summary of acute inhalation toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/L)	Value LC_{50} (mg/L)	Remarks	Reference
OECD 403	Inhalative	Rat, Sprague-Dawley 5M+5F	5.06	LC_{50} > 5.06	Dust, 4-h, nose only	Blagden, S.M. (1990); report no 282/56

5.2.3 Acute toxicity: dermal

Aclonifen was of very low acute dermal toxicity in rats. No deaths occurred. The only signs following treatment were yellow urine, indicating dermal absorption, and yellow skin which persisted up to days 7 and 14, respectively.

Table 5.2-3: Summary of acute dermal toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Remarks	Reference
OECD 402	Dermal	Rat, Wistar-AF/HAN-EMD 5M+5F	5000 (nominal)	LD_{50} >5000	Vehicle: aqueous 0.5% carboxy-methyl-cellulose Solubility in water 1.4 mg/L	Heusener, A. and Weiße, G. (1981); report no 4/105/81

5.2.4 Acute toxicity: other routes

Mortalities occurred up to 3 days after i.p. administration at doses of 3200 mg/kg bw and higher, affecting all animals at 5000 mg/kg bw, two males and four females at 4000 mg/kg bw, and two males and three five females at 3200 mg/kg bw. Clinical signs appeared 5-15 minutes after injection in all treated groups and consisted of reduced activity, ataxia, dyspnea and piloerection. Yellow staining of the urine was noted immediately after dosing and persisted up to day 6. Body weight was decreased up to day 3 after treatment. Gross necropsy of decedent animals showed deposition of the test material in the abdominal cavity, mucosal haemorrhages and erosions in the stomach as well as lung oedema in some animals. Gross necropsy of animals sacrificed after 15 days showed small depositions of the test material on the liver, adhesion of individual lobes of the liver as well as focal spleen capsular fibrosis.

Table 5.2-4: Summary of acute intraperitoneal toxicity

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Remarks	Reference
OECD 402	Intra-peritoneal	Rat, Wistar-AF/HAN-EMD 5M+5F	0-2500-3200-4000-5000	LD_{50} (M): 3742 LD_{50} (F): 3247	Vehicle: aqueous 0.5% carboxy-methyl cellulose	Heusener, A. and Weiße, G. (1981); report no 4/105/81

5.2.5 Summary and discussion of acute toxicity

Aclonifen is of very low acute toxicity by the oral (LD50 > 5000 mg/kg bw), dermal (LD50 > 5000 mg/kg bw) and inhalation route (LC50 > 5.06 mg/L) in the rat and also by the oral route in the mouse (LD50 > 5000 mg/kg bw). No classification is required.

5.3 Irritation

5.3.1 Skin

Aclonifen was very slightly and transiently irritating to rabbit skin when applied as moistened powder at a dose of 32 mg/cm^2.

Table 5.3-1: Summary of skin irritation

Method/ Guideline	Species, Strain, Sex, No/group	Average score 24, 48, 72 h		Reversibility yes/no	Results	Remarks	Reference
		Erythema	Oedema				
OECD 404	Rabbits, NZW 3M + 3F	0-0.3-0.5	0-0-0	yes	Not irritating	None	Heusener, A. and Weiße, G. (1981); report no 4/105/81

5.3.2 Eye

Aclonifen (100 mg/eye) was not irritating to the eyes of rabbits.

Table 5.3-2: Summary of eye irritation

Method/ Guideline	Species, Strain, Sex, No/group	Average Score 24, 48, 72 h				Reversi-bility yes/no	Results	Remarks	Reference
		Cornea	Iris	Redness Conjunc-tiva	Chemo-sis				
OECD 405	Rabbits, NZW 3M + 3F	0-0-0	0-0-0	0-0-0	0-0-0	Not applicable	Not irritating	None	Heusener, A. and Weiße, G. (1981); report no 4/105/81

5.3.3 Respiratory tract

No data are available. A slight potential for respiratory irritation may be deduced from the slight and transient findings in skin and from the reduced respiration rate in the acute inhalation toxicity study.

5.3.4 Summary and discussion of irritation

Very slight dermal and no ocular irritation was noted after application of aclonifen to the skin and eye of rabbits. Therefore no classification for irritation is required.

5.4 Corrosivity

In skin and eye irritation studies there was no evidence for a corrosive action of aclonifen.

5.5 Sensitisation

5.5.1 Skin

While in a Buehler test negative results were obtained, aclonifen caused delayed contact hypersensitivity in guinea pigs in a Magnusson & Kligman skin sensitisation test.

