ECHA
EUROPEAN CHEMICALS AGENCY

Committee for Risk Assessment
RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of

Amidosulfuron

EC Number: 407-380-0

CAS Number: 120923-37-7

ECHA/RAC/CLH-O-0000002509-70-01/A1

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

8 March 2012

CONTENTS

Part A.

Part B.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Amidosulfuron
EC number:	407-380-0
CAS number:	120923-37-7
Annex VI Index number:	-
Degree of purity:	≥ 970 g/kg
Impurities:	No relevant impurities according to Commission Directive 2008/40/EC to include Amidosulfuron in Annex I of Council Directive 91/414/EEC

1.2 Harmonised classification and labelling proposal

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

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	No current entry	No current entry
Current proposal for consideration by RAC	Aquatic Acute 1, H400 M=100 Aquatic Chronic 1, H410 M=10	N; R50/53 **SCLs** Where Cn is the concentration of amidosulfuron in the preparation. Classification / Concentration [Cn in %]: N, R50/53: Cn ≥ 0.25 N, R51/53: 0.025 ≤ Cn < 0.25 R52/53: 0.0025 ≤ Cn <0.025
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Aquatic Acute 1, H400 M=100 Aquatic Chronic 1, H410 M=10	N; R50/53 **SCLs** Where Cn is the concentration of amidosulfuron in the preparation Classification / Concentration [Cn in %]: N, R50/53: Cn ≥ 0.25 N, R51/53: 0.025 ≤ Cn < 0.25 R52/53: 0.0025 ≤ Cn <0.025

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

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	-	-	-	Technical substance does not present a danger of explosion under test condition (shock test, thermal sensitivity test, friction test)
2.2.	Flammable gases	-	-	-	No gas
2.3.	Flammable aerosols	-	-	-	No aerosol
2.4.	Oxidising gases	-	-	-	No gas
2.5.	Gases under pressure	-	-	-	No gas
2.6.	Flammable liquids	-	-	-	No liquid
2.7.	Flammable solids	-	-	-	Data conclusive, but not sufficient for classification (no indication if the wetting zone is able to stop the flame); burning time: 40 and 45 seconds
2.8.	Self-reactive substances and mixtures	-	-	-	Data lacking
2.9.	Pyrophoric liquids	-	-	-	No liquid
2.10.	Pyrophoric solids	-	-	-	No self ignition up to 402°C; no adequate test available
2.11.	Self-heating substances and mixtures	-	-	-	No self ignition up to 402°C; no adequate test available
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	-	-	Chemical structure does not contain metals or metalloids; in addition, the technical substance manufactured is washed with water
2.13.	Oxidising liquids	-	-	-	No liquid
2.14.	Oxidising solids	-	-	-	Test substance has no oxygen compound which might have oxidising effects on combustible compounds

2.15.	Organic peroxides	-	-	-	Test substance has no oxygen compound which might have oxidising effects on combustible compounds
2.16.	Substance and mixtures corrosive to metals	-	-	-	According to the nature of the test substance (contains no acidic or basic functional group) no adequate test available
3.1.	Acute toxicity - oral	-	-	-	LD_{50} > 5000 mg/kg bw
	Acute toxicity - dermal	-	-	-	LD_{50} > 5000 mg/kg bw
	Acute toxicity - inhalation	-	-	-	LC_{50} > 1.8 mg/L (highest achievable dose)
3.2.	Skin corrosion / irritation	-	-	-	Not irritating
3.3.	Serious eye damage / eye irritation	-	-	-	Not irritating
3.4.	Respiratory sensitisation	-	-	-	Not irritating
3.4.	Skin sensitisation	-	-	-	Not sensitising
3.5.	Germ cell mutagenicity	-	-	-	Negative in a battery of *in vitro* and *in vivo* genotoxicity studies
3.6.	Carcinogenicity	-	-	-	Not carcinogenic in rat and mouse
3.7.	Reproductive toxicity	-	-	-	No impairment of fertility No teratogenic potential
3.8.	Specific target organ toxicity – single exposure	-	-	-	No evidence from acute studies
3.9.	Specific target organ toxicity – repeated exposure	-	-	-	No evidence from repeated dose studies
3.10.	Aspiration hazard	-	-	-	no human evidence, no hydrocarbon
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1, H400 Aquatic Chronic 1, H410	M =100 Classification: Concentration [Cn in %] N, R50/53: Cn ≥ 0.25 N, R51/53: 0.025 ≤ Cn < 0.25 R52/53: 0.0025 ≤ Cn < 0.025		
5.1.	Hazardous to the ozone layer	No Data available			Data lacking

[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:	H400	Very toxic to aquatic life,
		H410	Very toxic to aquatic life with long lasting effects
	Precautionary statements:	P273	Avoid release to the environment
		P391	Collect spillage
		P501	Dispose of contents/container to ….
		EUH401	To avoid risks to human health and the environment, comply with the instructions for use

Proposed notes assigned to an entry:

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	-	-	-	Technical substance does not present a danger of explosion under test condition (shock test, thermal sensitivity test, friction test)
Oxidising properties	-	-	-	The technical substance has no oxygen compound which might have oxidising effects on combustible compounds
Flammability	-	-	-	Technical substance is not considered as "highly flammable" under test condition
Other physico-chemical properties *[Add rows when relevant]*	-	-	-	-
Thermal stability	-	-	-	Compound is not considered as auto-flammable under test condition
Acute toxicity	-	-	-	Oral LD_{50} > 5000 mg/kg bw Dermal LD_{50} > 5000 mg/kg bw Inhalation LC_{50} > 1.8 mg/L (highest achievable dose)
Acute toxicity – irreversible damage after single exposure	-	-	-	No evidence from acute studies
Repeated dose toxicity	-	-	-	No evidence from repeated dose studies
Irritation / Corrosion	-	-	-	Not irritating
Sensitisation	-	-	-	Not sensitising
Carcinogenicity	-	-	-	Not carcinogenic in rat and mouse
Mutagenicity – Genetic toxicity	-	-	-	Negative in a battery of *in vitro* and *in vivo* genotoxicity studies
Toxicity to reproduction – fertility	-	-	-	No impairment of fertility
Toxicity to reproduction – development	-	-	-	No teratogenic potential
Toxicity to reproduction – breastfed babies. Effects on or via	-	-	-	No evidence from multigeneration study

lactation				
Environment	N; R50/53			

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Indication of danger: Dangerous for the Environment

R-phrases:
- R50 Very toxic to aquatic organisms
- R53 May cause long term effects in the environment

S-phrases:
- S60 This material and its container must be disposed of as hazardous waste
- S61 Avoid release to the environment. Refer to special instructions/Safety Data Sheet

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Amidosulfuron is a sulfonylurea herbicide. In 2008 it was approved for Annex I listing as a third stage Part A Review compound under Council Directive 91/414/EEC, with Austria as Rapporteur Member State. In accordance with Article 36(2) of the CLP Regulation, amidosulfuron should now be considered for harmonised classification and labelling. Therefore, this proposal considers all physical and chemical properties, human health and environmental endpoints. This Annex VI dossier presents a classification and labelling proposal based mainly on the information presented in the assessment of amidosulfuron under Directive 91/414/EEC. This assessment (DAR) was based on one full data package submitted by one company. No other registration dossiers are available for amidosulfuron at time of the submission of the revised CLH report.

Amidosulfuron is not currently listed in Annex VI of Regulation EC 1272/2008 (CLP Regulation). Following evaluation of the data this proposal seeks to propose classification for the environment. No classification for physical and chemical properties and human health is proposed. No disagreement on classification and labelling proposal were given between Austria as Rapporteur Member State and other Member States during the peer review procedure for Annex I inclusion.

2.2 Short summary of the scientific justification for the CLH proposal

For Amidosulfuron, no classification and labelling has been proposed regarding physical and chemical properties and human health, neither by Rapporteur Member State (Austria) nor during the PRAPeR peer review.

Regarding environment (considering 2nd ATP criteria) following classification will be proposed:

DSD: N, R50/53 (DSD)
CLP: Aquatic Acute 1, H400, M=100; Aquatic Chronic 1, H410, M=10

Aquatic Acute classification is based on:

- E_rC50 value for *Lemna gibba* is <0.0092 mg/L (0.001 < L(E)C50 ≤ 0,01), resulting in N, R50 (DSD) and Aquatic Acute 1, H400, M =100 (CLP)
  Lemna gibba E_bC_{50}/E_rC_{50} (7 d) = 0.0092 mg/L, (Sowig 2002ag);

Aquatic chronic classification is based on:

- the results of a study on biodegradability which indicates that amidosulfuron can not be considered readily biodegradable. Therefore, R53 (DSD) classification is proposed.
- Amidosulfuron is not rapidly degradable (CLP) as the pass level of 60% of theoretical formation of CO2 was not reached within the 10 days window in a modified Sturm test in accordance with the OECD 301 B guideline and as the DT50 whole system obtained in an aerobic simulation study in water/sediment systems was 91 d (S1) and 16 d (S2) respectively.
- chronic aquatic toxicity studies
  Lemna gibba NOEC(14d) = 0.00874 mg/L, (Morrow J. E., (1993a))
  classification with Aquatic Chronic 1, H410 M=10 (CLP) is proposed.

2.3 Current harmonised classification and labelling

Amidosulfuron has not been previously discussed or agreed at TC C&L (Dir. 67/548/EEC); no harmonised classification and labelling exists.

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

No entry in Annex VI, Table 3.1.

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

No entry in Annex VI, Table 3.2.

2.4 Current self-classification and labelling

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

No current self-classification and labelling based on CLP Regulation criteria.

2.4.2 Current self-classification and labelling based on DSD criteria

The Notifier stated that "R52/53 Harmful to aquatic organisms, may cause long-term effects in the aquatic environment" would be warranted.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

No need for justification (Amidosulfuron is a pesticide).

Part B.

SCIENTIFIC EVALUATION OF THE DATA

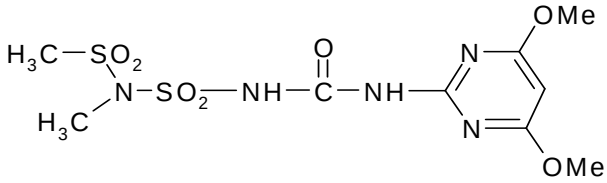
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	407-380-0
EC name:	3-(4,6-dimethoxypyrimidin-2-yl)-1-((N-methyl-N-methylsulfonyl-amino)sulfonyl)urea
CAS number (EC inventory):	-
CAS number:	120923-37-7
CAS name:	3,5-Dithia-2,4-diazahexanamide, N-(4,6-dimethoxy-2-pyrimidinyl)-4-methyl-, 3,3,5,5-tetraoxide
IUPAC name:	3-(4,6-dimethoxypyrimidin-2-yl)-1-((N-methyl-N-methylsulfonyl-amino)sulfonyl)urea
CLP Annex VI Index number:	-
Molecular formula:	$C_9H_{15}N_5O_7S_2$
Molecular weight range:	369.41 g/mol

Structural formula:



1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Amidosulfuron	>970 g/kg (purity)	No range, since minimal purity stated	-

Current Annex VI entry: no entry

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
No relevant impurities (according to Commission Directive 2008/40/EC for Inclusion of Amidosulfuron in Annex I of Council Directive 91/414/EC)	-	-	-

All impurities are presented in the confidental part of the DAR (Draft assessment report) and not included in the CLH report, but the document is flagged in IUCLID as such.

Current Annex VI entry: -

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
No additives	-	-	-	-

Current Annex VI entry: -

1.2.1 Composition of test material

Physico-chemical properties: see table 9 (purity of tested technical material in the range from 90.0% to 99.7%)

Human health hazard assessment: purity of tested technical material in the range from 94.0% to 99.7%

Environmental hazard assessment: purity of tested technical material in the range from 96.5% to 99.7%

1.3 Physico-chemical properties

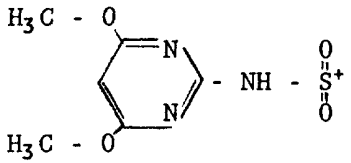
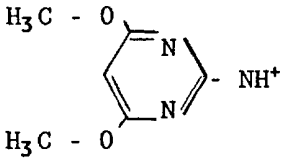
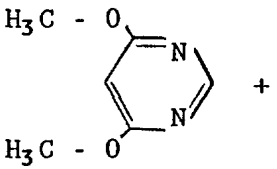
Table 9: Summary of physico - chemical properties

Property (Annex point as reference to the DAR)	Method	Results	Conclusion/Comment	Reference (Study)
B.2.1.1 Melting point, freezing point or solidification point (IIA 2.1.1)	OECD 102 (Differential scanning calorimetric method) GLP	Technical product (purity: 99.3% w/w) Melting point: 179 °C	Method OECD 102 is equivalent to EEC/A1 TGAI is used instead of purified material however, the purity is > 98 % w/w and can be accepted.	Smeykal H. (2004e) (Document C045781)
B.2.1.2 Boiling point (IIA 2.1.2)	OECD 103 GLP	Technical product (purity: 99.3% w/w) The substance has no boiling point at atmospheric pressure and the test item starts to decompose at 185 °C	Method OECD 103 is equivalent to EEC/A2 TGAI is used instead of purified material however, the purity is > 98 % w/w and can be accepted.	
B.2.1.3 Temperature of decomposition or sublimation (IIA 2.1.3)	OECD 113 (Differential thermal analysis) with a heating rate of 10 °C/min in aluminium crucibles with a hole GLP	Technical product (purity: 99.3% w/w) The exothermic reaction (=decomposition) starts at about 185 °C.	TGAI is used instead of purified material however the purity is > 99 % w/w and can be accepted.	
B.2.1.4 Relative density (IIA 2.2)	OECD 109 (Air comparison pycnometer) GLP	Technical product (purity: 99.0% w/w) $D^{R}_{4} = 1.51$ at ambient temperature R = 24.5 °C	Acceptable Remark: Method OECD 109 is equivalent to EEC/A3; according directive 94/37/EC relative density should be determined with the purified active substance. In this case, it is not expected that an increased purity will influence this result significantly	Franke J. (2001b) (Document C018324)

Property (Annex point as reference to the DAR)	**Method**	**Results**	**Conclusion/Comment**	**Reference (Study)**
B.2.1.5 Vapour pressure (IIA 2.3.1)	EEC/A4 (Effusion method: Vapour pressure balance)	Purified product (purity: 99.7% w/w) 1.3 x 10^{-5} Pa at 20°C 2.2 x 10^{-5} Pa at 25°C 2.2 x 10^{-4} Pa at 50°C	Acceptable	Grewer (1987a) (Document A40555)
B.2.1.6 Volatility, Henry's law constant (IIA 2.3.2)	Calculation	K = 5.22 x 10^{-4} Pa·m³·mol^{-1} at pH 4 at 20 °C K = 1.56 x 10^{-6} Pa·m³·mol^{-1} at pH 7 at 20 °C K = 6.76 x 10^{-6} Pa·m³·mol^{-1} at pH 9 at 20 °C <u>Parameter used for calculation:</u> water solubility: 9.2 mg/L at pH 4 at 20 °C 3.07g/L at pH 7 at 20 °C 7.10 g/L at pH 9 at 20 °C vapour pressure: 1.3 x 10^{-5} Pa at 20 °C		Bogdoll B. Lemke G. (2005a) (Document C048205))
B.2.1.7 Appearance: physical state (IIA 2.4.1)	Visual examination	Purified product (purity: 99.2% w/w) Fine powder, partially agglomerated to smooth lumps		Kocur J., Rexer K. (1989e) (Document A41822)
	Visual examination	Technical product (purity: 93.0% w/w) Fine powder, partially agglomerated to smooth lumps		Kocur J. (1989d) (Document A40686)
B.2.1.8 Appearance: colour (IIA 2.4.1)	Visual examination	Purified product (purity: 99.2% w/w) White		Kocur J., Rexer K. (1989c) (Document A41818)
	Visual examination	Technical product (purity: 93.0% w/w) White		Kocur J. (1989a) (Document A40679)
B.2.1.9 Appearance: odour (IIA 2.4.2)	Organoleptic examination	Purified product (purity: 99.2% w/w) Slightly acidulous		Kocur J., Rexer K. (1989d) (Document A41819)

Property (Annex point as reference to the DAR)	**Method**	**Results**			**Conclusion/Comment**	**Reference (Study)**
	Organoleptic examination	Technical product (purity: 93.0% w/w) Slightly acidulous				Kocur J. (1989c) (Document A41148)
B.2.1.10 Spectra of the active substance (IIA 2.5.1)	UV/VIS - Spectroscopy GLP	Technical product (purity: 99.3% w/w)		c = 11.2 mg/L	Acceptable	Muehlberger B., Eyrich U. (2004a) (Document C045777)
		Solvent	$\lambda_{max\ [nm]}$	ε_{max} [$L \cdot mol^{-1} \cdot cm^{-1}$]		
		MeOH	201 241 291	31649 14938 10		
		MeOH/HCl [90/10 (0.1 M) v/v]	201 241 291	33226 13978 20		
		MeOH/NaOH [90/10 (0.1 M) v/v]	241 291	22442 12		
		E at or above 290 nm are ≥10				

Property (Annex point as reference to the DAR)	**Method**	**Results**		**Conclusion/Comment**	**Reference (Study)**
	FTIR - Spectroscopy KBr disk, measured between 400 – 4000 cm^{-1}	Purified product (purity: 99.7%		Acceptable The IR spectrum of amidosulfuron is in agreement with the chemical structure	Sarafin R., Zeisberger E. (1989a) (Document A40147)
		wave number [cm^{-1}]	assignment		
		3400 3233 3000-2800 1711 1616 1573 1358 1242 1163 835	ν (O-H) ν (N-H) ν (C-H) ν (C=O) polysubstituted pyrimidine ring polysubstituted pyrimidine ring ν (S=O) ν (C-O-C) ν (S-O) polysubstituted pyrimidine ring		
	Fourier–Transform ^{1}H - NMR-Spectroscopy	Purified product (purity: 98.3% w/w)		Acceptable	Schumann C. (1989a) (Document A39960)
		Multiplicity	Chemical shift [ppm]		
		Singlet Singlet Singlet Singlet Singlet Singlet	3.26 3.53 3.94 5.78 7.32 13.13		

Property (Annex point as reference to the DAR)	**Method**	**Results**			**Conclusion/Comment**	**Reference (Study)**
	MS - Spectroscopy	Purified product (purity: 98.3% w/w)				Sarafin R., Winterscheidt G. (1989a) (Document A39855)
		m/z	intensity approx.	assignment		
	Direct insert probe at 62 eV Ionisation: electron impact (EI)	290	8	$[M - CH_3SO_2]^+$	Although the molecular ion at m/z 369 $[M^+]$ was not observed, the MS spectrum of amidosulfuron is in agreement with the chemical structure Acceptable	
		261	100	$[M - CH_3SO_2NCH_3]^+$		
		218	54			
		154	78			
		139	30			

Property (Annex point as reference to the DAR)	Method	Results	Conclusion/Comment	Reference (Study)
B.2.1.11 Spectra of impurities (IIA 2.5.2)			Not required, as the active substance contains no impurities of toxicological, ecotoxicological or environmental concern	
B.2.1.12 Solubility in water (IIA 2.6)	EEC/A6 Flask method GLP	Technical product (purity: 99.3% w/w) at 20 °C 9.2 mg/L in buffered solution (at pH 4) 3.07 g/L in buffered solution (at pH 7) 7.10 g/L in buffered solution (at pH 9)	Acceptable Deviations from method EEC/A6: stirring time was abridged to 8, 16 and 24 hours and temperature was reduced to 20 °C	Muehlberger B., Lemke G. (2004c) (Document C045907)
	OECD 105 Flask method analog GLP [1)]	Purified product (purity: 99.7% w/w) at 20 °C 9 mg/L in bidistilled water (pH 5.8) 3.3 mg/L at pH 3 13500 mg/L at pH 10	This study is only cited for information since the solubility in bidistilled water is determined as it is used in the study for the determination of surface tension. But the study report is only a conclusion and therefore the notifier has updated the study for solubility in water.	Goerlitz G., Eyrich U. (1987as) (Document A35801)
B.2.1.13 Solubility in organic solvents (IIA 2.7)	OECD 105 Flask method GLP	Purified product (purity: 99.7% w/w) solvent: solubility at 20 °C [g/L] n-hexane: 0.001 acetone: 8.1 toluene: 0.256 dichloromethane: 6.9 methanol: 0.865 isopropanol: 0.099 ethyl acetate: 3.0	Acceptable	Goerlitz G., Eyrich U. (1987aj) (Document A35798) Bogdoll B. (2005d) (Document C046705)
B.2.1.14	EEC/A8	Purified product (purity: 99.4% w/w)	Acceptable	• Muehlberger B., Wiche A. (2004a)

Property (Annex point as reference to the DAR)	**Method**	**Results**				**Conclusion/Comment**	**Reference (Study)**
Partition coefficient n-octanol/water (IIA 2.8)	Flask method GLP	pH	4.0 (23 °C)	7.0 (22 °C)	9.0 (23 °C)		(Document C044973)
		Log P_{ow}	1.07	-1.56	-2.21		
		P_{ow}	11.7	0.027	0.006		
B.2.1.15 Hydrolysis rate (IIA 2.9.1)	EPA N 161-1 GLP	Purified product (purity: 98.3% w/w) First order kinetics at all pH values tested. DT_{50} (25 °C) = 33.9 d at pH 5 DT_{50} (25 °C) > 365 d at pH 7 and 9 Two major degradation products: 2-amino-4,6-dimethoxypyrimidine and 4,6-dimethoxypyrimidine-2-yl-carbamoylamidosulfuric acid				Acceptable For details see B 8.4 Fate and behaviour in water	Schollmeier M.; Eyrich U. (1992i) (Document A48869) Schollmeier M. (1993a) (Document A51873)
	EPA N 161-1 GLP	Purified product (purity: 98.3% w/w) DT_{50} (25 °C) = 1.34 d at pH 3 DT_{50} (25 °C) = 3.87 d at pH 4 DT_{50} (25 °C) = 30.56 d at pH 5 DT_{50} (25 °C) = 237.10 d at pH 6 Amidosulfuron degrades rapidly under abiotic and acidic conditions and is stable in near neutral aqueous media				Acceptable For details see B 8.4 Fate and behaviour in water	Schollmeier M.; Britten I. (1992a) (Document A47707)