Table 5.5-1: Summary of skin sensitisation

Method/ Guideline	Species, Strain, Sex, No/group	Number of animals sensitised/Total number of animals	Results	Remarks	Reference
OECD 406 Buehler, 9-induction	Guinea pigs, Dunkin-Hartley 20F (treated) 10F (control)	0/20 (75 % aclonifen) 0/10 (control)	Not sensitising	Vehicle: topical induction and challenge: arachis oil	Tuffnell, P.P. (1990); report no. 282/55

Method/ Guideline	Species, Strain, Sex, No/group	Number of animals sensitised/Total number of animals	Results	Remarks	Reference
OECD 406 GPMT	Guinea pigs, Hartley Crl (HA) BR 10M + 10F (treated) 5M + 5F (control)	19/20 (1% aclonifen) erythema 24 h: discrete 11/20; moderate 8/20 erythema 48 h: discrete 9/20; moderate 10/20 oedema 48 h: 1/20 0/10 (control)	Sensitising	Vehicle: intradermal induction: 0.9 % aqueous NaCL/Freund' s Complete Adjuvant (FCA 1:1; topical induction and challenge: ethanol/water mixture (80:20 w/w)	Griffon, B. (2002); report no. 22624TSG

5.5.2 Respiratory system

No data are available. A potential for respiratory sensitisation could be deduced from the findings in the sensitisation test.

5.5.3 Summary and discussion of sensitisation

While in a Buehler test negative results were obtained, aclonifen caused delayed contact hypersensitivity in guinea pigs in a Magnusson & Kligman skin sensitisation test. With the exception of one animal all induced guinea pigs (95 %) showed a skin reaction after challenge. Based on these data a classification as **R43 "Irritant; May cause sensitisation by skin contact"** is required.

Classification and Labelling for acute toxicity according to Directive 67/548/EEC:

R43 (Irritant; May cause sensitisation by skin contact)

Classification and Labelling for acute toxicity according to GHS:

Skin Sens. 1; H317 (May cause an allergic skin reaction)

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

In three 90-day dietary rat studies generally similar effects have been reported, including decreased body weight gain, changes in blood chemistry indicative of liver damage, increased liver and kidney weights, liver and kidney pathology, haematuria, and changes indicative of thyroid hormone depletion. Changes were consistently more severe in males than in females. The lowest NOAEL obtained in these investigations for the rat was 3.6 mg/kg bw/d based on findings of follicular cell hypertrophy in the thyroid, histopathology and increased organ weights of the liver and the kidneys at higher doses.

Liver and kidney were also identified as target organs in the mouse. In addition, a reduction in the number of corpora lutea was seen in the ovary, but only at a dose greater than 12 g/kg bw. The

NOAEL in the mouse 28-day study was 780 ppm, equivalent to 121.2 mg/kg bw/day and 143.1 mg/kg bw/day in males and females, respectively.

In dogs the main findings after a 26-week dietary exposure were a decrease in body weight and increases in lymphoid cells, alkaline phosphatase, cholesterol and liver weight in the high dose. There were no treatment-related histopathology findings. The NOEL was 500 ppm (approximately 15 mg/kg bw/day).

Table 5.6-1: Summary of oral repeat dose toxicity

Method/ Guideline	**Route of exposure, Duration**	**Species, Strain, Sex, No/group**	**Dose levels ppm (mg/kg bw /d)**	**NO(A)EL ppm (mg/kg bw /d)**	**LO(A)EL ppm (mg/kg bw /d)**	**Results, Main effects/ Target organs**	**Remarks**	**Reference**
OECD 408	Oral/diet, 90 days	Rat, Wistar Chbb:THOM; 12M+12F	0-50-500-5000 (M: 0-2.6-26.4-258; F: 0-2.9-29.4-279)	500 (M: 26.4; F: 29.4)	5000 (M: 258; F: 279)	Bw gain↓; water consumption ↑; ALT, AP, bilirubin ↑; liver: weight ↑; kidney: weight ↑, nephropathy, haematuria, hydronephrosis , pyelonephritis	Recovery group: 12 M+12F, 5000 ppm over 8 weeks Kidney toxicity was not reversible in males	Paul, W. (1982); report no 127AB-433-03
OECD 408	Oral/diet 90 days	Rat, SD, 10M+10F	0-50-500-5000 (M: 0-3.6-34.4-341; F: 0-4.2-40.8-390)	50 (M: 3.6; F: 4.2)	500 (M: 35.4; F: 40.8)	RBC ↓; liver: hepatocellular hypertrophy; thyroid: follicular cell hypertrophy	None	Dange , M. (1997); report no. SA 96097
OECD 408	Oral/diet 90 days	Rat, Wistar RJ:WI(IOPS AF) 10M+10F	0-50-500-5000 (M: 0-2.9-29.4-295; F: 0-3.7-36.3-323)	500 (M: 29.4; F: 36.3)	5000 (M: 295, F: 323)	Bw gain ↓; cholesterol ↑ (M), ↓ (F), urea↑ (M), creatinine↑ (M); liver: weight↑ (M), hepatocellular hypertrophy; kidney: weight↑, urinary volume↑ (M), haematuria (M); nephrosis, nephritis, necrosis of papilla (M); thyroid: follicular cell hypertrophy (M), T4 ↓, TSH ↑		Wason, S. (2001); report no. SA00458