Property (Annex point as reference to the DAR)	**Method**	**Results**	**Conclusion/Comment**	**Reference (Study)**
B.2.1.16 Direct phototrans-formation (IIA 2.9.2)	EPA N 161-2 analog GLP [1)]	^{14}C pyrimidine-2 labeled amidosulfuron (radiochemical purity > 98% w/w) Test conditions: Sterilized aqueous buffer solutions (pH 7) using a xenon arc lamp which closely simulates sunlight at a temperature of 25 ± 1 °C. Application rate 62.0 µg/mL 52° N under outdoor conditions. Almost no photodegradation in aqueous solutions occurs DT_{50} > 365 d (2370 ± 1194 d) (Mass balance > 90 %) Identification of breakdown products was not possible due to its very low amounts	Acceptable For details see B 8.4 Fate and behaviour in water	Gildemeister H., Rockmann S. (1989a) (Document A40662)
B.2.1.17 Quantum yield (IIA 2.9.3)	--	Almost no photodegradation in aqueous solutions, calculation of the quantum yield and the theoretical lifetime in the top layer of aqueous systems and the real lifetime of the active substance is not possible	Acceptable For details see B 8.4 Fate and behaviour in water	Gildemeister H., Rockmann S. (1989a) (Document A40662)
B.2.1.18 Dissociation constant (pKa) (IIA 2.9.4)	Calculation from the rate constants of the abiotic hydrolysis	pK_A = 3.58	Acceptable	Goerlitz G. (1992o) (Document A48868)
B.2.1.19 Stability in air, photochemical oxidative degradation (IIA 2.10)	Atkinson calculation	An estimation of the photochemical-oxidative degradation of amidosulfuron in the atmosphere has been conducted according to the method of Atkinson. Overall OH-radical reaction rate constant: $K_{OH} = 63 \times 10^{-12}$ cm^3 molecule^{-1} s^{-1} t½ = 0.25 days ((OH) = $5 \cdot 10^5$ molecule/cm³)	Acceptable For details see B 8.4 Fate and behaviour in water	Rose (1993b) (Document C002027)

Property (Annex point as reference to the DAR)	**Method**	**Results**	**Conclusion/Comment**	**Reference (Study)**
B.2.1.20 Flammability (IIA 2.11)	92/69/EEC/A10 GLP	Technical product (purity: 99.6% w/w) The result of the preliminary screening test was: after ignition of the test substance the flame propagated only for 40 respectively 45 seconds and extinguished before reaching the endpoint. According EEC/A10 no further testing was required.	Acceptable Technical amidosulfuron is not considered as “highly flammable” under test condition	Hoffmann H. (1998m) (Document C001016)
B.2.1.21 Auto-flammability (IIA 2.11.2)	92/69/EEC/A16 GLP	Technical product (purity: 99.6% w/w) No self ignition up to 402°C	Acceptable Compound is not considered as auto-flammable under test condition	Hoffmann H. (1998n) (Document C001017) Franke J. (2005) (Document C046700)
B.2.1.22 Flash point (IIA 2.12)			Not applicable as the melting point is > 40°C	
B.2.1.23 Explosive properties (IIA 2.13)	92/69/EEC/A14 GLP	Technical product (purity: 99.6% w/w) Thermal sensitivity test: no explosion after 5 minutes (nozzle diameter: 2.0 mm) Shock test: no explosion occurred within 6 tests using a mass of 10 kg from a height of 0.4 m Friction test: no explosion occurred within 6 tests using a 360 N loading	Acceptable Technical amidosulfuron does not present a danger of explosion under test condition	Hoffmann H. (1998o) (Document C001018)
B.2.1.24 Surface tension (IIA 2.14)	OECD 115 GLP	Technical product (purity: 99.0% w/w) σ = 66.2 mN/m at 20°C c = 8.1 mg/L (90% of the water solubility of 9 mg/L)	Acceptable Method OECD 115 is equivalent to EEC/A5 The compound is not surface active	Franke J. (2001a) (Document C018325)

Property (Annex point as reference to the DAR)	**Method**	**Results**	**Conclusion/Comment**	**Reference (Study)**
B.2.1.25 Oxidising properties (IIA 2.15)	84/449/EEC/A17 Statement	Technical product (purity: 93.0% w/w) The notifier stated that technical amidosulfuron has no oxygen compound which might have oxidising effects on combustible compounds	Acceptable Amidosulfuron is not considered as an oxidant and does not have oxidising properties according test EEC/A17	Klais O., Rexer K. (1994ac) (Document A52702)

[1)] *analog GLP* means that in the laboratory conducting the study, GLP was implemented prior to 1990, but no certificate was available to this date, because no GLP – authority inspections were conducted before German Chemical Act of 1990 came into force.

According to Directive 91/414/EEC, granulometry is not required for active substances. Thus, no study considering this end-point has been provided. In addition, no study on stability in organic solvents and the identity of relevant degradation products have been provided for the evaluation of Annex I inclusion (Directive 91/414/EC) of the active substance amidosulfuron. Shelf live studies of the formulation containing amidosulfuron have been submitted showing that the contents of the active ingredient and the relevant physical chemical properties remained stable, after storage for 2 years at ambient temperature (the relevant study is described in the DAR, Volume 3, Annex B 2 physical chemical properties, B.2.2.17, *Kocur et at, 1996b; Helgers, 2005*). A summary is given below:

B.2.2.17 Shelf life (IIIA 2.7.3)				No significant reduction of active substance and no major changes of the tested physical properties after 2 years of storage	Kocur J., Rexer K. (1996b) (Document A56105) Helgers A. (2005) (Document C048203)
		Test	**initial**	**after 2 years at room temperature**	
	AL 33/88-0	content a.i.	77.4 % (w/w)	77.6 % (w/w)	Acceptable
	Visual estimation	appearance	beige coloured, free flowing granule	beige coloured, free flowing granule	Acceptable
	CIPAC MT 75	pH	4.5 (1%)	4.5 (1%)	Acceptable
			4.6 (10%)	4.8 (10%)	Acceptable

CIPAC MT 31.2 calculated as sulfuric acid	acidity	0.9 %	1.1 %	Acceptable
CIPAC MT 168 2.5 g suspended in 250 ml water of 342 mg/kg hardness	suspensibility	87 %	88 %	Acceptable
CIPAC MT 167	wet sieving	<0.1 % residue on a 125 micron sieve	<0.1 % residue on a 125 micron sieve	Acceptable
		<0.1 % residue on a 75 micron sieve	<0.1 % residue on a 75 micron sieve	Acceptable
CIPAC MT 53.3.1	wettability	at once	at once	Acceptable
CIPAC MT 174 c = 10 g/L	dispersibility	96 %	93 %	Acceptable
CIPAC MT 47.2 0.1% in water of 500 mg/kg hardness	persistent foam	< 60 mL after one minute	< 60 mL after one minute	Acceptable
		35 mL after 12 minute	40 mL after 12 minute	Acceptable
CIPAC MT 171 electronic dust-measuring apparatus	dustiness	0.4 optical dust factor (nearly dust-free)	0.4 optical dust factor (nearly dust-free)	Acceptable

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for Classification and Labelling.

2.2 Identified uses

Amidosulfuron is used as herbicide in agriculture and grassland.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Amidosulfuron pure and technical active substance is a fine white powder partially agglomerated to smooth lumps with slightly acidulous odour.

The melting point is 179 °C for the technical substance (99.3 % w/w). Decomposition starts at 185 °C. The relative density determined at 24.5 °C is 1.51. The vapour pressure of the active substance is low (1.3 x 10-5 Pa at 20 °C). The Henry´s constant was calculated to be 1.56 x 10-6 Pa·m³·mol-1 at pH 7 and 20°C. The IR-, MS- and NMR-spectra are in agreement with the chemical structure.

Solubility values in water are 9.2 mg/L at pH 4 , 3.07 g/L at pH 7 and 7.10 g/L at pH 9, all measured at 20 °C. The test substance is moderately or readily soluble in acetone, dichloromethane and ethyl acetate and slight solubility was observed in n-hexane, toluene and isopropanol. The log Pow of 1.07 (at pH 4 and 23 °C), -1.56 (at pH 7 and 22 °C) and -2.21 determined at pH 9 and 23 °C indicates that amidosulfuron has no potential for bioaccumulation. The pKa value is 3.58.

The active substance is not highly flammable, auto-flammable or explosive and has no oxidising properties.

Based on the information/studies provided, no classification for physico-chemical properties is required.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Adsorption, distribution, metabolism, excretion:
Absorption: Based on the results of single oral administrations to rats at dose levels of 10, 100 and 500 mg/kg bw/day, radiolabelled amidosulfuron is absorbed to a great extent. The urinary excretion (including cage wash) after 168 hours of administration was 82.4 – 91.4 % of administered dose after gavage application; after oral administration of 500 mg/kg bw/d to male rats via diet, the amount of radioactivity found in urine was 79.6 %. As faecal excretion occurred at a measurable rate for at least 168 hours after dosing (all oral studies provided), a biliary excretion of the compound can be suggested. As a result of an ADME study after intravenous administration, faecal excretion was shown to be in the range of faecal excretion after oral administration indicating a biliary excretion of the compound as well. The **enteral resorption** after oral administration can

therefore be assumed to be greater than the amount excreted via urine and is **> 80 %** of the administered dose.

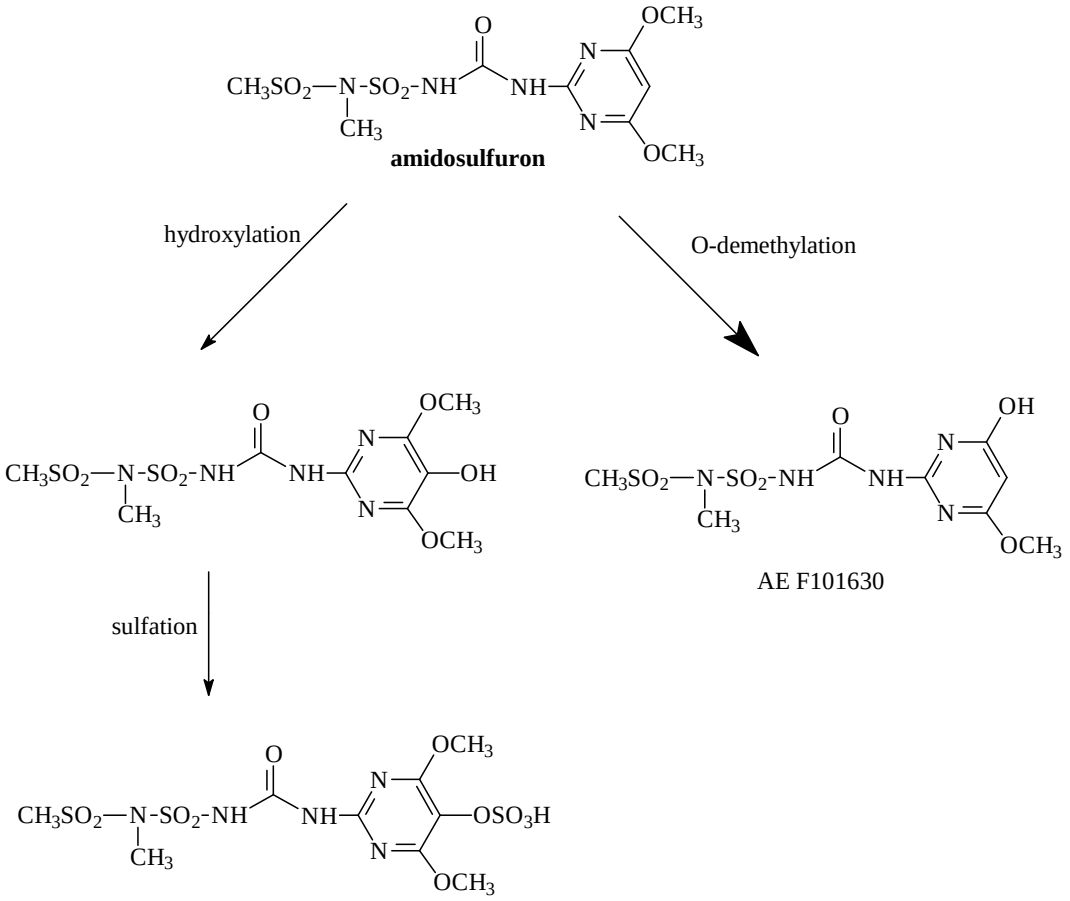
Pharmacokinetic parameter: The maximum whole blood level after oral administration of the test substance via gavage was reached after 0.3 – 1.0 hours (T_{max}); this value was slightly different after application of the test substance via diet (4.5 hours). The initial rapid elimination phase observed in blood (when most of the radioactivity was excreted) showed half lives of 1.0 – 1.89 hours. The longer terminal phase ($t_{1/2}$: 15.3 – 95.8 hours) accounted only for a small portion of the applied dose to be eliminated. After application of the test substance via diet, longer half lives of 3.16 and 130.9 hours were derived, showing influence of the different dosing regimes (gavage; via diet). No sex dependency could be observed with the exception of one terminal half live, that was rather short (15.3 hours) and could be explained by radioactivity levels in blood to be < LOD after 168 hours. Plasma results were very similar to the results obtained for the whole blood.

Distribution: Following oral administration of the radiolabelled test substance, radioactivity found in selected tissues and organs was rather low: after low dose administration (10 mg/kg bw), mean radioactivity residues ranged between <0.001 µg/g and 0.004 µg/g (tissues with detectable residues were lung, heart, retroperitoneal fat, skeletal muscle, blood, ovary) and after high dose application (500 mg/kg bw) between <0.01 µg/g and 0.59 µg/g (lung, heart, retroperitoneal fat, skeletal muscle, blood, plasma, subcutaneous fat, spleen, liver). Intravenous administration resulted in very low tissue residues: radioactivity above the limit of detection was found in lung, blood and spleen only. After 14 administrations of the test substance, the radioactivity found in tissues was higher only in a low extent compared to one oral application. 8 days after 14 daily oral administrations (depletion phase), no radioactivity could be detected in any tissues investigated except with low residues found in subcutaneous fat (males and females: 0.004 – 0.007 µg/g), blood (males and females: 0.043 µg/g), plasma (0.007 µg/g; females only) and kidneys (0.013 µg/g; females only). The plateau level (highest radioactive residues) in subcutaneous fat was reached after 4 oral administrations. Based on the results of the repeated dose study and considering the rate and extension of excretion and the rather short half live for elimination of the test substance, **no potential of bioaccumulation** can be assumed.

Excretion: After oral application of radioactive labelled amidosulfuron (all dose levels tested), the major route of excretion was via urine (80 – 90 % of administered radioactivity); faeces contained 5 – 10 %. >84 % of the applied radioactivity was excreted within 24 hours, showing a rapid elimination via urine and faeces. As faecal excretion occurred at a measurable rate for at least 168 hours after dosing and radioactivity was found in faeces after intravenous application of the test substance as well, a biliary excretion of the compound can be assumed. Repeated dosing did not show any impact on the rate and extent of excretion.

Metabolism: Metabolic investigation shows that unchanged parent was the main component in excreta samples (61.9 – 87.1 % of administered radioactivity). As main metabolit O-desmethyl amidosulfuron could be detected ranging from 8.0 – 29.4 % of applied radioactivity. Hydroxylation of the parent compound was identified to be a minor pathway of metabolism: the corresponding metabolite (ring hydroxylated amidosulfuron) was found in excreta (urine only) to be less than 1 % of administered radioactivity. Furthermore, in one metabolism study the sulphate conjugate of hydroxylated amidosulfuron has been detected.

Proposed metabolic pathway of amidosulfuron in mammals:



Dermal absorption: No study has been provided from the notifier with respect to the dermal absorption rate. According to "Guidance Document on Dermal Absorption, Sanco/222/2000 rev. 6", the dermal absorption rate can be derived based on physical and chemical properties (log $P_{O/W}$ as well as MG) in the absence of studies performed in the penetration rate. The relevant physical and chemical properties of amidosulfuron are presented below:

Table 10: Physico - chemical endpoints relevant for dermal absorption

Physical/chemical endpoint	Value	Conclusion with respect to dermal absorption
Partition coefficient n-octanol/water	log $P_{O/W}$ = 1.07 at pH 4/23 °C log $P_{O/W}$ = -1.56 at pH 7/22 °C	Log $P_{O/W}$ between -1 and 4/ < -1
Molecular mass	369.41	MG < 500

Based on these physical/chemical properties of amidosulfuron, a dermal absorption of 100 % would be applicable; however the results of the ADME studies provided show an enteral absorption rate of 80 % and can be used for refinement of the dermal absorption rate. It can assumed, that the dermal absorption will not exceed the enteral absorption. Based on these assumptions, a dermal absorption rate of 80 % (default value) would be appropriate.

4.1.2 Human information

No data available.

4.1.3 Summary and discussion on toxicokinetics

Absorption, distribution, excretion and metabolism (toxicokinetics)

Rate and extent of oral absorption	Rapid and almost complete-enteral absorption: >90% (based on urinary and assumed biliary excretion within 24 hours)
Distribution	Widely distributed; low radioactivity residues Mainly in lung, heart, fat, skeletal muscle, blood, plasma, spleen, liver
Potential for accumulation	No potential for accumulation
Rate and extent of excretion	Rapid-and mainly via urine (79.6 – 91.4 %)
Metabolism in animals	Poorly metabolised (> 60 % excreted as parent) Major metabolic pathway: O-demethylation of amidosulfuron; minor pathway: hydroxylation of parent and sulphate conjugation

After oral administration, the maximum blood concentration was reached 0.3-1.0 h after gavage and 4.5h after dietary administration. There is no potential for bioaccumulation. The excretion occurred mainly via urine (80-90% within 24h), but also via faeces (5-10% within 24h) with biliary excretion shown after intravenous administration. The enteral resorption was therefore assumed to be greater than the amount excreted via urine (>90%).

The metabolism was not extensive; the unchanged parent was the main component in excreta samples (up to 87%). The major metabolic pathway was O-desmethylation and minor pathways were hydroxylation and sulphate conjugation.

It can assumed, that the dermal absorption will not exceed the enteral absorption. Based on these assumptions, a dermal absorption rate of 80 % (default value) would be appropriate.

4.2 Acute toxicity

Table 11: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
Acute oral toxicity (according to US EPA Pesticide Assessment Guidelines, Subdivision F, § 81-1 and in compliance with GLP)	♂/♀ LD_{50} > 5000 mg/kg bw	Wistar rat, Purity 97.7%	Diehl & Leist, 1987(a)
Acute oral toxicity (OECD 401)	♂/♀ $LD_{50} \geq$ 5000 mg/kg bw	NMRI mouse Purity 97.1%	Diehl & Leist, 1988*(a)*
Acute dermal toxicity (according to US EPA Pesticide Assessment Guidelines, Subdivision F, § 81-2 and in compliance with GLP)	♂/♀ LD_{50} > 5000 mg/kg bw	Wistar rat Purity 97.7%	Diehl & Leist, 1987*(b)*
Acute inhalative toxicity (OECD 403)	♂/♀ LC_{50} > 1.8 mg/l air (technically highest administrable dose)	SPF Wistar rat, 4 hours nose only dust inhalation Purity 97.1%	Hofmann & Jung, 1988
Acute intraperitoneal toxicity (according to US EPA Pesticide Assessment Guidelines, Subdivision F, § 81-1 and in compliance with GLP)	♂/♀ 1000 <LD_{50} < 2000 mg/kg bw	Wistar rat Purity 95.7%	Diehl & Leist, 1987(e)

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Rat:

No mortality occurred after administration of 5000 mg/kg bw. Squatting position, high-legged gait, contracted flanks, reduced spontaneous activity, piloerection and irregular breathing were observed in males and females. These signs persisted up to the 2nd day after treatment in males and up to the 8th day after treatment in females. There was complete recovery in all rats by day 9. No treatment related effects on body weight gain were observed. Macroscopic examination showed kidneys with dark patches in one animal (male). All other animals were free of macroscopically visible changes.

The LD_{50} is higher than 5000 mg/kg bw in male and female rats.

Mouse:

One male animal (out of five) each died after administration of 4000 mg/kg bw and 5000 mg/kg bw, resp. Three female animals out of five were found dead after gavage of 5000 mg/kg bw (one female died on the 8th day after treatment, possibly as a result of a traumatic or infectious swelling of the

right front limp). Squatting position, high-legged gait, contracted flanks, reduced spontaneous activity, uncoordinated gait, ataxic gait, jerky breathing, increased respiratory rate, irregular breathing, abnormal respiratory sounds, blood crusted eye margins, narrowed palpebral fissures, lacrimation, trembling and poor general condition were observed in males and females. These signs persisted up to the 8th day after treatment. No treatment related effects on body weight gain were observed. Macroscopic examination of all animals died/killed during or at the end of the study showed no visible changes.

The LD_{50} is higher than 5000 mg/kg bw in male rats. For females, the LD_{50} could be calculated to be in the range of 5000 mg/kg bw: the death of one female (highest dose group) was not considered to be treatment related and therefore not taken into consideration for the estimation of the LD_{50} value.

RAC evaluation of acute oral toxicity
Summary of dossier submitter's proposal   The dossier submitter proposed not to classify Amidosulfuron for acute oral toxicity.
Comments received during public consultation   Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation   Not needed.
Outcome of RAC assessment - comparison with criteria and justification   Amidosulfuron has a low acute oral toxicity in rats and mice. The lowest LD50 reported was calculated to be in the range of 5000 mg/kg (female mice). Oral LD50 values need to be lower than 2000 mg/kg in order to classify a substance for acute oral toxicity (both CLP and DSD).   Thus RAC as well proposes not to classify Amidosulfuron for acute oral toxicity
Extended analysis of the key studies provided by the dossier submitter   Not needed.

4.2.1.2 Acute toxicity: inhalation

No mortality occurred under the condition of the study. Irregular breathing, high-legged and uncoordinated gait, piloerection, narrowed palpebral fissures and nasal discharge were observed for males and females. These signs persisted up to the 1st day after treatment. No treatment related effects on body weight gain were observed in both the males and the females. Macroscopic examination showed no macroscopically visible changes.

The acute inhalative LC_{50} is higher than 1.8 mg/l air in male and female rats (4 hours exposure to dust via nose-only inhalation). At 1.8 mg/l air no mortality occurred. 1.8 mg/l air was reported to be the technically highest administrable dose.

RAC evaluation of acute toxicity by inhalation
Summary of dossier submitter's proposal The dossier submitter proposed not to classify Amidosulfuron for acute toxicity by inhalation.
Comments received during public consultation Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation Not needed.
Outcome of RAC assessment - comparison with criteria and justification Amidosulfuron was tested for acute inhalative toxicity in rats. The test concentration of 1.8 mg/l air was reported to be the highest concentration that could technically be administered. At this air-borne concentration of 1.8 mg/l there was no mortality in exposed rats. Some unspecific clinical effects were reported. LC50 values need to be lower than 5 mg/l air in order to classify a substance (dust) for acute inhalative toxicity (both CLP and DSD). Because there was no lethality at the tested air-borne concentration of 1.8 mg/l RAC as well proposes not to classify Amidosulfuron for acute toxicity by inhalation.
Extended analysis of the key studies provided by the dossier submitter Not needed

4.2.1.3 Acute toxicity: dermal

No mortality occurred after administration of 5000 mg/kg bw to 5 rats/sex. Squatting position, contracted flanks, reduced spontaneous activity and irregular breathing were observed in males and females. These signs persisted up to the 9th day after treatment. No treatment related effects on body weight gain were observed in the males. The body weight gains of the females were impaired during the first week of the study. Macroscopic examination showed kidneys with dark patches in three animals of each sex. All other animals were free of macroscopically visible changes.

The LD_{50} is higher than 5000 mg/kg bw in male and female rats.

RAC evaluation of acute dermal toxicity
Summary of dossier submitter's proposal The dossier submitter proposed not to classify Amidosulfuron for acute dermal toxicity.
Comments received during public consultation Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation Not needed.
Outcome of RAC assessment - comparison with criteria and justification Amidosulfuron has a low acute dermal toxicity in rats. No mortality occurred after dermal application of 5000 mg/kg. Dermal LD50 values need to be lower than 2000 mg/kg in order to classify a substance for acute dermal toxicity (both CLP and DSD). Thus RAC as well proposes not to classify Amidosulfuron for acute dermal toxicity.
Extended analysis of the key studies provided by the dossier submitter Not needed

4.2.1.4 Acute toxicity: intraperitoneal

No mortality occurred after administration of 1000 mg/kg bw in 5 rats/sex. After application of 2000 mg/kg bw, all animals tested died on the day of administration. Reduced spontaneous activity, contracted flancs, uncoordinated gait, squatting position, high legged gait, ataxic gait, prone or lateral position, tonoclonic spasms, drowsiness and negative. placing reflex were observed. From the first day after treatment onwards, these clinical signs were reversible in the survivors. No treatment related effects on body weight gain were observed. Macroscopic examination of all animals found dead showed liver and kidneys light in colour as well as abdominal cavity filled with test substance and solvent. Some of the animals killed at termination (2/5 of the 1000 mg/kg bw group and 4/5 of the 2000 mg/kg bw group) exhibited adhesions of liver lobes, and white deposit on liver and spleen.

The LD_{50} after interperitoneal administration was shown to be between 1000 and 2000 mg/kg bw for males and femals.

4.2.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.2.3 Summary and discussion of acute toxicity

Amidosulfuron has low oral acute toxicity in rats and mouse, and low dermal and inhalative toxicity in rats (oral LD_{50} > 5000 mg/kg bw, dermal LD_{50} > 5000 mg/kg bw, LC_{50} > 1.8 mg/L air

(technically highest administrable dose)).After intraperitoneal administration in rats LD_{50} was between 1000 and 2000 mg/kg bw/d.

4.2.4 Comparison with criteria

All estimated LD_{50} and LC_{50} values are above the criteria for triggering classification and labelling (both DSD and CLP).

4.2.5 Conclusions on classification and labelling

No classification and labelling is proposed for amidosulfuron regarding acute toxicity.

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

No specific, non lethal, target organ toxicity after single exposure was observed in acute toxicity studies. The observed effects in acute toxicity studies covered mostly clinical signs like squatting position, high-legged gait, contracted flanks, reduced spontaneous activity, piloerection and irregular breathing. In addition, no human data are available that would support classification for this endpoint. No classification as STOT-SE under the CLP Regulation is proposed.

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

No specific target organ toxicity after single exposure was observed in acute toxicity studies. No acute neurotoxicity studies are provided.

4.3.2 Comparison with criteria

No effects observed in acute toxicity studies would trigger criteria for classification and labelling STOT SE.

4.3.3 Conclusions on classification and labelling

No classification and labelling is proposed for amidosulfuron regarding specific target organ toxicity after single exposure.

RAC evaluation of specific target organ toxicity / single exposure
Summary of dossier submitter's proposal The dossier submitter proposed not to classify Amidosulfuron for specific target organ toxicity / single exposure.
Comments received during public consultation Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation Not needed.
Outcome of RAC assessment - comparison with criteria and justification The observed effects in acute toxicity studies mostly covered clinical signs like e.g. squatting position, high-legged gait, contracted flanks, reduced spontaneous activity, piloerection and irregular breathing. These clinical signs are not considered to be the consequence of a specific non-lethal target organ toxicity. Thus RAC as well proposes not to classify Amidosulfuron for specific target organ toxicity / single exposure.
Extended analysis of the key studies provided by the dossier submitter Not needed

4.4 Irritation

4.4.1 Skin irritation

Table 12: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
Skin irritation (according to US EPA Pesticide Assessment Guidelines, Subdivision F, § 81-5 and in compliance with GLP)	Not irritating	Rabbit, Purity: 97.1%	Diehl & Leist, 1987(b)

4.4.1.1 Non-human information

No sign of irritation (oedema, erythema) could be noted at any time of examination; no signs of systemic toxicity were observed. Amidosulfuron showed a primary irritation score of 0.00 after application to intact rabbit skin.

According to the results of the study, amidosulfuron is not irritant to the intact shaved rabbit skin.

4.4.1.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.4.1.3 Summary and discussion of skin irritation

According to the results of the rabbit skin irritation study, amidosulfuron is not irritant to the intact shaved rabbit skin.

4.4.1.4 Comparison with criteria

Estimated skin irritation scores (0.00) are below the criteria for triggering classification and labelling (according to both DSD and CLP).

4.4.1.5 Conclusions on classification and labelling

No classification and labelling is proposed for amidosulfuron regarding skin irritation.

RAC evaluation of skin irritation
Summary of dossier submitter's proposal The dossier submitter proposed not to classify Amidosulfuron for skin irritation.
Comments received during public consultation Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation Not needed.
Outcome of RAC assessment - comparison with criteria and justification Amidosulfuron was tested for skin irritation in rabbits. No signs of irritation could be noted in exposed animals at any time of the examination. Thus RAC as well proposes not to classify Amidosulfuron for skin irritation.
Extended analysis of the key studies provided by the dossier submitter Not needed

4.4.2 Eye irritation

Table 13: Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference
Eye irritation (according to US EPA Pesticide Assessment Guidelines, Subdivision F, § 81-4 and in compliance with GLP)	Not irritating	Rabbit Purity: 97.7%	Diehl & Leist, 1987(c)

4.4.2.1 Non-human information

In the *eyes washed out after 1 minute* of exposure, only one animal out of three showed markedly injected conjunctival blood vessels (one hour after application only).

In the *eyes washed after 24 hours* of instillation, the following lesions could be observed: During the first 72 hours observation period, animals showed slight chemosis; redness of conjunctivae has been observed during 48 hours (marked injection of the vessels to diffuse crimson colouring, whereby individual vessels were not easy to discern). The iris of one animal showed 24 hours after treatment redness, but reaction to light was still possible. The signs of irritation were accompanied by slight discharge with moistening of the lids and hairs adjected to the lids. No effects on cornea could be observed.

7 days after application of the test substance, all signs of irritation did recede.

Mean scores (24 – 72 hours) in the 6 animals were 0.6 (conjunctival chemosis), 0.5 (conjunctival redness), 0.06 (inflammation of iris) and 0.0 (cornea: degree of opacity). With respect to EEC classification criteria outlined in Directive 93/21/EEC, the individual findings are summarised in the following table (eyes washed 24 hours after instillation):

Table 14: Summary of eye irritation scores

	Time after application			
	24 hours	48 hours	72 hours	
Animal No.	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	Mean score*
Conjunctivae				
chemosis	0 1 0 1 1 1	0 0 0 1 1 1	0 0 0 1 1 1	0.6
redness	0 1 0 2 1 1	0 1 0 1 1 1	0 0 0 0 0 0	0.5
Inflammation of iris	0 0 0 1 0 0	0 0 0 0 0 0	0 0 0 0 0 0	0.06
Cornea				
degree of opacity	0 0 0 0 0 0	0 0 0 0 0 0	0 0 0 0 0 0	0.0

* Mean score of all animals and all observation times (24, 48 and 72 hours)

According to the results of the study, amidosulfuron is slight irritant to the rabbit eye; according to classification criteria, classification and labelling is not warranted.

4.4.2.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.4.2.3 Summary and discussion of eye irritation

According to the results of the eye irritation study, amidosulfuron is slight irritant to the rabbit eye; according to classification criteria, classification and labelling is not warranted.

4.4.2.4 Comparison with criteria

Estimated eye irritation scores (24 – 72 hours; 0.6 (conjunctival chemosis), 0.5 (conjunctival redness), 0.06 (inflammation of iris) and 0.0 (cornea: degree of opacity)) are below the criteria for triggering classification and labelling (according to both DSD and CLP).

4.4.2.5 Conclusions on classification and labelling

No classification and labelling is proposed for amidosulfuron regarding eye irritation.

RAC evaluation of eye irritation
Summary of dossier submitter's proposal The dossier submitter proposed not to classify Amidosulfuron for eye irritation.
Comments received during public consultation Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation Not needed.
Outcome of RAC assessment - comparison with criteria and justification Amidosulfuron was tested for eye irritation in rabbits. The results of the study indicate slight irritating effects (conjunctivae and iris). No effects on cornea could be observed. All signs of irritation did recede by day 7 after application of the test substance. For the conjunctivae (chemosis and redness) the individual mean scores (24-72 hours) did not exceed the score of 1. The minimum individual score for conjunctival effects that trigger classification is the score of 2 (both CLP and DSD). There was one animal with an iris score of 1 at 24 hours; thus for the iris the minimum score for classification of 1 is not reached at all. Thus RAC as well proposes not to classify Amidosulfuron for eye irritation.
Extended analysis of the key studies provided by the dossier submitter Not needed

4.4.3 Respiratory tract irritation

Table 15: Summary table of relevant respiratory tract irritation studies

Method	Results	Remarks	Reference
Acute inhalation toxicity study (OECD 403)	No irritation of respiratory tract	SPF Wistar rat, 4 hours nose only dust inhalation Purity 97.1%	Hofmann & Jung, 1988
Subchronic inhalation toxicity (OECD 412)	No irritation of respiratory tract	SPF Wistar rat Purity 95.5%	Hofmann & Bube, 1992

4.4.3.1 Non-human information

Acute inhalation toxicity study (rat)

No mortality occurred under the condition of the acute inhalation toxicity study up to 1.8 mg/l air (technically highest administrable dose). Only clinical signs like irregular breathing, high-legged and uncoordinated gait, piloerection, narrowed palpebral fissures and nasal discharge were observed for males and females. No treatment related effects on body weight gain were observed in both the males and the females. Macroscopic examination showed no macroscopically visible changes. No signs of irritation on respiratory tract were observed.

Subchronic inhalation toxicity study (rat) *(Hofmann & Bube, 1992)*

Material and Methods:

Groups of 15 male and 15 female rats were exposed nose only to a dust aerosol of amidosulfuron (95.5% purity) at concentrations of 0, 0.04, 0.2 or 1 mg/L air for 6 hours/day on 5 days/week for a total of 21 exposures within 29 days. Ten males and females were killed at the end of the final exposure and necropsied whilst the remaining animals were killed and necropsied after a 29-day treatment free recovery period. The 0.04 mg/L dose group consisted of 10 animals only and recovery was not investigated in this dose group. At the start of the preliminary study phase rats were approximately 5 to 6 weeks old and weighed 150 to 168 g (males) and 162 to 174 g (females). Animals were acclimatised for ca. 5 days under test conditions.

All animals were observed at least daily for general health and clinical symptoms. Food consumption and body weights were recorded twice weekly and water consumption once per week. Ophthalmoscopic examinations were conducted prior to the start of and towards the end of treatment. Blood samples were collected at the end of the treatment and recovery periods for clinical chemistry and haematology. Urinalysis was conducted towards the end of treatment. All animals were killed and necropsied, major organs were weighed and all macroscopic and microscopic abnormalities recorded.

Test substance formulations were chemically analysed for homogeneity and accuracy of the preparation.

Findings:

The actual analytical concentrations of the formulations were 0.041, 0.18 and 0.96 mg/L air for the 0.04, 0.2 and 1 mg/l air groups, respectively. Particle distribution analysis showed the mean percentage of particles of < 3 µm was 56.7 - 67.9%, indicating a moderately high respirable fraction.

There was no mortality and no treatment related changes in animal behaviour or general condition. Irregular respiration and blood coloured encrusted noses were observed in all dose groups and control animals, without any dose response. Animals exposed to amidosulfuron showed narrowed palpebral fissures but this was considered to be a non specific reaction, since this symptom was observed in control animals as well. Body weight gain and food and water consumption remained unaffected by treatment.

No dose-dependant effects in haematology, clinical chemistry, urine analysis and ophthalmoscopic examination and organ weight analysis were observed. The histopathological examination revealed accumulations of macrophages in the lungs of some animals in all dose groups, without any dose-response (please see table below). No signs of irritation on respiratory tract were observed.

Table 16: Incidences of the macrophages in the lungs

Dose groups	**Incidences of foci of macrophages**			
	Animals sacrificed after final exposure		**Animals sacrificed after recovery period of 29 days**	
	males	**females**	**males**	**females**
Control	0(10)	0(10)	0(5)	0(5)
0.04 mg/l	0(10)	1(10)	Not investigated	Not investigated
0.2 mg/l	2(10)	0(10)	1(5)	0(5)
1 mg/l	1(10)	3(10)	0(5)	1(5)

Conclusion:

The NOAEC for systemic effects was 1.0 mg/L air (equivalent to a NOAEL of 270 mg/kg bw/day calculated from an estimated expiry volume of 45 L/kg bw/h for 6 hour exposure).

4.4.3.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.4.3.3 Summary and discussion of respiratory tract irritation

No respiratory tract irritation was observed, neither in acute inhalation toxicity study in rats nor in subchronic inhalation toxicity study with 21 applications within 29 days.

4.4.3.4 Comparison with criteria

No irritating effects on respiratory tract were observed neither in acute nor in subchronic inhalation studies with amidosulfuron (according to both DSD and CLP).

4.4.3.5 Conclusions on classification and labelling

No classification and labelling is proposed for amidosulfuron regarding respiratory tract irritation.

RAC evaluation of respiratory tract irritation
Summary of dossier submitter's proposal The dossier submitter proposed not to classify Amidosulfuron for respiratory tract irritation.
Comments received during public consultation Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation Not needed.
Outcome of RAC assessment - comparison with criteria and justification There is no human evidence for respiratory tract irritation. In addition, no irritating effects on the respiratory tract were observed in the acute and subchronic rat inhalation studies. Thus RAC as well proposes not to classify Amidosulfuron for respiratory tract irritation.
Extended analysis of the key studies provided by the dossier submitter Not needed

4.5 Corrosivity

Amidosulfuron did not show any corrosive properties in rabbit skin and eye irritation studies (see 4.4.1 and 4.4.2).

4.6 Sensitisation

4.6.1 Skin sensitisation

Table 17: Summary table of relevant skin sensitisation studies

Method	Results	Remarks	Reference
Skin sensitization, Maximisation test (according to US EPA Pesticide Assessment Guidelines, Subdivision F, § 81-6, OECD guideline 406)	Not a skin sensitiser	Guinea pig Purity: 95.7%	Diehl & Leist, 1987(d)
Skin sensitization Maximisation test (according to US EPA OPPTS 870.2600 Guideline, OECD guideline 406 (1992) and in compliance with GLP)	Not a skin sensitiser	Guinea pig Purity: 99.0%	Pelcot 2003

4.6.1.1 Non-human information

1. study (Diehl & Leist, 1987(d))

In the preliminary test, no signs of irritation were observed after application of the test concentrations (50, 10 and 2 %). As treatment of the animals with Freund´s Adjuvant can lower the threshold for irritation, 5 additional animals which had been treated with Freund´s Adjuvant were treated with a 50 % solution of amidosulfuron. 48 and 72 hours after application, one animal showed slight erythema. For this reason, the 10 % amidosulfuron solution was selected for the challenge treatment.
For the tolerance of intradermic administration, injections with 5, 1 and 0.2 % amidosulfuron caused slight redness and swelling; a 1 % preparation was therefore selected for the intradermic induction in the main test.

In the main test, no clinical signs of intoxication could be observed. The intradermic injections with Freund`s Adjuvant caused moderately severe to severe erythema, very slight to slight oedema and formation of necrosis.
24 and 48 hours after removal of the occlusive bandage (challenge phase), none of the animals showed any signs of irritation on the treated skin areas.

Table 18: Summary of results of sensitisation study

		Control and escort					Treated				
Time after intradermal induction (hour)		**24**	**48**	**72**	**96**	**120**	**24**	**48**	**72**	**96**	**120**
Site 1: 50% FA	Erythema	3	3	2	2	2	3	3	2	2	2
	Oedema	1	2	2	2	2	1	1	2	2	2
Site 2: Paraffin or 1% amidosulfuron in paraffin	Erythema	1	1	1	1	1	2	1	1	1	1
	Oedema	1	1	1	1	1	1	1	1	1	1
Site 3: 50% FA or 1% amidosulfuron in 50% FA	Erythema	2	2	2	2	2	2	3	2	2	2
	Oedema	1	2	2	2	2	1	2	2	2	2
Presence of necrosis (P)		-	-	-	-	-	-	-	-	P	P

According to the results of the study, amidosulfuron is non-sensitizing to guinea pig skin after dermal application.

2. study (Pelcot 2003)

In the preliminary test, irritation was observed after injection of all concentrations tested (0.01, 0.05, 0.1, 0.5 and 1 % amidosulfuron in corn oil) 24 and 48 hours after application. It was stated in the report, that 1 % was the maximum concentration that could pass through a needle and into the dermis. Topical administration of amidosulfuron showed discrete erythema at a concentration of 50 % and no visible changes at a concentration of 25 %. Based on the results of the preliminary study, 1 % was chosen for intradermic administration, 50 % for the dermal induction phase and 25 % for the challenge phase.

In the main test, a discrete erythema (grade 1) was observed in 2/10 *control animals* after 24 hours that persisted in 1/10 animals up to 48 hours as well as dryness of the skin noted in 3/10 animals at the 48 hours reading (2/10 on the left flank receiving the vehicle only and 1/10 on the treated flank).

For the *treated animals*, discrete erythema (grade 1) was noted in 3/20 animals at the 24 hours reading, that persisted in 1/20 animals up to 48 hours after challenge. In 8/20 animals (3/20 on the left flank receiving vehicle only and 6/20 on the treated flank) dryness of skin was observed.

As 3/20 animals (15 %) showed skin reactions (discrete erythema, grade 1) and the incidence and severity of these reactions compared to control animals as well as to the left flank of the treated animals receiving vehicle only (with respect to dryness of skin) are similar, the skin reactions were attributed to the irritant properties of the test item (vehicle: acetone). Therefore, according to the results of the study, amidosulfuron is non-sensitising to guinea pig skin.

4.6.1.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.6.1.3 Summary and discussion of skin sensitisation

According to the results of two skin sensitisation studies in guinea pig (Maximisation tests), amidosulfuron is not sensitising to guinea pig skin; according to classification criteria, classification and labelling is not warranted.

4.6.1.4 Comparison with criteria

Effects observed in two skin sensitisation studies on guinea pig are below the criteria for triggering classification and labelling (according to both DSD and CLP).

4.6.1.5 Conclusions on classification and labelling

No classification and labelling is proposed for amidosulfuron regarding skin sensitisation.

RAC evaluation of skin sensitisation
Summary of dossier submitter's proposal The dossier submitter proposed not to classify Amidosulfuron for skin sensitisation
Comments received during public consultation Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation Not needed.
Outcome of RAC assessment - comparison with criteria and justification For Amidosulfuron the results of two valid guinea pig maximisation tests are available. In the first study none of the 20 test animals showed any signs of irritation on the treated skin areas (challenge phase). In the second study 3/20 test animals showed skin reactions. However, incidence and severity of these reactions were similar in control animals and in those test animals receiving vehicle (acetone) in the chalenge phase alone. Thus there is no clear sensitising potential in the second study as well. Because test results from a GPMT need to exceed a 30% incidence level RAC as well proposes not to classify Amidosulfuron for skin sensitisation (CLP and DSD).

Extended analysis of the key studies provided by the dossier submitter
Not needed

4.6.2 Respiratory sensitisation

No data on respiratory sensitisation available.

4.7 Repeated dose toxicity

Table 19: Summary table of relevant repeated dose toxicity studies

Method	NOAEL	Remarks	Reference
Subchronic oral toxicity – dose range finding (*28-day feeding study*) (OECD 407)	2000 ppm (215 mg/kg bw/d for males and 199 mg/kg bw/d in females)	Wistar rat Purity: 97.1%	Diehl & Leist, 1988(c)
Subchronic oral toxicity (*13 week-feeding study* (OECD 408)	> 10000 ppm (> 792 mg/kg bw/d in males and 870 mg/kg bw/d in females); no effects observed	Wistar rat Purity: 98.2%	Schollmeier & Leist, 1989(a)
Subchronic oral toxicity – dose range finding – (*28-day feeding study*) (OECD 407)	> 8000 ppm (>1772 mg/kg bw/d); no effects observed	NMRI mouse Purity: 97.1%	Diehl & Leist., 1988(d)
Subchronic oral toxicity (*13-week feeding study*) (OECD 408)	> 8000 ppm (>1297.3 mg/kg bw/d in males and 1384.8 mg/kg bw/d in females); no effects observed.	NMRI mouse Purity: 98.2%	Schollmeier & Leist, 1989(b)
Testing for toxicity by repeated oral administration to Beagle dogs for *1 month* (Range-finding-Test) (US-EPA Guidelines Subdivision F, § 82-1 and in compliance with GLP)	400 ppm (25.6 mg/kg bw for males and 23.7 mg/kg bw for females)	Beagle dog Purity: 97.1%	Brunk, 1988
Testing for toxicity by repeated oral administration to Beagle dogs (*3-month* feeding study) (OECD 409)	2000 ppm (175.4 mg/kg bw for males and 144.1 mg/kg bw for males)	Beagle dog Purity: 94%	Brunk, 1989
52-week oral toxicity (feeding) study in the dog (OECD 452)	2000 ppm (72.3 mg/kg bw for males and 66.4 mg/kg bw for females)	Beagle dog Purity: 98.7%	Allen et al., 1993
Subchronic inhalation toxicity (*21 applications within 29 days)*, nose only (OECD 412)	NOAEC >1 mg/l (>270 mg/kg bw for both males and females	Wistar rat Purity: 95.5%	Hofmann & Bube., 1992
Cumulative dermal toxicity (*5 treatments in 8 days*) (OECD 410)	>1000 mg/kg bw/d for both males and males	Wistar rat Purity: 98.2%	Schollmeier & Leist., 1989(c)
Subchronic dermal toxicity (*21 treatments in 30 days*) (OECD 410)	>1000 mg/kg bw/d for both males and males	Wistar rat Purity: 98.2%	Schollmeier & Leist, 1990

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Rat:

28 days feeding study

In the 28 day dietary study in the rat, the NOAEL is proposed to be set at 2000 ppm in males and females (215 mg/kg bw in males and 199 mg/kg bw/d in females) based on the statistically significantly increased relative liver weight and increased ALT in males at 10000 ppm (1068 mg/kg bw/d) and statistically significant decrease in bilirubin and increase in uric acid in females at 10000 ppm (1028 mg/kg bw/d).

13 week feeding study

Based on the results of the study provided, no substance related effect could be observed at any dose level; therefore, the NOAEL was set at >10000 ppm (equivalent to 792 mg/kg bw for males and 870 mg/kg bw for females).

Mouse:

28 days feeding study

Based on the results of the 28 days dietary study on mice, no treatment related effects could be detected in any dose groups tested; the NOAEL is higher than the highest dose administered (8000 ppm equivalent to 1772 mg/kg bw for males and 1882 mg/kg bw for females).

13 week feeding study

Based on the results of the 90 days dietary study on mice, no adverse treatment related effects could be detected in any dose groups tested; the NOAEL is higher than the highest dose administered (8000 ppm equivalent to 1297.3 mg/kg bw/d for males and 1384.8 mg/kg bw/d for females).

Dog:

1 month feeding study

Based on the treatment related findings with respect to macroscopic (spleen: white pulp; discolouration of kidneys) and histological examinations (follicular hyperplasia of thyroid and spleen) in animals of the mid dose group tested (2000 ppm), the NOAEL can be set at 400 ppm (equivalent to 25.6 mg/kg bw/d for males and 23.7 mg/kg bw/d for females).