Method/ Guideline	Route of exposure, Duration	Species, Strain, Sex, No/group	Dose levels ppm (mg/kg bw /d)	NO(A)EL ppm (mg/kg bw /d)	LO(A)EL ppm (mg/kg bw /d)	Results, Main effects/ Target organs	Remarks	Reference
OECD 407	Oral/diet 28 days	Mouse, Crl:CD-1 12M+12F	0-780-3125-12500-50000 (M: 0-121-481-2003-8906 ; F: 0-143-555-2335-12403)	780 (M: 121 F: 143)	3125 (M: 481; F: 555)	Liver: hepatocyte hypertrophy; kidney: basophilic cortical tubules, at high dose necrosis and dilatation; ovary: corpora lutea ↓ at high dose	None	Amyes, S.J. (1988); report no. 87/RHA15 6/711
Similar to OECD 452	Oral/diet, 26 weeks	Dog, Beagle, 4M+4F	0-100-500-5000 (0-3-15-142)	500 (15)	5000 (142)	Bw ↓; lymphoid cells ↑; plasma: AP ↑, cholesterol ↑; liver: weight↑	None	Paul, W. (1982); document no. 127AB-437-02

5.6.2 Repeated dose toxicity: inhalation

No data are available. Based on the results of the acute toxicity study and the physical properties of aclonifen, repeated dose inhalation toxicity studies for use as a herbicide have not been required according to the data requirements of directive 91/414/EEC.

5.6.3 Repeated dose toxicity: dermal

Dermal exposure for 4 weeks was well tolerated by Sprague-Dawley rats at the local level as no cutaneous reactions or histopathological findings at the application site were observed. A reduction in body weight gain associated with reduced food consumption and lower glucose levels in males and decreased white blood cell counts in males and females were only observed at the highest dose-level. The NOAEL was 500 mg/kg bw/day.

Table 5.6-2: Summary of dermal repeat dose toxicity

Method/ Guideline	Route of exposure, Duration	Species, Strain, Sex, No/group	Dose levels mg/kg bw/d	NO(A)EL mg/kg bw/d	LO(A)EL mg/kg bw/d	Results, Main effects/ Target organs	Remarks	Reference
OECD 410	Dermal, 28 days	Rat, SD; 10M+10F	0-250-500-1000	500	1000	Bw gain ↓ (M); plasma glucose ↓ (M); WBC ↓	Vehicle: aqueous 0.5% methyl-cellulose	Chevalier, G. (2002); report no 21601TSR

5.6.4 Other relevant information

No other data are available.

5.6.5 Summary and discussion of repeated dose toxicity:

Liver and kidney have been identified as the main target organs. Toxic effects in these organs appear to be related to concentrations that overwhelm metabolic and/or excretional capacities. No classification for repeated dose toxicity is required.

5.7 Mutagenicity

5.7.1 In vitro data

Aclonifen did not induce gene or chromosome mutations in bacterial or mammalian cell assays and did not provoke unscheduled DNA synthesis.

Table 5.7-1: Summary of in vitro mutagenicity

Method/ Guideline	Test system (Organism, strain)	Concentra-tions tested (give range)	Results		Remarks give information on cytotoxicity and other	Reference
			+ S9	- S9		
Similar to OECD 471 Bacterial Reverse Mutation	*S. typhimurium*: TA1535, TA1537, TA1538, TA98, TA100	0-5000 µg/plate	Negative	Negative	Reduced number of revertants at ≥300 µg/plate –S9 and ≥400 µg/plate +S9	Kramer, P. J. (1982); report no. 4/42/82
OECD 471 Bacterial Reverse Mutation	*S. typhimurium*: TA1535, TA1537, TA102, TA98, TA100	0-5000 µg/plate	Negative	Negative	Bacterial growth inhibition at ≥16 µg/plate +/-/S); precipitation at 5000 µg/plate	Herbold, B. (2006); report no. AT02825
OECD 473 in vitro Mammalian Chromosome Aberration	Human lymphocytes	0-100 µg/mL +S9 0-30 µg/mL –S9	Negative	Negative	Reduced mitotic indices at ≥20 µg/mL –S9 and at 100 µg/mL +S9	Dance, C. A. (1992); report no. 92/RHA477/0471
Similar to OECD 476 in vitro Mammalian Cell Gene Mutation	Chinese hamster lung V79 cells	0-1000 µg/mL +S9 0-25 µg/mL –S9	Negative	Negative	Reduced cloning efficiency at ≥25 µg/mL –S9 and at ≥ 150 µg/mL +S9	Oesch, F. (1984); report no. SP 579/VT-19
OECD 482 in vitro Mammalian Cell Unscheduled DNA Synthesis	Rat hepatocytes	0-25 µg/mL +S9	Negative	Negative	Cytotoxicity at 25 µg/mL	Meli, C. (1991); report no. 121009-M-03691