3 months feeding study

Based on the results of the study provided, no treatment related effects could be detected in any dose groups tested; the NOAEL is higher than the highest dose administered (2000 ppm equivalent to 175.4 mg/kg bw for males and 144.1 mg/kg bw for males).

1 year feeding study

Based on the treatment related findings with respect to clinical parameter and urinalysis in animals of the highest dose group tested (8000 ppm), the NOAEL can be set at 2000 ppm (equivalent to 72.3 mg/kg bw for males and 66.4 mg/kg bw for females).

4.7.1.2 Repeated dose toxicity: inhalation

Rat:

Subchronic inhalation toxicity (21 applications within 29 days)

The actual analytical concentrations were 0.041, 0.18 and 0.96 mg/L air for the 0.04, 0.2 and 1 mg/l air groups, respectively. Particle distribution analysis showed the mean percentage of particles of < 3 μm was 56.7 - 67.9%, indicating a moderately high respirable fraction.

There was no mortality and no treatment related changes in animal behaviour or general condition. Irregular respiration and blood coloured encrusted noses were observed in all dose groups and control animals, without any dose response. Animals exposed to amidosulfuron showed narrowed palpebral fissures but this was considered to be a non specific reaction, since this symptom was observed in control animals as well. Body weight gain and food and water consumption remained unaffected by treatment. No dose-dependant effects in haematology, clinical chemistry, urine analysis and ophthalmoscopic examination and organ weight analysis were observed. The histopathological examination revealed accumulations of macrophages in the lungs of some animals in all dose groups, without any dose-response (please see 4.4.3.1). No signs of irritation on respiratory tract were observed.

The NOAEC for systemic effects was 1.0 mg/L air (equivalent to a NOAEL of 270 mg/kg bw/day calculated from an estimated expiry volume of 45 L/kg bw/h for 6 hour exposure). 1.0 mg/l is above the cut-off value for subchronic inhalative toxicity of 0.75 mg/l according to DSD and 0.6 mg/l according to CLP.

4.7.1.3 Repeated dose toxicity: dermal

Rat:

Cumulative dermal toxicity (*5 treatments in 8 days*)

Based on the results of the study provided, no treatment related effects could be detected in the dose group tested; the statistically significant increase of absolute liver weight (females) could be regarded as adaptive effect and therefore not as adverse. The NOAEL is higher than the highest dose administered (1000 mg/kg bw for both males and males).

Subchronic dermal toxicity (*21 treatments in 30 days*)

Based on the results of the study provided, no treatment related effects could be detected in the dose groups tested; the statistically significant changes in some parameter of clinical chemistry cannot regarded as substance related or are adaptive effects. The NOAEL is higher than the highest dose administered (1000 mg/kg bw for both males and males).

4.7.1.4 Repeated dose toxicity: other routes

No data.

4.7.1.5 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.7.1.6 Other relevant information

No other information available.

4.7.1.7 Summary and discussion of repeated dose toxicity

Oral studies

In 3 out of 4 oral repeated dose toxicity studies in rodents (rat, mouse) conducted for 28 and 90 days, no treatment related effects were observed – the NOAEL of the 90 days study in rat, 28 days study in mouse and 90 days study in mouse were set above the highest dose tested (90 days rat: (> 792 mg/kg bw/d in males and 870 mg/kg bw/d in females; 28 days mouse: > 1772 mg/kg bw/d; 90 days mouse: >1297.3 mg/kg bw/d in males and 1384.8 mg/kg bw/d in females).
In the fourth study (28 days rat study), the NOAEL was set at 2000 ppm (215 mg/kg bw/d in males and 199 mg/kg bw/d in females) based on the statistically significantly increased relative liver weight and increased ALT in males at 10000 ppm (1068 mg/kg bw/d) and statistically significant decrease in bilirubin and increase in uric acid in females at 10000 ppm (1028 mg/kg bw/d). Although the NOAEL of this study is below the STOT RE cut-off level for 28 days study of 300 mg/kg bw/d according to CLP (but not below the cut-off value of 150 mg/kg bw/d according to DSD), it should be considered that a) the LOAEL is above 1000 mg/kg bw/d and the huge dose spacing masks the real effect dose, b) no effects were observed in 90 days studies in rat and mouse far above the cut-off value of 100 mg/kg bw/d (according to CLP) for 90 days studies. Additionally, no adverse effects which nature could be relevant for classification and labelling of amidosulfuron with STOT RE (according to CLP and DSD) were observed in any study conducted with this active substance.
From the 3 repeated dose toxicity studies with dogs (1 months study, 3 months study and 1 year study), only in the 28 days study some effects (macroscopic (spleen: white pulp; discolouration of kidneys) and histological (follicular hyperplasia of thyroid and spleen)) were observed at dose level of 2000 ppm, which corresponds to 129 mg/kg bw/d in males and 121.2 mg/kg bw/d in females. The NOAEL was set at 400 ppm (equivalent to 25.6 mg/kg bw/d for males and 23.7 mg/kg bw/d for females). In longer lasting studies (3 months and 1 year study) no such effects were observed at comparable dose. For 3 months study the NOAEL was set > 175.4 mg/kg bw for males and >144.1 mg/kg bw for males (no effects observed). For one year study, the NOAEL was set at 72.3 mg/kg bw/d in males and 66.4 mg/kg bw/d in females, based on changes in potassium and magnesium level and urine gravity at 8000 ppm (261.4 mg/kg bw/d in males and 271.9 mg/kg bw/d in females).Therefore, the two studies of longer duration are considered more reliable than the conducted 28 days study, where the observed effects might not be treatment related. Since no cut-off value is set for STOT RE (according to CLP) based on dog studies, these observations can be taken only as supporting information. The results of the dog studies (no adverse effects which nature could be relevant for classification and labelling of amidosulfuron were observed) support the non-classification proposal for repeated dose toxicity for amidosulfuron.

In the subchronic **inhalation** toxicity study (21 applications within 29 days) the NOAEC for systemic effects was >1.0 mg/L air (equivalent to a NOAEL of 270 mg/kg bw/day calculated from

an estimated expiry volume of 45 L/kg bw/h for 6 hour exposure) based on absence of any treatment related effects and was above the cut-off values of 0.75 mg/l (DSD) and 0.6 mg/l (CLP).

In both **dermal** studies (cumulative dermal toxicity with 5 treatments in 8 days and in the subchronic dermal toxicity study with 21 treatment in 29 days) the NOAELs were > 1000 mg/kg bw/d, based on absence of effects and were above the cut-off values of 300 mg/kg bw/d (DSD) and 600 mg/kg bw/d (CLP).

According to the results of the subchronic (oral, inhalative and dermal) studies in rat, mouse and dog, no classification and labelling for repeated dose toxicity is warranted for amidosulfuron.

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

Effects observed in the oral subchronic studies in rat, mouse and dog were all above the cut-off values for classification and labelling for repeated dose toxicity (28 days rodent studies: 150 mg/kg bw/d; 90 days rodent studies: 50 mg/kg bw/d; no cut-off values for dog studies). Additionally, the nature of observed effects (liver weight and slight changes in some clinico chemical parameters) would not trigger classification and labelling for repeated dose toxicity.

The results of the subchronic inhalation study show no effects at 1.0 mg/L air, which is above the cut-off value of 0.75 mg/l.

The results of one subchronic dermal study show no effects at 1000 mg/kg bw/d, which is above the cut-off value of 300 mg/kg bw/d.

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

Please see 4.7.1.8

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

Effects observed in the subchronic (oral, inhalative and dermal) studies in rat, mouse and dog do not trigger the criteria for classification and labelling for repeated dose toxicity since they are above all cut-off values for oral, dermal and inhalative repeated dose toxicity according to DSD.

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

Effects observed in the oral subchronic studies in rat, mouse and dog were all above the cut-off values for classification and labelling for repeated dose toxicity (28 days rodent studies: 300 mg/kg bw/d; 90 days rodent studies: 100 mg/kg bw/d; no cut-off values for dog studies). Additionally, the nature of observed effects (liver weight and slight changes in some clinico chemical parameters) would not trigger classification and labelling for repeated dose toxicity.

The results of the subchronic inhalation study show no effects at 1.0 mg/L air, which is above the cut-off value of 0.6 mg/l.

The results of the subchronic dermal studies show no effects at 1000 mg/kg bw/d, which is above the cut-off value of 600 mg/kg bw/d.

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

Please see 4.8.1

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

Effects observed in the subchronic (oral, inhalative and dermal) studies in rat, mouse and dog do not trigger the criteria for classification and labelling for repeated dose toxicity since they are above all cut-off values for oral, dermal and inhalative repeated dose toxicity according to CLP.

RAC evaluation of Repeated Dose Toxicity (DSD) and Specific Target Organ Toxicity - Repeated Exposure (STOT-RE) (CLP)

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify amidosulfuron for repeated dose toxicity (DSD) or specific target organ toxicity – repeated exposure (STOT RE) (CLP).

Comments received during public consultation

Comments received during public consultation did not question the dossier submitter's proposal.

Detailed description on relevant arguments and information received during the public consultation

Not needed.

Outcome of RAC assessment - comparison with criteria and justification

Incidence and severity of the adverse effects observed in different oral studies are not sufficiently strong in order to characterise the corresponding doses as "effective doses". Even comparison of NOAELs/LOAELs with the duration-adjusted cut-off levels for the different CLP/DSD RDT categories do not imply the need for RDT classification. There is only one study (28-day dog) with the LOAEL below the highest cut-off level. However, this LOAEL is not considered an "effective dose". The 2 dog studies with longer duration did not reveal the adverse effects seen in the 28-day dog study. In both longer-term dog studies the NOAELs are higher than the highest cut-off level for classification.

For dermal toxicity and toxicity by inhalation no adverse effects were observed at the highest dose levels tested. The corresponding NOAELs are beyond the highest cut-off levels for these routes of application.

Thus RAC as well proposes not to classify amidosulfuron for repeated dose toxicity (DSD) or specific target organ toxicity – repeated exposure (STOT RE) (CLP).

Extended analysis of the key studies provided by the dossier submitter

The key results for RDT of amidosulfuron (28-day studies and longer) are summarised in the following table.

Table: Summary of key information on RDT of amidosulfuron

RDT oral (in mg/kg/d)								
Species	**Duration**	**R48/25**	**STOT RE 1**	**R48/22**	**STOT RE 2**	**Non-effective dose**	**Effective dose**	**CL proposal**
Rat	28 d	15	30	150	300	NOAEL m/f 215/199 LOAEL m 1068 (hdt): relative liver	-	no

						weight ↑ ALT ↑ LOAEL f 1028 (hdt): bilirubin ↓ uric acid ↑		
Mouse	28 d	15	30	150	300	NOAEL m/f >1772/1882 (hdt)	-	no
Dog	28 d	15	30	150	300	NOAEL m/f 25.6/23.7 LOAEL m/f 129/121.2 spleen: white pulp discolouration kidneys follicular hyperplasia of thyroid and spleen	-	no
Rat	90 d	5	10	50	100	NOAEL m/f >792/870 (hdt)	-	no
Mouse	90 d	5	10	50	100	NOAEL m/f > 1297/1384 (hdt)	-	no
Dog	90 d	5	10	50	100	NOAEL m/f 175/144 (hdt)	-	no
Dog	52 w	1.25	2.5	12.5	25	NOAEL m/f 72/ 66 (hdt)	-	no
Rat	2 y	0.6	1.2	6	12	NOAEL m 97 LOAEL m 495 (severity not checked) NOAEL f 614 LOAEL f 1300 (severity not checked)	severity of effects at LOAEL not checked	no

Mouse	~ 2 y	0.6	1.2	6	12	NOAEL m/f 961/1260 (hdt)		

Abbreviations: m = male; f = female; hdt = highest dose tested;

RDT dermal (in mg/kg/d)								
Species	**Duration**	**R48/24**	**STOT RE 1**	**R48/21**	**STOT RE 2**	**Non-effective dose**	**Effective dose**	**CL proposal**
	28 d	30	60	300	600	NOAEL m/f > 1000 (hdt)	-	no

RDT by inhalation (dust) (in mg/m³)								
Species	**Duration**	**STOT RE 1**	**R48/23**	**STOT RE 2**	**R48/20**	**Non-effective dose**	**Effective dose**	**CL proposal**
Rat	28 d	60	75	600	750	NOAEC m/f > 960 (hdt)	-	no

4.9 Germ cell mutagenicity (Mutagenicity)

Table 20: Summary table of relevant *in vitro* and *in vivo* mutagenicity studies

Method	Results	Dose range	Reference
In vitro studies			
Reverse mutation assay (*S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538; *E. coli* WP2uvrA) (OECD Guidelines 471 and 472)	Negative (+/- S-9 mix)	0, 4, 20, 100, 500, 2500 and 5000 µg/plate (dissolved in DMSO) Batch purity: 97.7%	Müller, W.; 1988a
Chinese hamster V79 cell/HGPRT locus gene mutation assay (OECD Guideline 476)	Negative (+/- S-9 mix)	500, 1000, 1500 and 2000 µg/ml (dissolved in DMSO) Batch purity: 97.1%	Müller, W.; 1988b
Chromosomal aberration assay in cultured human lymphocytes (OECD Guideline 473)	Negative (+/- S-9 mix)	0, 0.1, 0.6 and 1.1 mg/ml (dissolved in DMSO) Batch purity: 94%	Heidemann, A.; 1989
Unscheduled DNA synthesis assay in mammalian cells (permanent human cell line A 549) (OECD Guideline 482)	Negative (+/- S-9 mix)	0, 1, 3, 10, 30, 100, 300, 1000 µg/ml (dissolved in DMSO) Batch purity: 97.1%	Müller, W.; 1988c
In vivo studies			
Micronucleus test in NMRI mice (OECD Guideline 474)	Negative	0, 1250, 2500, 5000 mg/kg bw/d (suspended in starch mucilage) Batch purity: 95.7%	Müller, W.; 1987

4.9.1 Non-human information

4.9.1.1 In vitro data

Point mutation assay with bacteria

Amidosulfuron did not show an increase of the number of revertant colonies with any of the test strains tested at concentrations up to the level of cytotocxicity (2500 µg/plate) with or without metabolic activation. An increasing number of revertant colonies could be observed using the positive controls (known mutagene agents). The results of the mutagenicity testing are summarised in the following table:

Table 21: Summarised results of mutagenicity testing of amidosulfuron

Concentration [µg/plate]	Mean revertant colonies (three replicates per concentration)											
	TA 100		TA 1535		TA 1537		TA 1538		TA 98		WP2uvrA	
	-[1)]	+[2)]	-[1)]	+[2)]	-[1)]	+[2)]	-[1)]	+[2)]	-[1)]	+[2)]	-[1)]	+[2)]
0 (solvent control)	168	182	18	12	8	10	14	23	23	30	62	66
4	194	172	18	8	8	8	12	24	22	27	59	65
20	182	169	22	10	7	8	15	22	19	28	67	69

Concentration [µg/plate]	Mean revertant colonies (three replicates per concentration)											
	TA 100		TA 1535		TA 1537		TA 1538		TA 98		WP2uvrA	
	-[1]	+[2]	-[1]	+[2]	-[1]	+[2]	-[1]	+[2]	-[1]	+[2]	-[1]	+[2]
100	168	158	16	9	10	11	11	23	23	29	63	68
500	177	172	11	9	8	9	11	20	19	26	60	60
2500 (cytotoxicity)	17	18	0	0	1	1	1	2	3	3	49	59
5000 (precipitation)	1	0	0	0	0	0	0	0	0	0	44	43
Positive control												
Sodium-azide	601	-	442	-	-	-	-	-	-	-	-	-
9-aminoacridine	-	-	-	-	153	-	-	-	-	-	-	-
2-nitrofluorene	-	-	-	-	-	-	440	-	297	-	-	-
MNNG	-	-	-	-	-	-	-	-	-	-	323	-
2-aminoanthracene	-	590	-	69	-	59	-	268	-	383	-	329
Benzo[a]pyrene	-	583	-	23	-	107	-	133	-	549	-	85

1) without metabolic activation
2) with metabolic activation

The results of this study indicate that under the test conditions used amidosulfuron is not mutagenic in *Salmonella typhimurium* and *Escherichia coli*.

Gene mutation assay with mammalian cell

No relevant enhancement of the mutant colonies or mutant frequency over the range of the negative control was found at any of the concentrations tested (with or without metabolic activation). The sensitivity of the test system was demonstrated by enhanced mutation frequency in the cell cultures treated with positive control substances. The results of the mutagenicity assay are summarised in the table below:

Table 22: Mean number of mutant colonies (five subcultures per concentrate) and mutation frequency (mutant colonies per 10^6 cells) in CH V79 cells treated with amidosulfuron

Treatment [µg/ml]	Without metabolic activation		With metabolic activation	
	Number of mutant colonies	Mutation frequency	Number of mutant colonies	Mutation frequency
First experiment				
Negative control	12.4	56.5	22.2	105.2
Solvent control	12.6	68.2	14	51.8
Positive control (EMS)	92.8	379.2	-	-
Positive control (DMBA)	-	-	97.2	397.0
500	24.2	85.7	25.4	81.2
1000	17.4	68.9	11.8	43.4

Treatment [µg/ml]	Without metabolic activation		With metabolic activation	
	Number of mutant colonies	Mutation frequency	Number of mutant colonies	Mutation frequency
1500	19.8	90.0	16.2	87.1
2000	14.4	53.3	10.2	52.9
Second experiment				
Negative control	8.2	43.2	10.0	69.6
Solvent control	8.6	54.4	12.6	57.8
Positive control (EMS)	127.4	974.1	-	-
Positive control (DMBA)	-	-	106.0	663.4
500	14.0	84.1	18.2	85.0
1000	19.6	78.7	14.2	84.2
1500	13.8	73.6	12.4	63.2
2000	24.2	94.8	13.2	45.0

The results of this study indicate that under the test conditions used amidosulfuron is not mutagenic in the gene mutation assay in Chinese Hamster V79 cells.

Chromosomal mutation assay with mammalian cell

No relevant increase in the structural chromosomal aberration rate could be found when compared with the range of aberrations in the corresponding controls (excluding and including gaps) at any dose level and time interval investigated (with and without metabolic activation). The aberration rates (exclusive gaps) of the cells after treatment with amidosulfuron (0.5 – 2 %) were in the range of the control values (0 – 2 %).The positive controls showed distinct increases of structural chromosome aberrations. The results of the mutagenicity assay is summarised in table below:

Table 23: Mean % cells (duplicate cultures per concentrate; 100 metaphases per culture) with chromosomal aberrations in cultured lymphocytes treated with amidosulfuron

Treatment [mg/ml]	Mean % cells with aberrations[1)]			
	Without metabolic activation		With metabolic activation	
	incl. gaps	excl. gaps	incl. gaps	excl. gaps
24 hours				
Negative control	4	2	3	1
Solvent control	4	0.5	0.5	0
Positive control (EMS)	9.5	7	-	-
Positive control (CPA)	-	-	11	7
0.1	3	2	2.5	1.5
0.6	1	1	2.5	1
1.1	3	0.5	4	1.5

Treatment [mg/ml]	Mean % cells with aberrations[1)]			
	Without metabolic activation		With metabolic activation	
	incl. gaps	excl. gaps	incl. gaps	excl. gaps
48 hours				
Solvent control	1.5	1	2.5	1.5
1.1	6.5	2	2.5	1.5

1) 100 metaphases per culture

The results of this study indicate that under the test conditions used amidosulfuron does not induce structural chromosome aberrations in human lymphocytes *in vitro*.

DNA effect assay with mammalian cell

No relevant reproducible increase in the rate of unscheduled DNA synthesis was observed at any concentration of the test substance. A statistically significant induction of unscheduled DNA synthesis was observed with the positive control substances. The results of the UDS assay is summarised in table below:

Table 24: Mean radioactivity values (6 replicates per concentrate) in human cells (permanent human cell line A 549) treated with amidosulfuron

Treatment [µg/ml]	Radioactivity [dpm/µg DNA]			
	1st experiment		2nd experiment	
	Without metabolic activation	With metabolic activation	Without metabolic activation	With metabolic activation
Solvent control	1687	1097	899	590
Negative control	1687	1696	905	-
Positive control (BP)	1429	2848[1)]	877	1648[1)]
Positive control (NQO)	26763[1)]	-	14665[2)]	-
1	975	975	741	576
3	901	901	670	489
10	853	853	681	530
30	850	850	699	545
100	676	676	621	501
300	804	804	660	438
1000	571	571	485	435

1) statistically significant (level of significance: $p \leq 0.0001$; student`s t-test)
2) statistically significant (level of significance: p=0.00014; student`s t-test)

The results of this study indicate that under the test conditions used amidosulfuron is not mutagenic in the UDS assay in human cells in vitro.

4.9.1.2 In vivo data

Micronucleus test in male and female NMRI mice after oral administration

The incidence of micronucleated polychromatic erythrocytes was within the range of the negative control groups (no statistically significant increase has been observed). The number of normochromatic erythrocytes with micronuclei as well as the ratio of polychromatic to normochromatic erythrocytes did not differ significantly from the values of the corresponding control animals. The positive control (cyclophosphamid) induced a statistically significant increase of the number of polychromatic erythrocytes with micronuclei.
The results are summarised in the following table:

Table 25: Incidence of micronucleated erythrocytes (1000 polychromatic cells were counted for each animal) and the ration of polychromatic to normochromatic erythrocytes (group mean values)

Sampling time	Treatment [mg/kg bw/d]	Ratio pce/nce[1)]		Mutagenic index (polychromatic)[2)]		Mutagenic index (normochromatic)[2)]	
		male	female	Male	female	male	female
24 hours	0 (control)	1.12	1.01	1.0	1.0	1.0	1.0
	1250	1.16	1.05	0.6	0.2	1.4	1.0
	2500	1.21	0.97	0.5	0.2	0.6	1.0
	5000	0.93	1.02	0.6	0.4	0.4	4.0
	Positive control	0.84	1.05	13.2[3)]	11.2[3)]	2.0	12.0[3)]
48 hours	0 (control)	1.13	1.03	1.0	1.0	1.0	1.0
	1250	1.15	0.97	0.8	0.8	1.0	0.6
	2500	0.99	0.96	0.8	0.7	2.0	0.6
	5000	0.76	1.04	0.6	1.2	0.0	0.4
72 hours	0 (control)	0.87	0.95	1.0	1.0	1.0	1.0
	1250	1.09	0.98	0.6	0.3	0.4	0.2
	2500	1.09	1.26	1.0	1.2	0.4	0.4
	5000	1.25	1.22	1.2	0.8	0.4	0.6

1) pce: polychromatic erythrocytes; nce: normochromatic erythrocytes
2) mutagenic index: erythrocytes with micronuclei in the dose group / erythrocytes with micronuclei in the control group
3) statistically significant (level of significance: p = 0.05; test according to Wilcoxon)

The results of this study indicate that under the test conditions used amidosulfuron does not induce chromosomal damage leading to micronucleus formation in polychromatic erythrocytes of mice treated up to 5000 mg/kg bw/d.

4.9.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.9.3 Other relevant information

No other relevant information available.

4.9.4 Summary and discussion of mutagenicity

Amidosulfuron was tested in a sufficient range of *in vitro* and *in vivo* mutagenicity assays measuring different mutagenic endpoints like gene mutation in bacterial and mammalian cells, chromosomal mutation and unscheduled DNA synthesis *in vitro* as well as an *in vivo* micronucleus test in mice.

The results of all these studies mentioned show that **no mutagenic potential** attributed to amidosulfuron under the test conditions used can be derived.

4.9.5 Comparison with criteria

No genotoxic effects were observed in studies with amidosulfuron, neither in *in vivo* nor *in vitro* studies (according to both DSD and CLP).

4.9.6 Conclusions on classification and labelling

There is no evidence of genotoxic potential of amidosulfuron, therefore, no classification is proposed.

RAC evaluation of mutagenicity

Summary of dossier submitter's proposal

The dossier submitter proposed not to classify Amidosulfuron for mutagenicity

Comments received during public consultation

Comments received during public consultation did not question the dossier submitter's proposal.

Detailed description on relevant arguments and information received during the public consultation

Not needed.

Outcome of RAC assessment - comparison with criteria and justification

Amidosulfuron was tested in a range of *in vitro* mutagenicity assays measuring different mutagenic endpoints like gene mutation in bacterial and mammalian cells, chromosomal aberration and unscheduled DNA synthesis in vitro as well as in an *in vivo* micronucleus test in mice. All mutagenicity study results were negative.

Thus RAC as well proposes not to classify Amidosulfuron for mutagenicity.

Table: Mutagenicity testing of Amidosulfuron

Reverse mutation assay (S. typhimurium TA 98, TA 100, TA 1535, TA 1537 and TA 1538; E. coli WP2uvrA)
Chinese hamster V79 cell/HGPRT locus gene mutation assay
Chromosomal aberration assay in cultured human lymphocytes
Unscheduled DNA synthesis assay in mammalian cells (permanent human cell line A 549)
Micronucleus test in NMRI mice

Extended analysis of the key studies provided by the dossier submitter

Not needed

4.10 Carcinogenicity

Table 26: Summary table of relevant carcinogenicity studies

Method	NOAEL/Effects	Dose levels	Reference
Chronic toxicity/oncogenicity study in Wistar rats; oral via diet up to 111 weeks (OECD Guideline 453)	97.8 mg/kg bw/d (males) 614.2 mg/kg bw/d (females) Main effects: <u>Males</u>: - retarded body weight gain - decreased MCHC <u>Females</u>: - reduced water consumption - increased MCV - decreased glucose - increased calcium - increased albumin - decreased A2 globulin **no oncogenic potential**	0, 400, 2000, 10000, 20000 ppm equivalent to 0, 19.5, 97.8, 495.4, 1044.1 mg/kg bw/d (males) and 0, 23.6, 118.7, 614.2, 1300.5 mg/kg bw/d (females) Batch purity: 96.2%	Dotti et al.;1992a
Oncogenicity study in NMRI mice; oral via diet up to 78/91 weeks (OECD Guideline 451)	961 mg/kg bw/d (females) 1260.2 mg/kg bw/d (males) Main effects: No adverse effects up to the highest dose level tested **no oncogenic potential**	0, 400, 3500, 7000 ppm equivalent to 0, 54, 474.6, 961 mg/kg bw/d (males) and 0, 72.8, 671.7, 1260.2 mg/kg bw/d (females) Batch purity: 96.2%	Tennekes et al.; 1992

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

Rat

In a 2 year combined chronic toxicity/carcinogenicity study in rats, reduced body weight gain together with changes in haematological parameters were shown to be signs of toxicity in males of the two highest dose levels (i.e. 10000 and 20000 ppm in the diet). For females, reduced water consumption together with changes in parameter of haematology and clinical chemistry in the highest dose level tested were considered relevant for setting the NOAEL. The only <u>microscopic finding</u> considered to be treatment related was renal papillary injury found in 9 out of 50 animals of the highest dose group (males only). <u>There was no indication of treatment related carcinogenicity</u>. The number and types of neoplasms noted in rats of all dose groups were considered to be similar in both treated and control animals. The NOAEL for males can be set at 2000 ppm equivalent to 97.8 mg/kg bw and for females at 10000 ppm equivalent 614.2 mg/kg bw.

Table 27: Histopathology – non-neoplastic and neoplastic findings in rats

Diet concentration (ppm)	Males					Females				
	0	**400**	**2000**	**10000**	**20000**	**0**	**400**	**2000**	**10000**	**20000**
	Histopathology – Non-neoplastic lesions									
	Kidneys									
Papillary injury (week 104)	-	-	-	-	3/20	-	-	-	-	1/20
Papillary injury (week 110)	-	-	-	-	9/50	-	-	-	-	-
	Histopathology – Neoplastic lesions									
Animals with neoplasm (%)	86.0	90.0	76.0	82.0	84.0	92.0	96.0	98.0	90.0	95.9
Animals with more than one primary neoplasm (%)	42.0	40.0	42.0	32.0	34.0	48.0	54.0	58.0	48.0	51.0
Animals with metastases (%)	0.0	2.0	2.0	4.0	2.0	0.0	4.0	6.0	8.0	0.0

Table 28: Histopathology – benign neoplastic findings in rats at the study termination

Diet concentration (ppm)	Males					Females				
	0	**400**	**2000**	**10000**	**20000**	**0**	**400**	**2000**	**10000**	**20000**
Benign neoplasms										
Brain - granular cell tumor	1(50)	2(50)	3(50)	2(50)	3(50)	3(50)	2(50)	2(50)	1(50)	3(49)
Lungs - Bronch.alv.adenoma	-	2(50)	1(50)	-	-	-	1(50)	-	-	1(48)
Tongue - granular cell tumor	0(50)	1(50)	1(50)	-	-	1(50)	-	-	-	-
Liver - hepatocellular adenoma	3(50)	-	-	-	-	-	-	1(49)	1(50)	3(47)
Pancreas - Islet-cell adenoma - Acinar-cell adenoma	6(50) 2(50)	4(49) -	4(49) 1(49)	- -	4(50) -	- -	2(49) -	- -	1(48) -	1(47) -
Kidneys - cortical adenoma - lipoma	1(50) 1(50)	- -	1(50 -	- -	- -	- -	- -	1(49) -	- -	- -
Testes - Leydig cell tumor	3(50)	1(50)	1(50)	2(50)	2(50)					
Prostate - Adenoma	-	1(50)	-	-	-					
Ovaries -Theca-gran.C.tumor						-	3(50)	2(49)	-	-
Uterus - Endometrial polyp - Adenoma - Fibroma						5(49) - -	9(50) 1(50) -	9(49) 1(49) 1(49)	6(48) - 1(48)	4(47) 1(47) -
Pituitary gland - adenoma	21(49)	23(50)	21(49)	24(50)	25(50)	37(50)	32(50)	37(50)	32(50)	40(49)
Mammary gland area - Fibroadenoma	-	-	-	-	-	19(50)	17(50)	11(49)	10(49)	9(48)
Thyroid gland - C-cell adenoma - Follicular adenoma	3(49) 2(49)	7(50) -	1(49) 3(49)	8(50) 1(50)	6(50) 4(50)	8(50) 2(50)	4(50) -	14(49) 1(49)	6(48) 1(48)	6(48) 2(48)
Adrenal gl. /medulla - medullary tumor - cortical adenoma	- -	1(49) -	1(49) -	1(50) -	- -	1(50) -	1(50) 1(50)	- -	- -	1(47) -
Mesent. Lymph node - hemangioma - fibroma	7(49) -	3(49) -	6(48) -	6(48) -	9(50) 1(50)	2(49) -	1(49) 1(49)	3(49) -	4(47) -	2(47) -
Skin - Fibroma - Lipoma - Granular cell tumor - Squamous cell papilloma - Keratoacantheoma - Sebaceous adenoma - Hemangioma - Trichoepithelioma	2(48) 1(48) - 1(48) 2(48) - - -	3(49) 4(49) 1(49) - 2(49) 2(49) - -	2(49) - - - 4(49) 1(49) - -	1(49) - - 1(49) 3(49) 1(49) 1(49) 1(49)	- - - - 3(50) - - -	1(50) - - - - - - -	2(50) - - 1(50) - - - -	- - - - - - - -	- 1(50) - - - - - -	- - - - 1(48) - - -
Bone (other) - osteoma	-	-	-	-	-	-	-	-	-	1(1)
Sternum - osteoma	-	-	-	-	-	1(50)	-	-	-	-

Table 29: Histopathology – malign neoplastic findings in rats at the study termination

Diet concentration (ppm)	Males					Females				
	0	**400**	**2000**	**10000**	**20000**	**0**	**400**	**2000**	**10000**	**20000**
Malign neoplasms										
Brain										
- Meningeal sarcoma	1(50)	-	-	-	-	-	-	-	-	-
- Schwannoma	-	-	-	1(50)	-	-	-	-	-	1(49)
- Oligodendroglioma	1(50)	-	-	-	-	-	-	-	-	-
- Astrocytoma	1(50)	-	-	-	-	-	-	-	-	-
- Glioma	-	-	-	-	-	-	-	-	1(50)	-
Heart										
- Hemangiosarcoma	-	-	-	-	1(50)	-	-	-	-	-
- Sarcoma	-	1(50)	-	-	-	-	-	-	-	-
Stomach										
- Fibrosarcoma	-	-	-	-	1(49)	-	-	-	-	-
- Sarcoma	-	-	-	-	-	-	-	-	-	1(46)
Liver										
- hepatocellular carcinoma	-	-	1(50)	-	-	-	-	1(49)	-	-
Pancreas										
- Islet-cell carcinoma	1(50)	-	1(49)	-	-	-	-	-	-	-
Kidneys										
- cortical carcinoma	1(50)	-	-	-	-	-	1(50)	2(49)	1(50)	3(47)
- liposarcoma	1(50)	-	-	-	-	-	-	-	-	-
- mesenchymal tumour	-	-	-	-	-	-	-	-	1(50)	1(47)
Ovaries										
- Cystadenocarcinoma						-	-	1(49)	-	1(47)
- Adenocarcinoma						-	-	-	1(48)	-
Uterus										
- cystic sarcoma						-	1(50)	-	1(48)	1(47)
- adenocarcinoma						-	2(50)	3(49)	1(48)	3(47)
- stromal sarcoma						1(49)	-	1(49)	-	-
Prostate										
- Adenocarcinoma	-	-	-	1(49)	-					
- Carcinosarcoma	-	-	1(50)	-	-					
Mammary gland area										
- Adenocarcinoma	-	-	-	-	-	2(50)	2(50)	3(49)	1(49)	3(48)
Thyroid gland										
- C-cell carcinoma	1(49)	-	-	1(50)	1(50)	-	1(50)	1(49)	3(48)	-
- Follicular carcinoma	1(49)	2(50)	1(49)	1(50)	1(50)	-	-	-	-	2(48)
Adrenal gl. /medulla										
- medullary tumor	-	-	-	1(50)	1(50)	-	1(50)	1(49)	1(50)	-
- ganglioneuroma	1(50)	-	1(49)	-	-	-	-	-	1(50)	-
Hemolymphoret.system										
- Malignant lymphoma	-	2(50)	-	1(50)	-	2(50)	1(50)	2(50)	1(50)	1(49)
- Hystiocytic sarcoma	1(50)	-	-	-	-	-	-	-	1(50)	-
Spleen										
- Sarcoma	-	-	-	1(50)	-	-	-	-	-	-
- Hemangiosarcoma	-	-	-	-	-	-	-	1(49)	-	-
Thymus										
- adenocarcinoma	-	-	1(50)	-	-	-	-	-	-	-
- thymoma	-	-	-	-	-	-	-	-	-	1(46)

Diet concentration (ppm)	Males					Females				
	0	400	2000	10000	20000	0	400	2000	10000	20000
Skin										
- Squamous C. carcinoma	-	1(49)	-	-	-	-	-	-	-	-
- Solid carcinoma	-	-	-	-	1(50)	-	-	-	-	-
- Sarcoma	1(48)	-	-	1(49)	-	-	-	-	-	-
- Basal cell carcinoma		2(49)		1(49)		-	-	-	2(50)	-
- Fibrosarcoma	1(48)	2(49)	-	-	-	-	-	-	-	-
- Schwannoma	-	-	1(49)	-	-	-	-	1(49)	-	-
- Cystic sarcoma	-	-	-	1(49)	1(50)	-	-	-	-	-

Mouse

As result of the mouse carcinogenicity study, no treatment related effect up to the highest dose level tested (i.e. 7000 ppm in the diet) could be observed: statistically significant changes in parameters of haematology and clinical chemistry were not considered to be treatment related since no dose relationship could be observed. The decrease of the liver weight (males; mid dose group) was not dose related; the increase of the liver weight (females; highest dose group) were considered to be not adverse, as neither changes in clinical chemistry nor histopathological changes could be observed. Amidosulfuron did not reveal any oncogenic potential up to and including the highest dose level tested. The microscopic findings included non-neoplastic changes affecting mainly the parenchymateous organs and were not different between treated and not treated animals. The number and types of neoplasms noted in mice of all dose groups were considered to be similar in both treated and control animals. The NOAEL can be set at 7000 ppm (i.e. 961 mg/kg bw/d for males; 1260.2 mg/kg bw for females).

Table 30: Histopathology – non-neoplastic and neoplastic findings in mice

	Males				Females			
Diet concentration (ppm)	**0**	**400**	**3500**	**7000**	**0**	**400**	**3500**	**7000**
	Histopathology – Non-neoplastic lesions							
	No treatment-related findings							
	Histopathology – Neoplastic lesions							
Animals with neoplasm (%)	78.0	62.0	70.0	78.0	90.0	82.0	90.0	86.0
Number of primary neoplasm	73	49	54	64	76	61	72	72
Animals with more than one primary neoplasm (%)	42.0	20.0	28.0	40.0	40.0	32.0	38.0	42.0
Animals with metastases (%)	6.0	2.0	0.0	2.0	2.0	2.0	2.0	2.0

Table 31: Histopathology – benign neoplastic findings in mice at the study termination

	Males				Females			
Diet concentration (ppm)	**0**	**400**	**3500**	**7000**	**0**	**400**	**3500**	**7000**
Benign neoplasms								
Stomach - Adenomatous polyp - Squamous papilloma	 - -	 - 1(49)	 - -	 - -	 - -	 1(48) -	 - -	 2(50) 1(50)
Liver - hepatocellular adenoma	 6(50)	 2(50)	 3(50)	 4(49)	 -	 -	 1(50)	 1(50)
Pancreas - Islet-cell adenoma	 1(49)	 -	 -	 -	 1(48)	 -	 -	 -
Kidneys - tubular adenoma - hemangioma	 - 1(50)	 - -	 - -	 - -	 - -	 - -	 1(50) -	 - -
Testes - Leydig cell tumor	 3(50)	 -	 1(50)	 3(50)				
Epididymides - Granular cell tumor	 -	 1(50)	 1(50)	 -				
Seminal vesicles - Granular cell tumor	 -	 1(50)	 1(50)	 -				
Ovaries - Granulosa C. tumor - Luteoma - Sertoli cell tumor					 3(50) 3(50) 2(50)	 1(49) 2(49) 1(49)	 3(50) 3(50) 1(50)	 4(50) 2(50) 1(50)
Uterus - Leiomyoma - Hemangioma - Granular cell tumor					 1(50) 1(50) 2(50)	 - - -	 - - 1(50)	 - - 1(49)
Pituitary gland - Adenoma	 1(49)	 1(49)	 -	 2(49)	 4(49)	 1(50)	 6(50)	 8(50)
Thyroid gland - Follicular adenoma	 3(50)	 -	 -	 -	 -	 -	 -	 -
Parathyroid glands - Adenoma	 -	 1(45)	 1(44)	 -	 -	 1(45)	 2(44)	 2(45)
Adrenal cortex - Adenoma	 -	 -	 1(50)	 -	 -	 -	 -	 -
Adrenal medulla - benign medullar tumor	 1(48)	 -	 -	 1(50)	 -	 1(50)	 -	 1(50)
Mesent. Lymph node - Hemangioma	 2(50)	 -	 -	 -	 -	 1(50)	 -	 -
Harderian glands - Adenoma	 8(50)	 4(50)	 1(50)	 1(50)	 3(50)	 4(50)	 1(50)	 2(50)
Skin - Lipoma	 -	 1(50)	 -	 -	 -	 -	 -	 -

Table 32: Histopathology – benign neoplastic findings in mice at the study termination

	Males				Females			
Diet concentration (ppm)	**0**	**400**	**3500**	**7000**	**0**	**400**	**3500**	**7000**
Malign neoplasms								
Lungs - Bronchio/alveo tumor	20(50)	11(50)	17(49)	21(50)	6(49)	7(50)	7(50)	7(50)
Stomach - Ossifying sarcoma	-	-	-	-	1(48)	-	-	-
Liver - Hepatocellular carcinoma - Hepatoblastoma - Bile duct carcinoma - Hemangiosarcoma	5(50) - - -	5(50) - - 1(50)	2(50) 1(50) - -	5(49) - - 1(49)	- - - -	- - - -	- - 1(50) -	- - - -
Kidneys - tubular carcinoma	1(50)	-	-	-	-	-	-	-
Urinary bladder - Leiomyosarcoma	1(50)	-	-	-	-	-	-	-
Prostate - Adenocarcinoma	1(50)	-	-	-				
Ovaries - Granulosa C. tumor - Cystadenocarcinoma					1(50) -	- -	2(50) -	- 1(50)
Uterus - Leiomyosarcoma - Hemangiosarcoma					1(50) -	- 1(50)	- -	- -
Adrenal cortex - Carcinoma	-	-	-	1(50)	-	-	-	-
Adrenal medulla - Malig. Medull. tumor	-	-	1(50)	1(50)	-	-	1(50)	-
Hemolymphoret. System - Malignant lymphoma - Histiocytic sarcoma - Myeloid leukemia	13(50) 2(50) 1(50)	11(50) 2(50) 1(50)	19(50) 1(50) 1(50)	17(50) 2(50) 2(50)	37(50) - -	31(50) - -	35(50) 1(50) 1(50)	32(50) - -
Harderian glands - Adenocarcinoma	1(50)	3(50)	2(50)	2(50)	3(50)	3(50)	-	3(50)
Mammary gland area - Adenocarcinoma	-	-	-	-	3(50)	-	3(50)	3(48)
Skin - Squamous carcinoma - Malignant schwannoma - Sarcoma, NOS	- - -	1(50) - -	- - -	- - -	- - -	- 1(50) -	- - -	- - 1(50)
Bone (sternum) - Osteosarcoma	-	-	-	-	-	1(50)	-	-
Optic nerves - malignant schwannoma	-	-	1(39)	-	-	-	-	-

4.10.1.2 Carcinogenicity: inhalation

No data available.

4.10.1.3 Carcinogenicity: dermal

No data available.

4.10.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

4.10.3 Other relevant information

No other relevant information available.

4.10.4 Summary and discussion of carcinogenicity

Based on the results of both studies submitted (rats and mice), amidosulfuron can be regarded to have no carcinogenic potential.

4.10.5 Comparison with criteria

No treatment related carcinogenic effects were observed in studies conducted with amidosulfuron, neither in rat nor in mouse carcinogenicity studies (according to both DSD and CLP).

4.10.6 Conclusions on classification and labelling

There is no evidence of carcinogenic potential of amidosulfuron, therefore, no classification is proposed.

RAC evaluation of carcinogenicity
Summary of dossier submitter's proposal The dossier submitter proposed not to classify Amidosulfuron for carcinogenicity
Comments received during public consultation Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation Not needed.
Outcome of RAC assessment - comparison with criteria and justification Carcinogenicity of Amidosulfuron was (validly) tested in rats and mice (chronic toxicity/oncogenicity study in Wistar rats; via diet up to 111 weeks, highest dose tested 1044/1300 mg/kg/d; oncogenicity study in NMRI mice, via diet up to 78/91 weeks, highest dose tested 961/1260 mg/kg/d). The incidence data of benign and malign neoplastic findings (see histopathology tables in the CLH report) were considered to be similar in both treated and control animals; there was no statistical significance for neoplasms of treated versus control animals. Overall, Amidosulfuron did not reveal a carcinogenic potential in rats and mice. Thus RAC as well proposes not to classify Amidosulfuron for carcinogenicity.
Extended analysis of the key studies provided by the dossier submitter Not needed

4.11 Toxicity for reproduction

Table 33: Summary table of relevant reproductive toxicity studies

Method	NOAEL	Remarks	Reference
Two generation study in rats (OECD 416)	Reproduction: 570 mg/kg bw/d Parental: 22.5 mg/kg bw/d Offspring: 22.5 mg/kg bw/d	Wistar rat Purity: 95.5%	Dottie et al., 1992b
Testing for embriotoxicity in the Wistar rat after oral administration (Limit test) (OECD 414)	Maternal: > 1000 mg/kg bw/d Developmental: > 1000 mg/kg bw/d	Wistar rat Purity: 97.1%	Baeder, 1988a
Testing for embriotoxicity and effects on post-natal development in Wistar rats after oral administration (Limit test) (OECD 414)	Maternal: > 1000 mg/kg bw/d Developmental: > 1000 mg/kg bw/d	Wistar rat Purity: 94.1%	Baeder, 1990
Testing for embriotoxicity in the Himalayan rabbit after oral administration (Limit test)	Maternal: > 1000 mg/kg bw/d Developmental: > 1000 mg/kg bw/d	Himalayan rabbit Purity: 98.1%	Baeder, 1988b

4.11.1 Effects on fertility

4.11.1.1 Non-human information

Two generation study in rats

Groups of 25 rats/sex and dose group (strain: Wistar/HAN rat; source: Biological Research Laboratories, Switzerland) of the *F_0 generation* received amidosulfuron (batch no. 3/89; purity: 95.5 %) via diet at dose levels of 0, 400, 2000 and 10000 ppm during a 70-day prepairing period and also during the pairing, gestation and lactating periods. The animals were paired one male/one female for a period of 8 days. On day 4 post partum, the litters obtained were randomly adjusted to 8 pups each; the remaining pups were reared until weaning (day 21 post partum). 25 male and 25 female pups of the *F_1 generation* were randomly selected to produce the next generation (day 21 post partum). Following selection of the F_1 pups, excess pups as well as F_0 animals were sacrificed and examined macroscopically. The selected F_1 animals were reared on their respective diets (same concentrations as the parents) for 126 days prior to pairing and during the pairing, gestation and lactating period. Pairing was done again on the basis of one male : one female. The litters obtained were randomly adjusted to 8 pups each (day 4 post partum). The *F_2 offspring* was reared until weaning. At day 21 post partum, all F_2 pups and F_1 animals were sacrificed and examined macroscopically.
The amidosulfuron levels on an mg/kg bw/day basis are compiled in the following table:

Table 34: Group mean intakes of amidosulfuron (mg/kg bw/day) at different segments of the study

		F_0-generation			F_1-generation		
Dose level [ppm]		400	2000	10000	400	2000	10000
Group mean intakes [mg/kg bw/day]							
Males	pre-pairing	32.0	160.8	777.5	29.3	146.8	734.9
	post-pairing	23.2	117.1	568.0	22.5	113.2	570.0

Dose level [ppm]		F_0-generation			F_1-generation		
		400	2000	10000	400	2000	10000
Females	pre-pairing	35.7	181.7	882.9	33.1	168.0	828.6
	gestation	29.9	153.6	750.9	29.7	153.4	732.3
	lactation	65.0	329.5	1641.9	57.6	294.0	1512.7

The observations during the study included mortality (checked at least twice daily) and signs and symptoms (again at least twice daily). The body weights were recorded at weekly intervals together with food consumption. The reproductive parameters like mating data (daily vaginal smears), duration of gestation, pregnancy rate, litter size, live birth, still birth, gross anomalies, sex ratio and individual weights of pups on days 0 or 1, 4, 7, 14 and 21 of lactation were investigated. The dams and the pups were observed daily for survival, behavioural abnormalities in nesting and nursing. At necropsy, all F_0 and F_1 adult animals, the excess of F_1 pups after standasrdisation of litter sizes as well as F_1 pups not selected for pairing and all F_2 pups were investigated for macroscopic anomalies. From all F_0 and F_1 animals selected for pairing and from one male and female pup of each F_1 and F_2 litter samples of selected organs and tissues were taken: gross lesions, ovaries, pituitary gland, prostate, seminal vesicles, testes with epididymides, uterus and cervix as well as vagina. Histopathology has been performed from all high dose and control F_0 and F_1 animals selected for pairing, from all animals killed in extremis and from one male and female pup of each F_2 litter (high dose and control). Organs with macroscopic abnormalities were examined histologically as well as the reproductive organs of all infertile males and females of all groups (F_0 and F_1). Organ weights were recorded from all F_0 and F_1 parent animals and from one male and female pup of each F_1 and F_2 litter (brain, kidneys, liver, ovaries, prostate, seminal vesicles, testes and uterus).