5.7.2 In vivo data

The high dose level in the micronucleus assay appeared to be a borderline effective dose for a beginning impairment of erythropoiesis in mice. However, aclonifen administration did not produce any increase in the number of micronuclei at any time point.

Table 5.7-2: Summary of in vivo mutagenicity

Method/ Guideline	Species, Strain, Sex, No/group	Route, Frequency of application	Sampling times	Dose levels mg/kg bw	Results	Remarks	Reference
OECD 474 (Micronucle-us assay)	Mouse, NMRI, 5M+5F	Oral, single dose	16, 24, 48 hours	0-578-1650-7260	Negative	Only 24-h timepoint investigated at 578 and 1650 mg/kg bw	Engelhardt, G. (1984); report no. 26M0286/8332

5.7.3 Human data

A test for clastogenicity in vitro was performed with human lymphocytes. Aclonifen was negative in this assay. No other human data are available regarding this endpoint.

5.7.4 Other relevant information

The binding of aclonifen (or metabolites) to liver and urinary bladder DNA and chromatin protein was determined in male CD1 mice after a single oral dose of 900 mg/kg bw (Sagelsdorff, P., 1995, report no. CB95/24). The animals excreted about 34 % of the administered radioactivity in the urine within 24 hours. This amount would have been available for binding to the analytes in bladder cells. Chromatin protein isolated from liver retained 177 - 275 pmol aclonifen-derived material/mg protein; an even higher value (319 pmol/mg protein) was obtained for the bladder. In contrast, no relevant interaction was detected with the DNA.

5.7.5 Summary and discussion of mutagenicity

Aclonifen did not induce gene mutations in procaryotes or mammalian cell cultures, chromosome aberrations in cultured human lymphocytes or in vivo in bone marrow cells from NMRI mice, nor did it lead to DNA damage in mammalian cells in the *in vitro* UDS assay. Aclonifen (or metabolites) does not bind to DNA *in vivo*, but has been shown to interact with chromatin proteins (specific interaction partners were not identified). Therefore, it may produce epigenetic changes on chromosomes and on gene expression. Taken together, the results demonstrate that aclonifen is not genotoxic and is unlikely to present a genotoxic hazard to humans. Classification for genotoxicity is not required.

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

Two 2-year combined chronic/carcinogenicity studies in rats identified the liver as a target organ. Liver findings included hepatocellular hyperplasia and increases in plasma albumin. Females showed reduced body weight gains and food consumption at ≥ 60 mg/kg bw/d. The systemic NOAEL is 7.6 mg/kg bw/d, based on these findings. A slightly higher incidence of thyroid C-cell carcinoma, seen in the females of the first study, was not confirmed after peer review (Grasso, P., 1990; Rittinghausen, S., 1995). Moreover, no evidence of an oncogenic effect on the thyroid was

seen in the second, more recent study. However, in this second study malignant astrocytomas were observed in the brains of 4/60 females at the high dose (86 mg/kg bw/d) at final necropsy. This incidence rate was outside the small laboratory data base (7/240 in males and 0/240 in females) and the Registry of Industrial Toxicology Animal Data (4/4061 in males and 1/3963 in females).

In the mouse carcinogenicity study the systemic NOAEL was 7.1 mg/kg bw/d based on decreased body weight gain and urinary bladder transitional cell hyperplasia. At the highest dose (7000 ppm) urinary bladder tumours were found in two males and one female.

Table 5.8-1: Summary of oral carcinogenicity

Method/ Guideline Route of exposure	Route of exposure, duration	Species, Strain, Sex, No/group	Dose levels ppm (mg/kg bw/d)	Results Main effects/ Target organs/ Tumors	NO(A)EL ppm (mg/kg bw/d)	LO(A)EL ppm (mg/kg bw/d)	Remarks	Reference
OECD 453	Oral/diet 12 and 24 months	Rat, Wistar Chbb:THOM 10M + 10F 60M + 60F	0-40-200-1600 (M: 0-1.6-8.1-66.9; F: 0-1.7-8.5-67.1)	1600 ppm: bw ↓ (F); total protein ↑, albumin ↑; triglycerides ↓	200 (8)	1600 (67)	combined chronic toxicity/ carcinogenicity study	Kirsch, P., Kühborth, B. (1989); report no. 71S0001/8401
OECD 453	Oral/diet 12 and 24 months	Rat, Wistar WI-IOPS 10M + 10F 60M + 60F	0-20-40-200-1600 (M: 0-0.8-1.5-7.6-61;F: 0-1.1-2.1-11-86)	1600 ppm: bw ↓ (F); liver hypertrophy; malignant astrocytoma in 4/60 (F)	200 (7.6)	1600 (61)	combined chronic toxicity/ carcinogenicity study	Wason, S. (2004); report no. SA 00591
US-EPA Guideline No 83-5	Oral/diet 39 and 80 weeks	Mouse, Crl:CD-1 12M + 12F 24M + 24F for T3, T4 measurement and reversibility 52M + 52F	0-70-700-7000 (M: 0-7.1-75.6-892; F: 0-8.3-80.1-984)	≥700 ppm: bw gain ↓, urinary bladder transitional cell hyperplasia (M) 7000 ppm: liver wt ↑, kidney wt ↑, urinary bladder inflammation (4M, 6F), bladder tumours (2M, 1F)	70 (M: 7.1; F: 8.3)	700 (M: 75.6; F: 80.1)	combined chronic toxicity/ carcinogenicity study	Amyes, S.J. (1991); report no. 89/RHA157/1047

5.8.2 Carcinogenicity: inhalation

No data are available.

5.8.3 Carcinogenicity: dermal

No data are available.

5.8.4 Carcinogenicity: human data

No data are available.

5.8.5 Other relevant information

As described in 5.7.4, aclonifen did not bind to DNA in cells of the urinary bladder and liver of mice *in vivo*. Binding to chromatin proteins, however, was observed, indicating an opportunity to exert effects on epigenetic markers (histone modifications, DNA methylation).

5.8.6 Summary and discussion of carcinogenicity

In the carcinogenicity study in mice, urinary bladder tumours were found in two males and one female at the highest dose (7000 ppm). Taking into account the lack of genotoxicity and that the kidney is responsible for the excretion of a major part of the dose, these tumours are attributed to the continuous irritation of the tissue at high doses of aclonifen. A similar mechanism can be excluded with respect to the astrocytomas seen in four out of sixty female rats in the high dose group. According to the toxicokinetic data aclonifen/metabolite levels in male and female rat brains are low, even at time points with the highest blood and plasma concentrations; unless astrocytes have a mechanism of concentrating the test substance or unless the blood-brain barrier becomes leaky with age or prolonged treatment, very little exposure should occur. In addition, male rats experience higher blood, plasma and brain levels of aclonifen-related material than females and should therefore be at a larger risk for a tumourigenic effect on astrocytes. Thus no mechanistic explanation could be found. However, due to the rarity of this tumour type in control groups, the finding in female rats remains a concern and is considered as limited evidence of carcinogenicity. Consequently, a classification of aclonifen as a carcinogen is proposed.

Classification and Labelling for carcinogenicity according to Directive 67/548/EEC:

Carc. Cat. 3 R40 (Harmful; Limited evidence of a carcinogenic effect)

Classification and Labelling for carcinogenicity according to GHS:

Carc. 2; H351 (Suspected of causing cancer)

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

In a two-generation study only very minor signs of toxicity were seen. In the parental generations a slight decrease in body weight gain and food consumption was noted at 2000 and 500 ppm. Fertility was normal at all dose levels. Pup weights at birth and at weaning were decreased for both the F1- and the F2-generation in the 2000 ppm group. A small decrement in weight gain was also observed in offspring at 500 ppm; however, this was not regarded to be test substance-related as it occurred in the F1-generation only. The NOAELs were 125 ppm (equivalent to approximately 8 mg/kg bw/d)

for parental toxicity, 500 ppm (equivalent to approximately 35 mg/kg bw/d) for offspring toxicity, and 2000 ppm (equivalent to approximately 120-140 mg/kg bw/d) for reproductive effects.