No spontaneous or test compound related deaths were observed among F_0 and F_1 animals of any dose group. One male (10000 ppm) and one female (2000 ppm) of F_1 generation were killed in extremis (due to skin lesions with bacterial infection [male] and a mass on the left side on the thorax [female]), but this finding was not considered to be treatment related. No clinical signs with respect to treatment with the test substance have been observed in any group of any generation. With respect to food consumption of the F_0 anf F_1 parents, no treatment related changes have been observed in F_0 *males*; for F_1 males, statistically significant changes were noted on days 43 – 50 of the prepairing period only (10000 ppm). For *females*, food consumption of F_0 females of the highest dose group during prepairing period (days 1-8, 15-22, 29-36 and 43-50) and the gestation period (days 0 and 7) was statistically significant reduced; the food consumption of F_1 females showed statistically significant differences during 8 weeks of the pre-pairing period and between days 0 – 7 and 14 – 21 of the gestation period (10000 ppm); at 2000 ppm, food consumption was decreased showing statistically significance for the prepairing period between days 15 and 22 only. Body weight: Body weights of the F_0 and F_1 male as well as F_0 female parents were not affected by treatment with the test article. For F_1 females of the highest dose group, body weight was statistically reduced at observation periods of the pre-pairing (except day 1), gestation period and lactation period; the females of the 2000 ppm dose group showed statistically significant decreased body weights during the prepairing period (days 15 – 29 and 106 – 113), gestation and lactation period as well (all the findings showed clear dose relationships). The relevant findings with respect do body weight of the F_1 females are presented in the following table:

Table 35: Group mean body weights [g] of F_1 females at different segments of the study (pre-pairing period, gestation period; lactation period)

Time of investigation [days]	Dose Group levels [ppm]			
	0	400	2000	10000
Mean body weights [g]				
Pre-pairing period				
1	101	100	95	95
8	130	129	124	122[1)]
15	151	147	142[1)]	140[2)]
22	168	164	158[1)]	157[1)]
29	183	180	173[1)]	172[1)]
36	194	192	184	181[1)]
43	202	201	192	189[1)]
50	210	208	200	197[1)]
57	217	214	207	204[1)]
64	221	218	211	208[1)]
71	226	223	215	214[1)]
78	229	226	218	216[1)]
85	232	229	221	220
92	235	232	224	221[1)]
99	236	234	224	223[1)]
106	241	237	227[1)]	226[1)]
113	243	240	229[1)]	229[1)]
120	244	240	231	229[1)]
126	246	242	233	232[1)]
Gestation period				
0	247	242	229[2)]	228[2)]
7	268	260	248[2)]	246[2)]
14	292	284	270[2)]	269[2)]
21	347	342	325[2)]	328[1)]
Lactation period				
1	263	258	244[1)]	239[2)]
4	274	271	257[1)]	256[1)]
7	280	278	263[1)]	261[1)]
14	289	287	270[1)]	272[1)]
21	289	285	272[1)]	273

1) statistically significant (level of significance: $p \leq 0.05$; Dunnet test on pooled variance)
2) statistically significant (level of significance: $p \leq 0.01$; Dunnet test on pooled variance)

With respect to reproduction data of the *F_0 generation*, the mean precoital time, percentage of animals mating, fertility index, conception rate, gestation index, mean number of implantation sites

per dam and post natal losses as well as breeding losses and number of dead and living pups showed no statistically significant differences to the concurrent control. For the animals of the lowest dose group tested (400 ppm), a statistically significant increase of post-implantation losses have been observed. This finding was not regarded to be treatment related, since the values were within the range of deviations common for this rat strain, the values noted from the control were very low and no dose relationship could be observed. For the *F_1 generation parents*, the mean precoital time, percentage of animals mating, fertility index, conception rate, gestation index, mean number of implantation sites per dam, post-implantation losses, post natal losses as well as breeding losses and number of dead and living pups showed no statistically significant differences to the concurrent control.

Table 36: Reproduction parameter in F0 and F1 generation

Group (ppm)	F0				F1			
	0	400	2000	10000	0	400	2000	10000
Number of females paired	25	25	25	25	25	25	24	25
Number of females mated	25	25	25	25	25	25	24	25
Number of females pregnant	25	24	24	24	19	23	22	22
Fertility index (%)	100	96	96	96	76	92	91.7	88
Number of females bearing	25	24	24	24	19	23	22	22
Gestation index (%)	100	100	100	100	94.7	95.7	100	100
Number of females rearing the pups	25	24	24	24	18	22	22	22
Mean precoital time	2.3	2.4	2.7	2.7	3.0	2.9	3.6	2.6
Mean duration of gestation (days)	21.5	21.5	21.3	21.5	21.9	21.7	21.8	21.6
Number of implantations per dam (mean)	12.1	12.5	12.5	12.3	11.3	12.1	11.0	12.5
Post implantation loss - % of implantations - Litters affected	 7.6 9	 8.7 18##	 8.7 14	 6.1 9	 14.3 12	 17.6 17	 13.3 13	 11.3 16
Dead pups at first litter check (mean)	0.0	0.5	0.2	0.1	0.5	0.1	0.3	0.0
Living pups at first litter check (mean)	11.2	10.9	11.2	11.5	9.2	9.9	9.2	11.1
Postnatal loss days 0-4 pp - % of living pups - Litters affected	 1.1 3	 1.9 3	 0.7 2	 0.0 0	 4.8 5	 3.7 4	 0.5 1	 1.2 3
Living pups day 4 pp (mean)	7.8	7.7	7.9	7.9	7.1	7.5	7.3	7.9
Postnatal loss days 5-21 pp - % of living pups at day 4 pp - Litters affected	 1.0 2	 1.6 2	 2.1 4	 0.0 0	 0.0 0	 0.6 1	 0.0 0	 1.2 2
Living pups day 21 pp (mean)	7.7	7.6	7.8	7.9	7.1	7.5	7.3	7.8

: Fisher's exact test significant at 1% level

Litter data: External examination of pups of the *F_1 generation* did not show any treatment related abnormal findings; there were no evidence of an effect of the test substance on the sex ratios. The body weights of F_1 were statistically significant reduced at the highest dose level tested for females (including pooled males and females) at day 21 only. The relevant findings with respect to body weight were summarised in table below.
For the pups of the *F_2 generation*, no treatment related abnormal findings were noted in any group at external examination. Sex ratios were not affected by application of the test substance. Body

weights of male and female pups (10000 ppm) were reduced with statistical significance on day 0 until day 4 post partum. The body weights of F_2 pups were compiled in the following table.

Table 37: Group mean body weights [g] of F_1 and F2 pups at different days post partum

Dose levels [ppm]	Mean body weights of pups per group and sex [g]											
	0 days p.p		1 days p.p.		4 days p.p.		7 days p.p.		14 days p.p.		21 days p.p.	
	F_1	F_2	F_1	F_2	F_1	F_2	F_1	F_2	F_1	F_2	F_1	F_2
0												
m	5.7	6.2	6.1	6.3	8.8	9.6	14.2	14.9	28.9	28.8	46.6	46.3
f	5.6	5.7	5.8	6.0	8.6	9.5	13.8	14.5	28.2	28.4	45.4	44.9
m + f	5.7	6.0	5.9	6.2	8.7	9.5	14.0	14.7	28.5	28.6	45.9	45.7
400												
m	6.4	5.9	6.0	6.3	8.9	9.5	14.1	14.7	28.6	28.3	45.6	45.8
f	6.0	5.6	5.7	6.0	8.6	9.0	13.7	14.1	28.3	27.7	44.9	44.3
m + f	6.2	5.7	5.9	6.1	8.8	9.2	13.9	14.3	28.6	27.9	45.4	45.0
2000												
m	5.8	5.9	5.9	6.4	8.6	9.7	13.7	14.6	28.3	27.7	44.8	44.7
f	5.4	5.5	5.6	6.0	8.2	9.2	13.4	14.1	27.8	27.0	43.9	43.0
m + f	5.5	5.7	5.7	6.2	8.4	9.4	13.5	14.3	28.0	27.1	44.3	43.6
10000												
m	5.4	5.6[1)]	5.9	5.9	8.7	8.6[1)]	13.8	14.0	27.8	27.2	44.1	43.5
f	5.2	5.5	5.7	5.6[1)]	8.4	8.4[1)]	13.5	13.6	27.5	26.6	42.9[1)]	42.1
m + f	5.3	5.5[1)]	5.8	5.7[1)]	8.5	8.5[1)]	13.7	13.8	27.6	26.9	43.5[1)]	42.8

m males
f females
m + f pooled males and females
1) statistically significant (Dunnett test on pooled variance; p: 0.05)

Organ weights: Statistically significant changes in the organ/tissue weight have been observed for F_0 *parents* of the highest dose group (males: absolute testes weight). For F_1 parents of the 10000 ppm dose group (males: prostate and seminal vesicles; females: liver) and of the 2000 ppm dose group (females: liver), the corresponding organ weights were statistically significant increased. Changes in organ weights of kidneys of the F_1 females showing statistic significance were not regarded as relevant since no dose relationship has been observed. The relevant findings with respect to organ weight changes are compiled in tables below:

Table 38: Reproductive study in rats: relevant organ weight [g] changes (group mean values) for F_0 parents

Organ	Dose Group levels [ppm]							
	Males							
	0		400		2000		10000	
	abs[1]	rel[2]	Abs[1]	rel[2]	abs[1]	rel[2]	abs[1]	rel[2]
Testes	3.56	0.83	3.80	0.89[3]	3.70	0.87	3.89[4]	0.88
Prostate	1.24	0.29	1.15	0.27	1.17	0.27	1.26	0.29

1) absolute organ weight [g]
2) relative organ weight – organ body weight ratios [%]
3) statistically significant (level of significance: $p \leq 0.05$; Dunnet test on pooled variance)
4) statistically significant (level of significance: $p \leq 0.01$; Dunnet test on pooled variance)

Table 39: Reproductive study in rats: relevant organ weight [g] changes (group mean values) for F_1 parents

Organ	Dose Group levels [ppm]							
	Males				Females			
	0	400	2000	10000	0	400	2000	10000
Prostate								
abs[1)]	0.83	0.90	0.89	0.99[4)]	-	-	-	-
rel[2)]	0.19	0.20	0.20	0.23[4)]	-	-	-	-
Seminal vesicles								
abs[1)]	1.37	1.57	1.42	1.65[3)]	-	-	-	-
rel[2)]	0.31	0.35	0.32	0.38[4)]	-	-	-	-
Liver								
abs[1)]	14.0	15.1	14.4	14.2	11.1	12.1	12.1	12.0
rel[2)]	3.16	3.33	3.24	3.26	4.13	4.52	4.66[4)]	4.66[4)]
Kidneys								
abs[1)]	2.30	2.45	2.33	2.38	1.78	1.90	1.85	1.81
rel[2)]	0.53	0.54	0.52	0.54	0.66	0.71[3)]	0.71[3)]	0.70

1) absolute organ weight [g]
2) relative organ weight – organ body weight ratios [%]
3) statistically significant (level of significance: $p \leq 0.05$; Dunnet test on pooled variance)
4) statistically significant (level of significance: $p \leq 0.01$; Dunnet test on pooled variance)

The following statistically significant differences from control values were noted for organ weights of F_1 *pups*: seminal vesicles (males of the two higher dose groups) as well as brain and kidneys (females of the highest dose group). For F_2 pups, changes with statistic significance were observed in organ weights of brain (males: 2000 and 10000 ppm dose group).
The relevant findings with respect to organ weight changes are compiled in tables below:

Table 40: reproductive study in rats: relevant organ weight [g] changes (group mean values) for F_1 pups

Organ	Dose Group levels [ppm]							
	Males				Females			
	0	400	2000	10000	0	400	2000	10000
Seminal vesicles								
abs[1)]	0.024	0.020	0.018[3)]	0.019[4)]	-	-	-	-
rel[2)]	0.052	0.044	0.041[4)]	0.043	-	-	-	-
Brain								
abs[1)]	1.46	1.46	1.43	1.43	1.41	1.40	1.40	1.44
rel[2)]	3.18	3.23	3.29	3.31	3.19	3.22	3.29	3.44[4)]
Kidney								
abs[1)]	0.49	0.49	0.47	0.47	0.49	0.49	0.48	0.48
rel[2)]	1.07	1.08	1.07	1.08	1.10	1.13	1.13	1.15[4]

1) absolute organ weight [g]
2) relative organ weight – organ body weight ratios [%]
3) statistically significant (level of significance: $p \leq 0.05$; Dunnet test on pooled variance)
4) statistically significant (level of significance: $p \leq 0.01$; Dunnet test on pooled variance)

Table 41: reproductive study in rats: relevant organ weight [g] changes (group mean values) for F_2 pups

Organ	Dose Group levels [ppm]							
	Males							
	0		400		2000		10000	
	abs[1)]	rel[2)]	abs[1)]	rel[2)]	abs[1)]	rel[2)]	abs[1)]	rel[2)]
brain	1.49	3.30	1.45	3.25	1.44[3)]	3.33	1.42[4)]	3.36

1) absolute organ weight [g]
2) relative organ weight – organ body weight ratios [%]
3) statistically significant (level of significance: $p \leq 0.05$; Dunnet test on pooled variance)
4) statistically significant (level of significance: $p \leq 0.01$; Dunnet test on pooled variance)

At necropsy, no treatment related abnormal macroscopic and microscopic findings were noted in any parents of the F_0 and F_1 generation and in any pups of the F_1 and F_2 generation as well.

Based on the results of the two generation study on rats, none of the fertility parameters was affected by the administration of the test substance. At the two highest dose groups, reduced body weight for F_1 females have been observed showing a clear dose relationship. Reduced body weight with statistical significance for F_1 and F_2 pups were evident in the highest dose level only. Organ weight changes were noted in parents and pups of the 2000 ppm and the 10000 ppm dose level. Based on the results of the study, the NOAEL for both parental and developmental effects is set at 400 ppm equivalent to 22.5 mg/kg bw/day (males) and 29.7 mg/kg bw/day (females).

4.11.1.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

RAC evaluation of effects on fertility
Summary of dossier submitter's proposal The dossier submitter proposed not to classify amidosulfuron for effects on fertility
Comments received during public consultation Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation Not needed.
Outcome of RAC assessment - comparison with criteria and justification Amidosulfuron was tested in a 2-generation reproduction study in Wistar/HAN rats (see the table in the section "Extended analysis of the key studies provided by the dossier submitter"). No effects on fertility were observed both in the F0 and F1 parents. The findings of the developmental toxicity studies (see chapter on developmental toxicity) did not reveal any indications for amidosulfuron related effects on fertility.

Thus RAC as well proposes not to classify amidosulfuron for effects on fertility.

Extended analysis of the key studies provided by the dossier submitter

The key findings of the amidosulfuron 2-generation reproduction study are summarized in the table below.

Table: Summary of key findings of the amidosulfuron 2-generation reproduction study

		400 ppm	2000 ppm	10000 ppm
F0 parents	Body weight (m/f)	-	-	-
	Organ weight	-	-	Testis ↑
	Reproduction data	-	-	-
F1 pups	Body weight (f)	-	-	↓ (day 21)
	Organ weights (m)	-	Sem. ves. ↓	Sem. ves. ↓
	Organ weights (f)	-	-	Brain ↑ Kidney ↑
F1 parents	Body weight (f)	-	↓	↓
	Organ weights (m)			Prostrate ↑ Sem. ves. ↑
	Organ weights (f)	-	Liver ↑	Liver ↑
	Reproduction data	-	-	-
F2 pups	Body weight (m)	-	-	↓ (up to day 4)
	Body weight (f)	-	-	↓ (up to day 4)
	Organ weights (m)	-	Brain ↓	Brain ↓

Notes: "-" = not affected; Sem. ves. = Seminal vesicles

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

Developmental toxicity of amidosulfuron has been tested in rats and rabbits; furthermore, one post-natal developmental study in rats has been provided. In accordance with OECD Guideline 414/1981, the studies submitted were performed at one high dose level only (1000 mg/kg bw/day); since this dose level does not show any evidence of embrio toxicity or teratogenicity and the test substance is of low toxicity, studies at other dose levels (as normally required) are not considered necessary.

Rat:

Testing for embriotoxicity in the Wistar rat after oral administration (Limit test), *Baeder*, 1988a

Before the start of the study, amidosulfuron had been administered in an oral *range finding study* (reported in summary form only) to groups of 2 or 3 gravid Wistar rats at dose levels of 1000 and 2000 mg/kg bw/day. Treatment took place once daily from days 7 – 16 after mating. On day 21 of gravidity, the animals were sacrificed and delivered by caesarean section.
For the *main study*, groups of 20 – 21 female pregnant Wistar rats (mating ratio: one male to one female; the presence of implantation sites in the uterus was taken as confirmation of pregnancy status) received amidosulfuron (batch No. H 224; purity: 97.1 %; test substance was mixed in starch mucilage at a concentration of 200 g/l) from day 7 to 16 of pregnancy. The dose levels were 0 (vehicle control) and 1000 mg/kg bw/day. The test substance was mixed freshly every day; the stability and homogenicity of the mixtures were guaranteed for 24 hours.
General behaviour and general health condition were observed daily; food consumption and body weight gain were determined once weekly and again one day after final application.
21 days after mating, the animals were sacrificed and delivered by caesarean section: live and dead foetuses, resorption sites, the placentae and the corpora lutea were counted and macroscopically examined. The diameters of the resorption sites and the placental weights were determined as well. The organs of the dams were examined macroscopically; heart, liver, kidneys and spleen were weighed.
The number and distribution of live and dead foetuses as well as the external anomalies, body weight and sex were examined. About half of the foetuses from each litter were processed for the examination of skeletal abnormalities and the reminder were subjected to investigation of anomalies of the organs.

Range finding study:
At the dose level of 1000 mg/kg bw, a live foetus of one dam and a retarded foetus of the other were red and oedematous; no effects have been observed for the dams and the other foetuses. The dams treated with 2000 mg/kg bw exhibited piloerection beginning with application 6 onwards; the foetuses were normally developed. Since no effects were seen at 2000 mg/kg bw, the red and oedematous foetuses were regarded as spontaneous occurrences. Based on these results, the limit test using one dose level only (1000 mg/kg bw) was decided.

Main study – maternal effects:
No deaths or any disturbances with respect to behaviour and general health conditions have been observed; only one dam of the dose group exhibited alopecia on the abdomen from day 16 of gravidity and on both forelimbs from day 17 of gravidity onwards as one dam of the control group on the throat from day 9 of gravidity onwards. It is noted in the study report, that local hairness is known to be a spontaneous effect occurring in animals of this strain; since alopecia was observed in control animals as well, this effect was not attributed to treatment with amidosulfuron.
The food consumption of the dams treated remained within the range of the control animals.
Body weight gain was not affected by treatment of the test substance.
The number of corpora lutea, implantation sites and live foetuses of the dams of the treated group were comparable with those of the control group. The autopsy of the dams revealed slight to severe dilatation of the renal pelvis (3 dams from the dose group) and moderate dilatation of the right renal pelvis and slight dilatation of the right ureter (1 dam from the dose group); two dams of the control group showed moderate dilatation of the right renal pelvis. It is noted in the study report, that dilatation of pelvis renalis is known to be a spontaneous effect occurring in animals of this strain; since dilatation was observed in control animals as well, this effect was not attributed to treatment with amidosulfuron. No other macroscopically visible changes have been observed. The organ weights were shown to be comparable with those of the control animals.

Main study – litter data/fetal parameters:
The number of implantations and live foetuses as well as the distribution of male and female foetuses, the extent of pre- and postimplantation losses, the mean foetal and placental weights of the live foetuses (including macroscopical abnormities of the placenta) gave no indication of a treatment relationship.
External anomalies could not be observed in any of the foetuses.
Organ cross section examination of the foetuses showed a haematoma in the accessory lobe of the liver of one foetus of the dose group; a number of foetuses of both the dose and the control group exhibited unilateral or bilateral renal pelvic distension. A bilateral pelvic and uratral distension was observed in one foetus of the dose group. Furthermore, haematoma in the tail was found in one foetus of the dose as well as of the control group. These findings are classified as variations/minor anomalies, since these deviations from normal development is considered not to have any detrimental effect on fetal survival, development or function; renal distension and caudal haematomas occurred in control foetuses as well. No statistical difference from control has been observed (Exact Fisher Test; simultaneous comparison with control in a contingency table; p: 0.05). The relevant findings are summarised in table below.

Table 42: Developmental effects in rats: relevant findings with respect to visceral abnormalities (foetuses with variations/minor anomalies; % of foetuses examined)

Variations/anomalies	Dose group level [mg/kg bw]	
	Control group [no. of foetuses examined: 125]	1000 [no. of foetuses examined: 121]
Haematoma in left accessory lobe of the liver	0 [0 %]	1 [0.8 %]
Distension of renal pelvis on one or both sides	4 [3.2 %]	5 [4.1 %]
Distension of renal pelvis and ureter on both sides	0 [0 %]	1 [0.8 %]

Examination of the foetuses for skeletal abnormalities showed an increase compared to the concurrent control with respect to anomalies (waved or thickened rips; sternebrae fragmented, dysplastic or longitudinally displaced; scapula bent costad on both sides) and variations (short rib on the 7th cervical vertebra on left or both sides; thoracic vertebra with a short 14th rib on left or both sides) but showing no statistically significance. The only effect observed remained statistically significant was slight or missing ossification of one or more sternebrae (retardation); however, this finding was within the range of comparable historical control data. The relevant findings are summarised in table below.