Table 5.9-1: Summary of effects on fertility

Method/ Guideline	Route of exposure	Species, Strain, Sex, No/group	Dose levels ppm	Critical effect Parental, Offspring (F1, F2)	NO(A)EL Parental toxicity ppm (mg/kg bw/d)	NO(A)EL reproductive toxicity ppm (mg/kg bw/d)	NO(A)EL offspring toxicity ppm (mg/kg bw/d)	Reference
OECD 416	Oral/diet	Rat, Wistar KFM-Han, 25M, 25F	0-125-500-2000	P: bw gain ↓ F1, F2: birth wt ↓, bw gain ↓	125 (M: 8; F: 10)	2000 (120-140)	500 (35)	Becker, H. (1985); report no. 030644

5.9.2 Developmental toxicity

Aclonifen was not teratogenic in the rat developmental toxicity study. The NOAEL for maternal and developmental effects of 60 mg/kg bw/d was derived from decreased bw gain of the dams and reduced foetal weights at 600 mg/kg bw/d. In rabbits the highest dose level of 25 mg/kg bw/d did not exert any maternal toxicity and as aclonifen was also devoid of any embryotoxicity the maternal and developmental NOAEL were set at this dose.

Table 5.9-2: Summary for developmental toxicity

Method/ Guideline	Route of exposure, Duration	Species, Strain, No/group	Dose levels mg/kg bw	Critical effects 1) dams 2) fetuses	NO(A)EL Maternal toxicity mg/kg bw/d	NO(A)EL Teratogenicity Embryotoxicity mg/kg bw/d	Remarks	Reference
OECD 414	Oral, pregnancy day 6-20	Rat, Wistar Chbb:THOM, 25F	0-6-60-600	1) Food ↓, bw gain ↓ 2) Bw ↓	60	60	Vehicle: 0.5% aqueous Tween 80-0.9% HCl	Niggeschulze, A. et al. (1982); document no. 127AB-451-02
OECD 414	Oral, pregnancy day 6-18	Rabbit, Chinchilla Hybrid 16F	0-1-5-25	1) - 2) -	25	25	Vehicle: 2% aqueous carboxy-methyl cellulose	Becker, H. (1984); report no. 025525

5.9.3 Human data

No data are available.

5.9.4 Other relevant information

No other relevant information is available.

5.9.5 Summary and discussion of reproductive toxicity

Aclonifen did not affect reproduction and influenced developmental parameters only at a dose that also induced systemic effects in the dams. The decrease in the number of corpora lutea observed in the 28-day mouse study at a dose of 12 g/kg bw/day is not considered a specific effect on reproduction. As no specific impairments of fertility and embryo-foetal development have been observed a classification for fertility effects or developmental toxicity is not required.

5.10 Other effects

5.10.1 Neurotoxicity

Based on the chemical structure and the mode of action of aclonifen no neurotoxicity studies are necessary. Evaluation of neurotoxicity endpoints (various reflex tests) in a 90-day dietary study in rats (Wason, S., 2001, report no. SA00458) did not reveal any evidence of a neurotoxic potential.

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

Aclonifen (technical) is not explosive in the sense of EEC method A14.

6.2 Flammability

Aclonifen (technical) is not highly flammable in the sense of EEC method A10.

6.3 Oxidising potential

Aclonifen (technical) has no oxidising properties in the sense of EEC method A17.

7 ENVIRONMENTAL HAZARD ASSESSMENT

The environmental hazard assessment for aclonifen is based on the Draft Assessment Report and Proposed Decision of Germany prepared in the context of the possible inclusion of aclonifen in Annex I of Council Directive 91/414/EEC (DAR August 2006 + Final addendum June 2008, RMS Germany). – see IUCLID 5 dossier, chapter 13

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Short-term toxicity to fish

The acute toxicity of aclonifen to fish is summarised in Table 7.1-1.

Table 7.1-1: Acute toxicity of aclonifen to fish

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (h)	Endpoint	Value (mg/L)	
OECD 203	*Oncorhynchus mykiss*	flow trough	96	LC_{50}	0.67 nom	Douglas M.T. et al. (1991), Document No: R007151
OECD 203	*Cyprinus carpio*	flow trough	96	LC_{50}	1.7 m.m.[1)]	Douglas, M.T. et al. (1991), Document No: R007155

[1)] m.m. … mean measured

Long-term toxicity to fish

The long term toxicity of aclonifen to fish is summarised in Table 7.1-2.

Table 7.1-2: Long-term toxicity of aclonifen to fish

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (d)	Endpoint	Value (mg/L)	

OECD 204	*Oncorhynchus mykiss*	flow trough	21	NOEC	0.01 nom	Douglas M.T. et al. (1991), Document No: R007156
OECD 204	*Oncorhynchus mykiss*	flow trough	21	NOEC	0.009 nom	Jenkins, C.A. (1993), Document No.: R007413
OECD 210, USEPA 72-4	*Pimephales promelas*	ELS, flow trough	35	NOEC	0.005 nom growth 0.011 nom hatch	Mc Elligott, A. (1997), Document No.: R007440

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

The acute toxicity of aclonifen to invertebrates is summarised in Table 7.1-3

Table 7.1-3: Long-term toxicity of aclonifen to invertebrates

Guideline/ Test method	**Species**	**Exposure**		**Results**		**Reference**
		Design	**Duration (h)**	**Endpoint**	**Value (mg/L)**	
OECD 202, part 1	*Daphnia magna*	static	48	EC_{50}	1.2 nom	Douglas M.T. et al. (1991), Document No: R007149

Long-term toxicity to aquatic invertebrates

The long-term toxicity of aclonifen to invertebrates is summarized in Table 7.1-4.

Table 7.1-4: Long-term toxicity of aclonifen to invertebrates

Guideline/ Test method	**Species**	**Exposure**		**Results**		**Reference**
		Design	**Duration (d)**	**Endpoint**	**Value (mg/L)**	
OECD 202, part 2	*Daphnia magna*	Semi-static	21	NOEC	0.016 m.m.[1)]	Douglas M.T. et al. (1991), Document No: R007153

[1)] m.m. … mean measured

7.1.1.3 Algae and aquatic plants

The toxicity of aclonifen to algae and aquatic plants is summarised in Table 7.1-5

Table 7.1-5: Long-term toxicity of aclonifen to algae and aquatic plants

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (h)	Endpoint	Value (mg/L)	
OECD 201	*Desmodesmus subspicatus*	static	96	E_rC_{50} NOEC	0.0067 nom 0.0025 nom	Handley, J.W. et al. (1990), Document No: R007145
OECD 201	*Navicula pelliculosa*	static	72	E_rC_{50} NOErC	1.2 m.m.[1)] 0.23 m.m.[1)]	Hoberg, J.R. (1998), Document No.: R005692
USEPA (= EPA) 122-2, USEPA (= EPA) 123-2	*Lemna gibba*	static	14 d	E_rC_{50} NOErC	0.012 m.m.[1)] 0.0012 m.m.[1)]	Hoberg, J.R. (1998), Document No.: R005693

[1)] m.m. … mean measured

The study with algae *Desmodesmus subspicatus* can be regarded as the key study for the aquatic toxicity of aclonifen and hence for classification and labelling. Therefore the study is presented in more detail below:

Toxicity of aclonifen to *Desmodesmus subspicatus*

Author: Handley, J.W. et al. (1990)
Report: The algistatic activity of aclonifen CME 127. Rhone-Poulenc; Safepharm Laboratories Limited, Derby U.K.
Report No.: 423883; 282/53; AT282/001; unpublished report
Document No: R007145
Guidelines: OECD 201
Deviations: None
GLP/GEP: Yes
Validity: Acceptable

Material and methods:

Test substance: aclonifen, CME 127 (batch n° DA 618), appearance: yellow powder, purity: 91.3 %.

Algal cultures of Desmodesmus subspicatus were exposed to nominal concentrations of aclonifen equal to 1.25, 2.5, 5, 10 and 20 µg/L plus a control and a solvent control (100 acetone µL/L), each in triplicate, over a 96 hour period. The test was conducted in 250 mL conical flasks containing 100 mL test solution. At initiation of the study the culture contained a nominal cell density of 6.47 x 104 cells/mL. Test chambers were held at a temperature of 24 °C. The target light intensity was approximately 8000 lux. The test media were not aerated.

Measurements of growth were performed at 0, 24, 48, 72 and 96 hours. Mean cell density of the controls was determined at test initiation and termination. pH values were recorded at 0 and 96 hours. The nominal concentrations of aclonifen were verified by chemical analysis (HPLC method) at 0 and 96 hours.

Findings:

The measured pH at initiation was 7.9 and 8.0 to 8.9 at test termination. Analytical measurements showed actual test levels to be equal or somewhat in excess of the nominal values (average mean measured concentration over the study period = 106 % of the nominal values). Measured concentrations ranged 97.3 % to 124 % of the nominal concentrations at study initiation and 90.8 to 109.0 % after 96 hours, showing the substance to be stable in water under the conditions of the test.

All results are expressed in terms of nominal rather than actual measured test levels.

The percent of inhibition after 96 hours of incubation were indicated in the following table:

Table 7.1-6: Percent of inhibition after 96 hours of incubation

Nominal concentration (mg/L)	**Percent inhibition based on (%)**	
	Area under the growth curve	**Growth rate**
Control	-	-
Solvent control	-	-
0.00125	1	1
0.0025	4	9
0.0050	29	24
0.010	72	68
0.020	93	83

Algal growth was inhibited at levels of 5 µg/L and above. Microscopical examination of algal cells revealed no aberrations indicating aclonifen to exert an algistatic rather than an algicidal effect.