Table 43: Developmental effects in rats: relevant findings with respect to skeletal abnormalities (number of foetuses with anomalies/variations /retardations; % of foetuses examined)

Variations/anomalies/ retardations	Dose group level [mg/kg bw]		Historical control data
	Control group [no. of foetuses examined: 132]	1000 [no. of foetuses examined: 134]	17471 foetuses included (147 studies)
Waved or thickened rips	3 [3.2 %]	4 [3 %]	No HCD

Variations/anomalies/ retardations	Dose group level [mg/kg bw]		Historical control data
	Control group [no. of foetuses examined: 132]	1000 [no. of foetuses examined: 134]	17471 foetuses included (147 studies)
Sternebrae fragmented, dysplastic or longitudinally displaced	4 [3 %]	7 [5.2 %]	No HCD
Scapula bent costad on both sides	0 [0 %]	1 [0.8 %]	No HCD
Short rib on the 7th cervical vertebra on left or both sides	1 [0.8 %]	1 [0.8 %]	No HCD
14th thoracic vertebra with a short 14th rib on left or both sides	2 [1.5 %]	6 [4.5 %]	No HCD
Slight or missing ossification of one or more sternebrae	45 [34.1 %]	59[1)] [44 %]	6288 [5.9 – 61.5 %]

1) Statistically significant (Exact Fisher Test; simultaneous comparison with control in a contingency table; p: 0.05) but within the range of historical control

Based on the results of the limit test provided, no treatment related effects could be observed for dams. The abnormalities with respect to findings after organ cross section examination were not statistically significant and regarded to have no detrimental effect on fetal survival, development or function. The increase in skeletal abnormalities (anomalies, variations, retardations) was not statistically significant from the concurrent control and/or within the range of historical control. There was no teratogenic effect observed at the dose level tested. The maternal as well as the fetal NOAEL can be established at > 1000 mg/kg bw/day.

Testing for embriotoxicity and effects on post-natal development in Wistar rats after oral administration (Limit test), *Baeder*, 1990

Groups of 20 – 22 female pregnant Wistar rats (strain: Wistar rat WISKf(SPF71); source: HOECHST breeding colony; mating ratio: one male to one female; the presence of implantation sites in the uterus was taken as confirmation of pregnancy status) received amidosulfuron (batch No. 1/87 + 1/88; purity: 94.1 %; test substance was mixed in starch mucilage at a concentration of 200 g/l) from day 7 to 16 of pregnancy. The dose levels were 0 (vehicle control) and 1000 mg/kg bw/day. The test substance was mixed freshly every day; the stability and homogenicity of the mixtures were guaranteed for 24 hours.
General behaviour and general health condition were observed daily; food consumption and body weight gain were determined once weekly and again one day after final application (body weight gain was recorded after delivery as well).

All of the females were to deliver normally and rear their offspring for 21 days: live and dead offsprings, times of birth, body weights, sex and any external anomalies of the offsprings were recorded. During the 21 day lactation period, the viability and general behaviour of the offsprings were noted; the body weight were determined on the day of delivery, on days 4 and 7 after birth and once weekly thereafter. For the examinations of physical development, the times of pinna separation, coat growth start, incisor eruption and eyelid opening were recorded. The dams and offsprings were killed between days 21 and 23 after delivery. The organs of all animals were

examined macroscopically; heart, liver, kidneys and spleen were weighed. Kidneys were cross-sectioned and the implantation sites were counted in the isolated uterus. Skeletal anomalies of the pups were not investigated.
No deaths or any disturbances with respect to behaviour and general health conditions have been observed for the dams; three dams of the dose group as well as 2 dams of the control group exhibited alopecia on the abdomen, neck, flanks or limbs. One dam from each group was associated with scab formation. It is noted in the study report, that local hairness and scab formation is known to be a spontaneous effect occurring in animals of this strain; since alopecia and scab formation were observed in control animals as well, these effects were not attributed to treatment with amidosulfuron.
The food consumption of the dams treated remained within the range of the control animals.
Body weight gain of the dams treated was somewhat lower than those of the control animals; since the body weight of the treated animals were lower than those of the control animals at the start of the study, it can be concluded that treatment did not affect the body weight (gain).
With exception of one dam of the treated group (one dead pup only; the disturbance of gravidity was stated to be a spontaneous occurrence because litter size of the other dams treated were within the range of previous control values and no increase of stillbirths was found), all dams delivered live pups. The duration of gravidity, the number of implantation and the ratio of male and female pups were not affected by treatment of the test substance.
Autopsy of the dams showed unilateral or bilateral dilatation of the renal pelvis (2 dams from the dose group and 4 control animals). It is noted in the study report, that dilatation of pelvis renalis is known to be a spontaneous effect occurring in animals of this strain; since dilatation was observed in control animals as well, this effect was not attributed to treatment with amidosulfuron. No other macroscopically visible changes have been observed. The organ weights were shown to be comparable with those of the control animals.
The pups delivered in the substance group were normally developed and their body weights after birth were comparable with these of the control group. No external anomalies were observed.
Examination during the lactating period showed normal general behaviour and health condition of the pups. Death of 13 pups of one litter 2 – 3 days after birth (reduced body temperature and insufficient suckling have been noticed) was considered to be a random finding as disturbances of lactating could not be observed in any of the other litters in this study and in the two-generation reproduction study in the rat up to 10000 ppm. The body weight gains of the pups throughout the lactation period corresponded to those of the control pups. The viability of the pups of the treated group was lower than the control group, but not statistically significant and within the range of historical control data. The physical development of the pups was regarded to be normal. The macroscopic examination the organs of the pups showed slight to marked pelvic distension in one or both kidneys of 7 pups from the substance group and 14 pups of the control group; as this effect was seen in the control group as well, no substance relationship can be assumed. The organ weights were within the range of the control group.

Based on the results of the limit test provided, no treatment related effects could be observed for dams and for pups. The sporadic effects observed (alopecia of the dams, dilatation of the renal pelvis of the dams, death of 13 pups of one litter 2 – 3 days after birth) were regarded as spontaneous incidents and not caused by the treatment. No skeletal anomalies were investigated. As a result of this study provided, maternal as well as the fetal NOAEL can be established at > 1000 mg/kg bw/day.

Rabbit:

Testing for embriotoxicity in the Himalayan rabbit after oral administration (Limit test), *Baeder*, 1988b

Before the start of the study, amidosulfuron had been administered in an oral *range finding study* (reported in summary form only) to groups of 2 gravid Himalayan rabbits at dose levels of 1000 and 2000 mg/kg bw/day. Treatment took place once daily from days 6 – 18 after mating. The animals were sacrified and delivered by caesarean section.
For the *main study*, groups of 15 female pregnant rabbits (mating ratio: one male to one female; the presence of implantation sites in the uterus was taken as confirmation of pregnancy status) received amidosulfuron (batch No. H 224; purity: 97.1 %; test substance was mixed in starch mucilage at a concentration of 200 g/l) from day 6 to 18 of pregnancy. The dose levels were 0 (vehicle control) and 1000 mg/kg bw/day. The test substance was mixed freshly every day; the stability and homogenicity of the mixtures were guaranteed for 24 hours.
General behaviour and general health condition were observed daily; food consumption and body weight gain were determined once weekly during the first three weeks, before the first treatment, on the day after the final treatment and again on day 29 of gravidity.
29 days after mating, the animals were sacrified and delivered by caesarean section: live and dead foetuses, resorption sites, the placentae and the corpora lutea were counted and macroscopically examined. The diameters of the resorption sites and the placental weights were determined as well. The organs of the dams were examined macroscopically; heart, liver, kidneys and spleen were weighed.
The number and distribution of live and dead foetuses as well as the external anomalies, body weight and sex were examined. All of the foetuses were processed for the examination of skeletal abnormalities and for investigation of anomalies of the organs.

Range finding study:
At the dose level of 1000 mg/kg bw one of the dams and at 2000 mg/kg bw both dams presented one and two dead conceptuses in addition to normally developed live foetuses. The second dam of 1000 mg/kg bw group had two live and two dead foetuses as well as two conceptuses under resorption. Based on these results, the limit test using one dose level only (1000 mg/kg bw) was decided.

Main study – maternal effects:
No deaths or any disturbances with respect to behaviour and general health conditions have been observed; only low amounts of faeces were excreted by one dam in the dose group and by one control animal.
The food consumption of the dams treated remained within the range of the control animals.
Body weight gain was not affected by treatment of the test substance.
The number of corpora lutea, implantation sites and live foetuses of the dams of the treated group were comparable with those of the control group. The autopsy of the dams revealed no changes in the internal organs; the organ weights were shown to be comparable with those of the control animals.
Main study – litter data/fetal parameters:
The number of implantations and live foetuses as well as the distribution of male and female foetuses, the mean foetal and placental weights of the live foetuses (including macroscopical abnormities of the placenta) gave no indication of a treatment relationship. The survival rate of the foetuses in the dose group showed no difference from that of the control foetuses. One dam of the dose group presented nine resorptions and another two resorptions; as one dam of the control group showed four resorptions, the number of resorptions in the dose group was shown to be higher, but

within the range of previous control values (as reported in the study report). External anomalies could not be observed in any of the foetuses.
Organ cross section examination of the foetuses showed no statistically significant increase of abnormities (blood in abdomal cavity) when compared to the concurrent control group; no other abnormities with respect to anomalies of the inner organs have been observed.
Examination of the foetuses for skeletal abnormalities showed an increase compared to the concurrent control with respect to anomalies (crack in parietal bone on right side, dysplastic or fused sternebrae), variations (short rib on the 7th cervical vertebra on one or both sides) and retardations (missing ossifiacation of the 5th sternebra) but showing no statistically significance. The only effect observed remaining statistically significant was a short and/or normally long 13th rib on one or both sides (variation); however, it this finding is within the limits of the spontaneous rate - historical control data with respect to retardation.The relevant findings are summarised in table below.

Table 44: Teratogenicity in rabbits: relevant findings with respect to skeletal abnormalities (number of foetuses with anomalies/variations/retardations; % of foetuses examined)

Variations/anomalies/ retardations	Dose group level [mg/kg bw]		Historical control data
	Control group [no. of foetuses examined: 79]	1000 [no. of foetuses examined: 73]	7642 foetuses included (120 studies)
Crack in parietal bone on right side	0 [0 %]	1 [1.4 %]	-
Dysplastic or fused sternebrae	5 [6.3 %]	1 [1.4 %]	-
Short rib on the 7th cervical vertebra on one or both sides	3 [3.8 %]	6 [8.2 %]	-
Short and/or normally long 13th rib on one or both sides	0 [0 %]	5 [6.8 %]1)	161 [0 – 11.6 %]
Missing ossification of the 5th sternebra	27 [34.2 %]	31 [42.5 %]	-

1) Statistically significant (Exact Fisher Test; p: 0.05) but within the limits of spontaneous rate

Based on the results of the limit test provided, no treatment related effects could be observed for dams. The increase in skeletal abnormalities (anomalies, variations, retardations) was not statistically significant from the concurrent control and/or within the range of historical control. There was no teratogenic effect observed at the dose level tested. The maternal as well as the fetal NOAEL can be established at > 1000 mg/kg bw/day.

4.11.2.2 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

RAC evaluation of developmental toxicity
Summary of dossier submitter's proposal The dossier submitter proposed not to classify amidosulfuron for developmental toxicity.
Comments received during public consultation

Comments received during public consultation did not question the dossier submitter's proposal.

Detailed description on relevant arguments and information received during the public consultation

Not needed.

Outcome of RAC assessment - comparison with criteria and justification

Developmental toxicity of amidosulfuron has been tested in Wistar rats and Himalayan rabbits; furthermore a postnatal developmental study in rats has been provided. The studies submitted were performed at the limit dose level of 1000 mg/kg/d. Isolated developmental findings were thoroughly discussed in the CLH dossier. The table in the section "Extended analysis of the key studies provided by the dossier submitter" contains those findings which showed statistical significance. The skeletal findings with significant increase in tested animals were graded as retardations and variations within historical control incidences. These findings (retardations and variations) are not considered sufficiently severe in order to trigger a classification for developmental toxicity.

Thus RAC as well proposes not to classify amidosulfuron for developmental toxicity.

Extended analysis of the key studies provided by the dossier submitter

The key findings of amidosulfuron developmental toxicity studies are summarized in the table below.

Table: Short summary of amidosulfuron key findings (developmental toxicity)

	Developmental toxicity study Wistar rats gd 7-16, 1000 mg/kg/d	Developmental toxicity study Himalayan rabbits gd 6-18, 1000 mg/kg/d	Post-natal developmental toxicity study Wistar rats gd 7-16, 1000 mg/kg/d
Maternal toxicity	-	-	-
Gestational parameters including embryo-/foetal lethality	-	-	-
External anomalies	-	-	-
Visceral findings	-	-	n.a.
Skeletal findings	Slight or missing ossification of one or more sternebrae 34.1% -> 44% within HCD	Short and/or normally long 13th rib on one or both sides 0% -> 6.8% within HCD	n.a.

Pup findings including functional deficits	n.a.	n.a.	- (reduced viability of pups not considered treatment-related)

Notes: n.a. = not applicable, gd = gestation day, HCD = historical control data

4.11.3 Other relevant information

No other information available.

4.11.4 Summary and discussion of reproductive toxicity

Amidosulfuron was tested in one 2-generation reproduction study in rats, two developmental studies in rats and one developmental study in rabbits. No effects on fertility were observed in the multigeneration study with rats. The lower body weight of foetuses after birth was observed only in highest dose group in presence of maternal toxicity and was not consistent between generations (F1 and F2) and between measuring time points (day 0, 1, 4, 7, 14 and 21). No treatment related effects on development were observed below the maternal toxicity, neither in the multigeneration study in rat nor in the developmental studies in rats and rabbits (up to 1000 mg/kg bw/d). No malformations were observed in foetuses of treated groups.

4.11.5 Comparison with criteria

No treatment related effects on fertility or development were observed in studies conducted with amidosulfuron, neither in rat multigeneration study, nor in rat and rabbit developmental studies which would trigger the classification for reproductive toxicity (according to both DSD and CLP).

4.11.6 Conclusions on classification and labelling

There is no evidence of effects on reproduction and development caused by amidosulfuron, therefore, no classification is proposed.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Amidosulfuron is not a substance with structures that are similar or related to those capable of inducing neurotoxicity. In all studies provided, amidosulfuron exhibited no signs of neurotoxicity such as CNS symptoms, behaviour abnormalities or histopathological changes with respect to brain, spinal cord or peripheral nerves. Therefore, studies on neurotoxicity after single or repeated oral exposure are not considered necessary.

RAC evaluation of neurotoxicity
Summary of dossier submitter's proposal The dossier submitter proposed not to classify Amidosulfuron for neurotoxicity
Comments received during public consultation Comments received during public consultation did not question the dossier submitter's proposal.
Detailed description on relevant arguments and information received during the public consultation Not needed.
Outcome of RAC assessment - comparison with criteria and justification In all studies provided Amidosulfuron did not exhibit signs of neurotoxicity such as CNS symptoms, behaviour abnormalities or histopathological changes with respect to brain, spinal cord or peripheral nerves. Thus RAC as well proposes not to classify Amidosulfuron for neurotoxicity.
Extended analysis of the key studies provided by the dossier submitter Not needed

4.12.1.2 Immunotoxicity

According to the available acute, subchronic and chronic studies, there was no indication of an immunotoxic potential.

4.12.1.3 Specific investigations: other studies

No other data available.

4.12.1.4 Human information

No information available from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 45: Summary of relevant information on degradation

(Annex point as reference to the DAR)	Method	Results	Remarks	Reference
B.8.4.1.1 Hydrolysis rate (IIA 2.9.1)	Hydrolysis Guideline: No	DT_{50} pH 3 = 1.34 d pH 4 = 3.87 d pH 5 = 30.56 d pH 6 = 237.1 d		Schollmeier M., Britten I. (1992) Document No: A47707
B.8.4.1.1 Hydrolysis rate (IIA 2.9.1)	Hydrolysis Guideline: No	pH 5 = 33.9 d pH 7 = > 365 d pH 9 = > 365 d		Schollmeier M., Eyrich U. (1992) Document No: A48869
B.8.4.1.2 Direct phototrans-formation (IIA 2.9.2)	Photolysis Guideline: No	DT_{50} Latitude 52°N, 2370 ± 1194 d, photolytically stable		Gildemeister H. (1989) Document No: A40662
B.8.4.2 Biological degradation (A II 7.2.1.3.2)	Biological degradation OECD guideline 301 B	Not ready biodegradable		Noack M., Wolf U., Noack U. (1991c) Document No. A54662
B.8.4.2.1 Water/Sedi ment Study (A II 7.2.1.3.2)	Water/Sediment Study SETAC guideline	Water: DT_{50}: 73 d (S1), 10 d (S2) Whole system: DT_{50}: 91 d (S1), 16 d (S2)		Knoch E. (2000) Document No: C009793

5.1.1 Stability

Hydrolysis

Reference: Schollmeier M., Britten I. (1992a): Determination of abiotic hydrolysis as a function of pH. (Hoe 075032 00 ZB98 0001). Document No: A47707

Material and methods: Amidosulfuron (batch H 225/1+2, purity 98.5 %) was applied to sodium citrate monohydrate buffer solutions of pH 3, 4, 5, 6. 19.9 mg amidosulfuron were dissolved in 25 mL acetonitrile. Two mL of this solution were pipetted into a 1000 mL volumetric flask and filled to the mark with the respective buffer solution resulting in a concentration of 1.592 mg/L.. The test solutions were incubated in the dark at 25 °C up to 30 days. PH values and microbial activity was

controlled at each sampling time on days 0, 1, 2, 3, 4, 7, 11, 14, 18, 21, 25, 28, 30. Samples were analysed by HPLC. The accuracy and precision of the analysis method was examined with a dilution series with the ai of 3.11 mg ai/L to 0.016 mg ai/L (4 replicates at each concentration and pH). Mean recovery rates of the test substance were in the range of 98.3 to 100.32 % for the high concentrations series and 87.5 to 100 % of nominal concentration for the lowest concentration series.

Findings: The pH values remained sufficiently constant during the entire testing period (pH 3, 2.96 ± 0.017; pH 4, 3.97 ± 0.022; pH 5, 4.99 ± 0.012; pH 6, 6.02 ± 0.018). Several test samples were contaminated by bacteria/fungi. The values derived from contaminated samples were not included in the calculation of DT_{50} values. The calculation of DT_{50} values was based on first order kinetics. Half lives were calculated by linear regression analysis ($\ln C_t = \ln C_0 - k*t$) to be 1.34, 3.87, 30.56 and 237.1 days at pH 3, 4, 5 and 6, respectively. The corresponding correlation coefficients (r^2) were 0.9995, 0.9998, 0.9986 and 0.8316. One metabolite was identified as Hoe 092944. The structure of the second metabolite was not determined in this study but an attempt to identify this metabolite was made in the study of Schollmeeier M., Eyrich U., (1992) (see below). The metabolite Hoe 092944 reached a maximum concentration at the end of the study of 21.7 % ai equivalents at pH 3 and 20.3 % ai equivalents at pH4. At pH 5 and 6 the metabolite Hoe 092944 was found in proportions of less than 10 % ai equivalents.

Conclusion: Amidosulfuron is hydrolytically rapidly degraded at low pH values but is stable at an environmentally relevant pH value. DT_{50} pH 4 = 3.87 d, DT_{50} at pH 6 = 237.1 d.

Reference: Schollmeier M., Eyrich U. (1992): Hoe 075032 Determination of abiotic hydrolysis as a function of pH (Hoe 075032 00 ZB98 0001). Document No: A48869

Material and methods: The hydrolytic degradation of amidosulfuron (code Hoe 075032 00 ZB98 0001, purity 98.5 %) was tested at pH 5, 7 and 8. Citric acid, potassium dihydrogenphosphate and potassium chloride were used for preparation of the buffer solutions. 47.59 mg amidosulfuron were dissolved in 100 mL acetonitrile. An aliquot of 10 mL was pipetted to a 1000 mL volumetric flask and filled to the mark with the respective buffer solutions, resulting in a concentration of 4.759 mg ai/L. The test samples were incubated in the dark at 25 ± 1 °C for 30 days. The pH values and the microbial activity were controlled at an interval of 8 days and 10 days, respectively. Two samples were taken for analysis on days 0, 5, 9, 13, 16, 20, 23, 27 and 30. Samples were analysed by HPLC.

Findings: The pH values remained constant during the entire experimental period (pH 5: 5.1 ± 0.021, pH 7: 7.03 ± 0.015, pH 9: 9.05 ± 0.03. High bacterial counts were found at pH 9. Nevertheless, no significant degradation was observed at pH 9. Therefore it was assumed that the bacterial activity did not have any influence on the degradation kinetics. The accuracy and precision of the analytical method was investigated in the study of Schollmeier M., Britten I. (1989). The calculation of DT_{50} values was based on first order kinetics according to the formula: $\ln C_t = \ln C_0 - k*t$. The DT50 values were 33.9, > 365 and > 365 days at pH 5, 7 and 9. The correlation coefficient (r^2) was high at pH 5 ($r^2 = 0.9967$) but low at pH 7 and 9 ($r^2 = 0.5545$ and 0.5842). Two degradation products were observed. One was identified as Hoe 092944. The second metabolite (which was also observed in the hydrolysis study of Schollmeier M., Britten I. 1992) was assumed to be 4, 6-dimethoxypyrimidin but the final identity proof failed. Hoe 092944 and the second metabolite reached maximum values of 21.4 % and 22.7 % ai equivalents at the end of the study at pH 5. The proportion of Hoe 092944 remained well below 10 % of ai equivalents at pH 7 and pH 9. The second metabolite was not detected at pH 7 and 9.

Conclusion: The DT_{50} of amidosulfuron was 33.9 d under acidic conditions (pH 5, 25 °C). Amidosulfuron is stable at neutral and alkaline aqueous conditions (pH 7 and 9, 25 °C).

Photolysis:

Reference: Gildemeister H. (1989): Hoe 075032-^{14}C Photodegradation in water. Document No: A40662

Material and methods:

Radiolabelled amidosulfuron (batch 17040 I, purity > 98 %) was dissolved in acetonitrile and a sterile 0.01 molar phosphate buffer solution (pH 7) to a concentration of 62 µg ai/L. Duplicates have been continuously irradiated with an xenon arc lamp for 240 hours, corresponding to 122 - 123 days of sunlight at 52 °N. Wavelengths below 290 nm were cut off by filters. The incubation temperature was maintained at 25 ± 1 °C. Samples were taken from the test solutions and the dark control after 0, 6, 24, 48, 72, 96 and 240 hours and analysed by HPLC.

Findings:

Recoveries were in the range of 97.6 – 102.6 % of applied radioactivity. The photodegradation of amidosulfuron was slow. Hoe 075032 absorbs UV light with a wavelength of 200 – 270 nm. The absorption spectrum did practically not overlap with the emission spectrum of the xenon arc lamp. Two degradation products M1 and M2 were detected. M1 and M2 reached a maximum of 7 % and 2.8 %, respectively. M2 was also present in the dark control. The DT_{50} values were calculated assuming first order kinetics ($\ln C = \ln C_0 - k*t$, $DT_{50} = \ln 2 / k$). The average DT_{50} value under outdoor conditions (52 °N) was calculated to be 2370 ± 1194 days.

Conclusion: Amidosulfuron is photolytically stable, DT_{50} (52 °N) = 2370 ± 1194 days.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

As measured data are available estimation is not relevant for this dossier.