Conclusion:

Based on nominal concentrations, confirmed by chemical analysis, the 96 hour E_bC_{50} (based on biomass) and E_rC_{50} (based on growth rate) values in *Desmodesmus subspicatus* were highly similar at 6.7 and 6.9 µg/L, respectively. The 96-hour NOEC was determined to be 2.5 µg/L.

7.1.1.4 Sediment organisms

The toxicity of aclonifen to sediment dwelling organism is summarised in

Table 7.1-7: Long-term toxicity of aclonifen to invertebrates

Guideline/ Test method	Species	Exposure		Results		Reference
		Design	Duration (d)	Endpoint	Value (mg/L)	
BBA Draft guideline 1995	*Chironomus riparius*	Static, spiked water	28	NOEC (emergence / develoment)	0.472 initial measured concentration	Suteau, P. (1996), Document No: R007434
BBA Draft guideline 1995	*Chironomus riparius*	Static, spiked water	28	NOEC (emergence / develoment)	32 mg/kg nom	Sewell, I. and McKenzie, J. (2004), Document No: C039873

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

Not relevant for this type of dossier.

7.2 Terrestrial compartment

Not relevant for this type of dossier.

7.3 Atmospheric compartment

Not relevant for this type of dossier.

7.4 Microbiological activity in sewage treatment systems

Not relevant for this type of dossier.

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

Not relevant for this type of dossier.

7.6 Conclusion on the environmental classification and labelling

Aclonifen is hydrolytically stable. Aclonifen was found to be not readily biodegradable within 28 days in the Sturm test (OECD guideline 301B).

Aclonifen has a log Kow of 4.37. In a BCF study, a BCF value of 2896 was obtained based on plateau total radioactive residue in whole fish and average total radioactive residue in water, whereas a BCF value of 2248 was obtained based on uptake and elimination rate constants.

Aclonifen shows a high toxicity to algae (ErC_{50} = 0.0067 mg/L) and aquatic plants (ErC_{50} = 0.012 mg/L). The lowest endpoints in long- term studies were observed with fish (35-d early life stage study NOEC = 0.005 mg/L). The toxicity of aclonifen to fish and invertebrates is in the mg/L range with a toxicity of LC_{50} = 0.67 mg/L to fish and of EC_{50} = 1.2 mg/L to invertebrates.

Conclusion of environmental classification according to Directive 67/548/EEC

In aquatic toxicity studies, ErC_{50} values for algae and aquatic plants and LC_{50} value for fish were obtained at aclonifen concentrations < 1 mg/L. Aclonifen is not readily biodegradable according to the Sturm test (OECD 301B). Aclonifen has a log Kow of 4.37. The experimentally derived steady state BCF of 2896 and kinetic BCF of 2248 are above the trigger of 100 (criterion for bioaccumulating potential conform Directive 67/548/EEC) for not rapidly biodegradable substances. Aclonifen therefore fulfils the criteria for classification with N; R50-53.

Based on the toxicity data for *Desmodesmus subspicatus* (ErC50 0.0067 mg/L) the following specific concentration limits should be applied:

Concentration	Classification
$C \geq 0.25\%$	N; R50-53
$0.025\% \leq C < 0.25\%$	N; R51-53
$0.0025\% \leq C < 0.025\%$	R52-53

where C is the concentration of aclonifen in the preparation.

Conclusion of environmental classification according to Regulation EC 1272/2008

In aquatic toxicity studies, ErC_{50} values for algae and aquatic plants and LC_{50} value for fish were obtained at aclonifen concentrations < 1 mg/L. Aclonifen is not readily biodegradable according to the Sturm test (OECD 301B). The experimentally derived steady state BCF of 2896 and kinetic BCF of 2248 are above the trigger of 500 (criterion for bioaccumulating potential conform Regulation EC 1272/2008) for not rapidly biodegradable substances. Aclonifen therefore fulfils the criteria for classification as aquatic environmental hazard acute category 1, H400 and aquatic environmental hazard chronic category 1, H410.

The M-factor for aclonifen is 100. This value is based on ErC50 value of 0.0067 mg/L obtained for the algae *Desmodesmus subspicatus* in a 96-h static study.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

Aclonifen is an active substance in the meaning of Directive 91/414/EEC and therefore subject to harmonised classification and labelling (Regulation EC 1272/2008 article 36.2).

OTHER INFORMATION

This proposal for harmonised classification and labelling is based on the data provided for the registration of the active substance aclonifen according to Directive 91/414/EEC. The summaries included in this proposal are partly copied from the DAR and the final addendum to the DAR. Some details of the summaries were not included when considered not relevant for a decision on the classification and labelling of this substance. For more details the reader is referred to the DAR and its addendum.

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