5.1.2.2 Screening tests

Readily biodegradability

Reference: Noack M., Wolf U., Noack U. (1991c): Biological degradability of Hoe 075032 in a modified Sturm test in accordance with the OECD guideline 301 B for testing of chemicals of 19 September 1984. Document No. A54662

Material and methods:

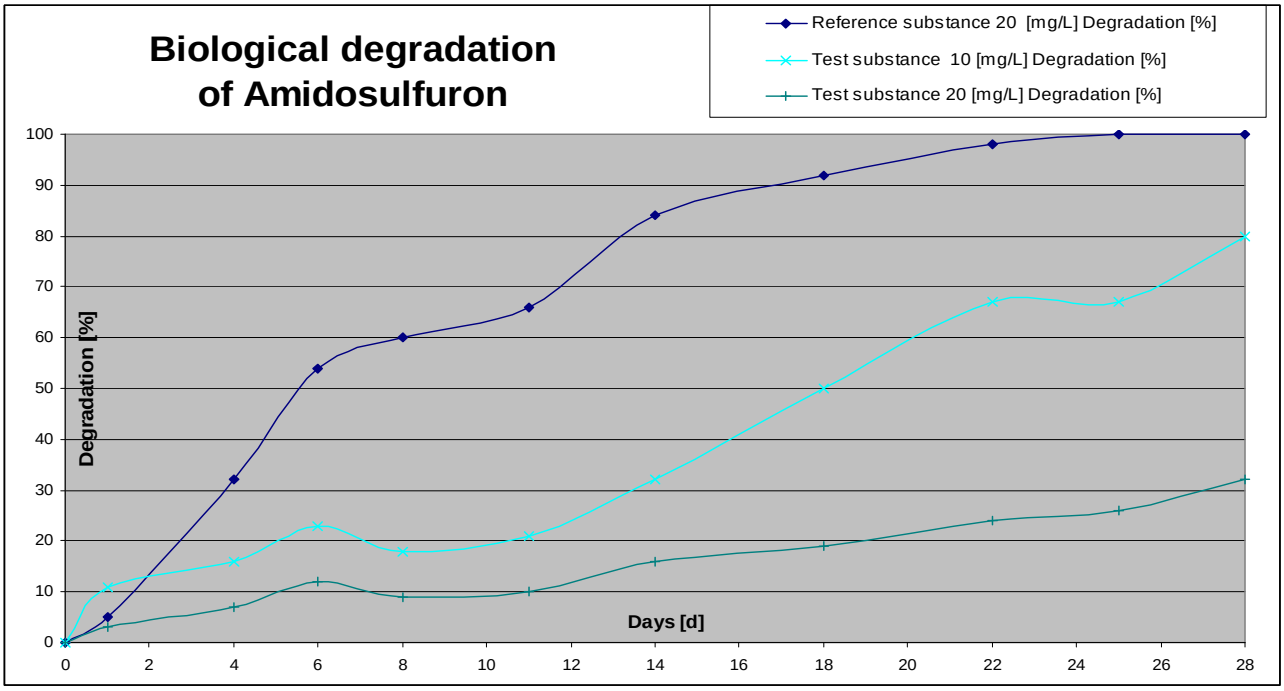
The biodegradability of amidosulfuron (Hoe 075032 00 ZD96 0002, batch 6-9+12/88, Roe 15729, purity 95 %) was tested in non-adapted activated sludge from a sewage plant. The ai was applied at concentrations of 10 and 20 mg/L (one test vessel per concentration; testvolume = 3L). Control with blank value batch is also conducted over 28 days.The cell density of bacteria was $2 * 10^6$ (N/ml). Sodium acetate served as a reverence substance at a concentration of 20 mg/L. CO_2 was trapped with $Ba(OH)_2$. The incubation temperature was 22 – 24 °C. CO_2 production was measured at 0, 1, 4, 6, 8, 11, 14, 18, 22, 25 and 28 days. The CO_2 formation in the test batches was compared to the theoretical CO_2 formation of the test substance. The pH value in the test batches was measured on day 27. The DOC value was determined at the beginning and end of test.

Findings:

Table 46: CO_2 production and biological degradation in the control, reference and test preparations/batches (test volume = 3L):

Date	Control [blank value batch]	Reference substance 20 [mg/L]			Test substance 10 [mg/L]			Test substance 20 [mg/L]		
	mg CO_2	mg CO_2		Degradation	mg CO_2		Degradation	mg CO_2		Degradation
		gross	net	[%]	gross	net	[%]	gross	net	[%]
13.Sep	1.4	4.3	2.9	5	4.8	3.4	11	3.5	2.I	3
16.Sep	5.5	26.3	20.8	32	10.5	5	16	10.1	4.6	7
18.Sep	7.7	42.5	34.8	54	15.1	7.4	23	15.4	7.7	12
20.Sep	14	52.2	38.2	60	19.7	5.7	18	20	6	9
23.Sep	17.5	59.6	42.1	66	24.3	6.8	21	24.2	6.7	10
26.Sep	22.5	76.7	54.2	84	32.9	10.4	32	32.7	10.2	16
30.Sep	27.7	86.9	59.2	92	43.7	16	50	40.1	12.4	19
04.Oct	33.4	96.3	62.9	98	55	21.6	67	48.6	15.2	24
07.Oct	39.8	103.8	64	100	61.3	21.5	67	56.2	16.4	26
10.Oct	46.5	112.1	65.6	100	72.2	25.7	80	67	20.5	32
thCO$_2$ Reference substance = 64.2 [mg/3L]; thCO$_2$Test substance 10/20 [mg/L] = 32.1/64.2 [mg/3L]										

Graph: biological degradation of Amidosulfuron (Testsubstance = Amidosulfuron)



Sodium acetate was 100 % metabolised after 28 days demonstrating sufficient activity of the activated sludge. The development of CO_2 increased markedly in both test concentrations after day 11. The biological degradation of amidosulfuron was 80 % (10 mg ai/L) and 32 % (20 mg ai/L) after 28 days of incubation. The pass level of 60 % of theoretical formation of CO_2 was not reached within the 10 day window.

Conclusion: According to screening test criteria in CLP Amidosulfuron is not considered as readily biodegradable since the pass level of 60% of ThCO2 was not reached within 10 day window.

5.1.2.3 Simulation tests

Biodegradation in water/sediment systems

Reference: Knoch E. (2000): Degradability and fate of amidosulfuron in the aquatic environment (water/sediment system). Document No: C009793

Guideline: SETAC guideline "Procedures for assessing the environmental fate and ecotoxicity of pesticides", part 1, 8.2 of march 1995 to satisfy the data requirements of EU Directive 95/36/EC, Annex 1, section 7, part 7.2.1.3.2 of July 1995

Material and methods: The degradation of radiolabelled amidosulfuron (^{14}C in the 2-position of the pyrimidine ring, AE F075032-[pyrimidyl-2-14C], charge Z 29052-1, chemical purity 99.7 %) was examined in two water/sediment systems. The sediment/water samples (sand and clayish silt) originated from two brooks in Germany (Bickenbach and Widersheim). Water/sediment systems were incubated in the dark at 20 ± 2 °C. After three weeks of acclimatisation stable values of redox potential of water and sediment, oxygen content and pH value of water were reached and the test systems were fortified with the test compound.

Total recoveries ranged from 95 to 106.6 % of applied radioactivity. Radioactivity in the water phase of both systems declined steadily to 39.8 % (Bickenbach) and 9.5 % (Unter Widdersheim) until day 180. The proportion of radioactivity bound to the NER fraction of the sediment rose until the end of test to levels of 27.2 % (S 1) and 60.6 % (S 2).

Mineralization was an important degradation pathway reaching a value of 18.78 % CO_2 in S 1 (Bickenbach) and 25.2 % CO_2 in S 2 (Unter Widdersheim). AE F101630 and AE F094206 were identified as major metabolites in both systems. AE F 094206 reached a maximum of 14.6 % and 17.1 % of applied radioactivity in the water phase of S 1 and S 2, respectively. AE F101630 reached a maximum proportion of 12.3 % in the water phase of S 2. Additionally a minor metabolite AE F092944 was identified with max. amounts of 6.4 % in S 1 (Bickenbach). Two unknown degradates were found in the water phase of both systems at concentrations ranging from 2.4 to 8.4 %. In the sediment phase of both systems the proportion of the three metabolites was clearly less than 10 % of applied radioactivity. The limit of quantification was set 2 % of the applied radioactivity. Sediment samples taken on day 120 were subject to further characterization of the NER fraction. 5.6 % (S 1) and 54 % (S 2) of applied radioactivity were found to be bound to the humin fraction at day 120.

The single first order DT_{50} and DT_{90}values for amidosulfuron were calculated to be as follows:

Table 47: The single first order DT_{50} and DT_{90}values:

Bickenbach (S 1)				Unter Widdersheim (S 2)			
	DT_{50}	DT_{90}	r^2		DT_{50}	DT_{90}	r^2
water	73 d	244 d	0.994	water	10 d	34	0.989
water/sediment	91 d	302 d	0.997	water/sediment	16 d	54	0.981

Conclusion: Amidosulfuron degraded steadily in both water/sediment systems. The ai disappeared much faster from S 2 whose sediment was characterized by a high content of organic material. The applied radioactivity was bound as NER to the humin fraction. The DT50 values for the water and the whole system were 73 d / 91 d (S 1) and 10 d / 16 d (S 2), respectively. AE F 094206 and AE F101630 were major metabolites with maximum concentrations of 17.1 % and 12.3 % in the water phase. Mineralization was an important degradation pathway reaching a value of 18.78 % CO_2 in S 1 and 25.2 % CO_2.in S 2.

Comment (RMS): The limit of quantification for unknown residues was 2 % which has probably led to the (relatively small) differences in the mass balance of the total extractable residues and the summarized radioactivity of the ai and the metabolites in the sediment.

Study considered to be acceptable.

5.1.3 Summary and discussion of degradation

Hydrolysis: Amidosulfuron is hydrolytically rapidly degraded at low pH values but is stable at an environmentally relevant pH values. DT_{50} pH 4 = 3.87 d, DT_{50} at pH 6 = 237.1 d.

Photolysis: Amidosulfuron is photolytically stable, DT_{50} (52 °N) = 2370 ± 1194 days.

Ready biodegradability: Amidosulfuron is biologically degradable, but it did not meet the criteria for ready biodegradability.

Water/sediment study: Amidosulfuron degraded steadily in both water/sediment systems. The ai disappeared much faster from S 2 whose sediment was characterized by a high content of organic material. The applied radioactivity was bound as NER to the humin fraction. The DT50 values for the water and the whole system were 73 d / 91 d (S 1) and 10 d / 16 d (S 2), respectively. AE F 094206 and AE F101630 were the main metabolites with maximum concentrations of 17.1 % and 12.3 % in the water phase. Mineralization was an important degradation pathway reaching a value of 18.78 % CO_2 in S 1 (Bickenbach) and 25.2 % CO_2.in S 2 (Unter Widdersheim).

5.2 Environmental distribution

The metabolism of Amidosulfuron in soil under aerobic conditions was studied in three laboratory metabolism studies using six different soils. In the first study with four different soils (sandy loam, sand, loamy sand, silt loam) two metabolites accounting for > 10 % AR were detected. One of it ("metabolite B") reached a maximum of 49.6 % AR after 7 days in a loamy sand soil and was identified as HOE 101630, which is formed by demethylation of the parent substance. Another metabolite ("metabolite A") reached a maximum of 25.8 % AR after 100 days. This metabolite was later identified as HOE 128870, which is formed by hydroxylation from HOE 101630. Three other metabolites (metabolites "C", "D" and "E") were detected. With a few exceptions metabolites D and E could not be separated by HPLC analyses. Metabolite C and HOE 101630 could also not be separated at later sampling points during the course of the study. Attempts have been made to estimate single values for these metabolites by extrapolating the proportion of the single metabolites from those sampling points where separation was possible to the later sampling points. Unknown metabolite "C" occurred in maximum amounts of 7.7 % AR (day 14), 4.8 % AR (day 14), 4.3 % AR (day 3) and 6.2 % AR (day 3) in the four soils. Unknown metabolite "D" occurred in maximum amounts of 5.0 % AR (day 28) 8.1 % AR (day 21) and 8.8 % AR (day 70; extrapolated value) in three of the soils, respectively. In one of the soils this extrapolation was not possible for metabolite "D" as no single values at all for this metabolite were available in this soil. But from the data it can be assumed that in this soil the amount of metabolite "D" would be very small. Metabolite E

occurred in maximum amounts of 8.6 % AR (day 49), 9.1 % AR (day 21) and 12.1 % AR (day 35; extrapolated value) in three soils, respectively. In the fourth soil no single value was available for this metabolite and thus no extrapolation was possible. From the data it can be assumed that also in this soil the amount of metabolite "E" is in the range of 8-12 %. Metabolite "E" was later identified as ring-hydroxylated amidosulfuron (later assigned as AE 1569309) by comparing chromatograms (relative retention times, HPLC conditions) from the soil study with chromatograms from studies on residues in wheat plants. It is an important fact that both, metabolite AE F128870 and AE 1569309, can not be synthesised and identification is only possible by indirect methods, as no standard solutions are available. Therefore separate studies on fate and behaviour or ecotoxicology are not possible with these metabolites.

In the second study with one soil (sandy clay loam) metabolite HOE 101630 reached a maximum of only 5.2 % AR after 14 days. "Metabolite A" (AE F128870) reached a maximum of 16.6 % AR after 70 days. All other not identified metabolites accounted for not more than 2.1 % AR.

In the third study with one soil (loamy sand) metabolite HOE 101630 reached a maximum of 8.4 % AR after 7 days, and two not identified metabolites "U2" and "U4" reached maxima of 38.6 % AR after 56 days and 10.8 % AR after 41 days, respectively. Due to its retention time metabolite "U2" was proposed by the notifier to be AE F128870. Comparing chromatograms and relative retention times metabolite U4 was found to be identical with metabolite "E" of the first study and thus can be identified as metabolite AE 1569309. One identified minor metabolite (AE F094206) reached a maximum of 1.5 % AR.

Under aerobic conditions the formation of CO_2 was in the range of 3 to 47% after 91-100 days. Not extractable radioactivity amounted for up to 16 - 59% after 91-100 days.

Under anaerobic conditions amidosulfuron is very slowly degraded in soil showing a DT_{50} >300 d. The metabolism starts with o-demethylation to form metabolite AE F101630, which may be followed by another demethylation step. Metabolite AE F094206 is formed by cleavage of the urea moiety. Ring opening and oxidation into CO_2 does not take place under anaerobic conditions.

Major metabolites (> 10 % AR) were AE F101630 and AE F094206, which were found in the water phase in the study with the flooded soil.

The rate of degradation under aerobic conditions of amidosulfuron was investigated in 5 studies and 8 different soils. The tests were carried out at 20° C and a soil moisture of 38-40 % MWHC. The calculated DT_{50} values for amidosulfuron (1^{st} order kinetics) as stated in the study reports were in the range of 3 – 29 days (mean 19.2 days). The calculated DT_{90} were in the range of 10 – 97 days (mean 63.7 days).

The degradation rates, calculated on the basis of single 1^{st} order kinetics, are summarised in the tables below:

Table 48: Degradation rates of amidosulfuron in the laboratory under standard conditions

Reference	Soil	As stated in the original study		
		DT_{50}	**DT_{90}**	**r^2 or B**
Till, 1989; Doc. A40368	**Sandy loam**	24	81	0.998
	Sand	29	97	0.994
	Loamy sand	3	10	0.988
	Silt loam	28	92	0.994

Reference	Soil	As stated in the original study		
		DT_{50}	DT_{90}	r^2 or B
Till, 1991a; Doc. A46505	**Sandy clay loam**	21	71	0.982
Dorn, 2001; Doc. C012457	**Loamy sand**	9.5	31.5	0.996
Gildemeister, 1993a; Doc. A49610	**Sandy loam**	21* (24)+	70* (79)+	0.990
Gildemeister, 1993b; Doc. A49611	**Loamy silt**	15* (17)+	49* (55)+	0.998
	Silty loam	22* (20)+	72* (65)+	0.911
Arithm. mean		19.2 (19.5)	63.7 (64.6)	
Geometric mean		16.3 (16.6)	54.1 (55)	
Median		21 (21)	71 (71)	

* Timme and Frehse, best fit.
+ For the three soils degradation rates were recalculated by the RMS using single 1st order kinetics (values in parenthesis).
** Moisture corrected values calculated from the DT_{50} values which were stated in the original study.

At lower temperatures the degradation of amidosulfuron follows the same route as at 20° C. The degradation study at 10° C was done with one of the soils used in a 20° C study (Till, 1989). When comparing the results of the identical soils (loamy sand) it can be concluded that the degradation of amidosulfuron is reduced at lower temperatures. The half life at 10° C was calculated to be 21 days, whereas the half life at 20° C in the same soil was calculated to be 3 days. At 10° C the amounts of bound residues and mineralization to CO_2 were significantly reduced. Metabolite AE F128870 reached a maximum of 9.8 % AR after 70 days of incubation, the maximum of metabolite AE F101630 was reached after 49 days (40.4 % AR). The sum of not identified metabolites reached its maximum of 8.7 % AR after 70 days.

Two studies on the photolytic degradation of amidosulfuron on soil surface were submitted. In an old study three metabolic fractions (which could not be identified) were detected one of them reaching 11.2-19.0 % AR at the end of the study (6 days). In the second, new, study beside minor fractions one main fraction reached a maximum of 11.5 % at the end of the study (15.5 days; corresponds to 30 days sunshine 30° N). This fraction could be resolved into a number of components with a largest fraction accounting for 6.7 % AR in maximum (at study termination).

In both studies almost no degradation of amidosulfuron was observed in the dark controls. Degradation in irradiated samples was very slow with half-lives of 520 hours in the first study (corresponding to 104 days at 52° N, 12 hours day light) and 1362 hours in the second study.

Photolytic degradation on soil surface was shown to be only a minor pathway for the elimination of amidosulfuron from soil.

Field study: A soil dissipation study was conducted with formulated amidosulfuron in winter wheat at three locations in Germany. The product was applied in amounts equivalent to 0.03 kg ai/ha or 0.06 kg ai/ha at growth stage 29-31. After application of 0.03 kg ai/ha initial residues ranged between 0.009 – 0.013 mg/kg in the upper soil layer (0-20 cm). This soil layer was free of residues above the LOQ (< 0.002 mg/kg) after one to three month, pending on the location. No residues above the LOQ were found in any of the soil samples from the lower soil layer (20-40 cm).

After application of 0.06 kg ai/ha initial residues ranged between 0.0183 – 0.035 mg/kg in the 0-20 cm soil layer. After approx. 2-3 months residues in this soil layer were below the LOQ. In the 20-40

cm soil layer only one out of 15 samples from this application rate residues of amidosulfuron were detectable at the level of the LOQ (0.0023 mg/kg). It was not possible to estimate the degradation rate for amidosulfuron from the data available. Metabolites were not investigated in this study.

5.2.1 Adsorption/Desorption

The adsorption behaviour of amidosulfuron was studied in seven soils using the batch equilibrium method. The K_f values were in the range of 0.06 to 2.37 L/kg. The $K_{F,OC}$ values were calculated to be in the range of 5.7 to 83.3 L/kg with an arithmetic mean of 36.4 L/kg, indicating high mobility. The Freundlich coefficient 1/n was in the range of 0.91 to 1.1 with an arithmetic mean of 0.98.

5.2.2 Volatilisation

With a Henry´s constant of 1.6 x 10^{-6} Pa m^3/mol (20° C) and a vapour pressure of 1.3 x 10^{-5} Pa (20° C) amidosulfuron is not expected to volatilise in significant amounts. Amidosulfuron is quickly eliminated by photochemical oxidative degradation in the troposphere, for which a DT_{50} of 0.25 days was calculated (Atkinson method). Therefore no significant residues in the atmosphere are expected.

5.2.3 Distribution modelling

5.3 Aquatic Bioaccumulation

Table 49: Summary of relevant information on aquatic bioaccumulation

(Annex point as reference to the DAR)	Method	Results				Remarks	Reference
B.2.1.14 Partition coefficient n-octanol/water (IIA 2.8)	Partition coefficient n-octanol/water	pH	4.0 (23 °C)	7.0 (22 °C)	9.0 (23 °C)		Muehlberger B., Wiche A. (2004a) (Document C044973)
		Log P_{ow}	1.07	-1.56	-2.21		
		P_{ow}	11.7	0.027	0.006		

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

The bioconcentration potential of of amidosulfuron is low (log_{Pow} = 1.07 at pH 4, 23°C), therefore no bioaccumulation study is necessary.

5.3.1.2 Measured bioaccumulation data

No experimental data are available.

5.3.2 Summary and discussion of aquatic bioaccumulation

Based on the measured log Pow values (log_{Pow} = 1.07) amidosulforon is considered to have a low bioaccumulation potential.

5.4 Aquatic toxicity

Table 50: Summary of relevant information on aquatic toxicity (All studies here presented refer to the Draft assessment report)

(Annex point as reference to the DAR)	Method	Results						Remarks	Reference
		testorganism	testcondition	exp. time	endpoint	NOEC (mg ai/L)	EC50/LC50 (mg ai/L)		
IIA, 8.2.1. Acute toxicity to fish	EPA-660/3-75-009 (1975), BBA Leaflet no. 33 (1975)	*Oncorhynchus mykiss*	static	96 h	LC50	100	> 320		Fischer R. (1987af): Document No. A35829
IIA 8.2.2. Chronic toxicity to fish	OECD 204 (1984)	*Oncorhynchus mykiss*	flow through	21 d	NOEC	6.41*	> 320*		Fischer R. (1991d): Document No. A45487
IIA, 8.2.1. Acute toxicity to fish	EPA-660/3-75-009	*Lepomis macrochirus*	static	96 h	LC50	100	> 100		Fischer R. (1987ah): Document No. A37697
IIA, 8.2.1. Acute toxicity to fish	EPA-660/3-75-009	*Lepomis macrochirus*	static	96 h	LC50	100	> 100		R., Schulze E. F. (1988a): Document No. A38908
IIA, 8.2.1. Acute toxicity to fish	EPA 540/9-85-009 (1985)	*Cyprinodon variegatus*	static	96 h	LC50	94	> 94		Boeri R.L. (1989f): Document No. A40984
IIA, 8.2.4. Acute toxicity to aquatic invertebrate	OECD 202(1984)	*Daphnia magna*	static	48 h	EC50	18	55		Fischer R., Schulze E. F. (1988b): Document No. A38705
IIA, 8.2.4. Acute toxicity to aquatic invertebrate	EPA-660/3-75-009(1975)	*Daphnia magna*	static	48 h	EC50	10	36		Fischer R. (1987ag): Document No. A37699
IIA, 8.2.5. Chronic toxicity to aquatic invertebrates	OECD 202 (1984)	*Daphnia magna*	flow through	21 d	NOEC	1	3.2		Heusel R. (1991cz): Document No. A46125
IIA, 8.2.4. Acute toxicity to aquatic invertebrate	EPA 540/9-85-010(1985)	*Mysidopsis bahia*	static	96 h	LC50	56	75		Boeri R. L. (1989e): Document No. A40985
IIA, 8.2.6. Effects on algal growth and growth rate	OECD 201 (1984)	*Scenedesmus subspicatus*	static	72 h	EbC50	3.2	47		Fischer R., Schulze E. F. (1988c): Document No. A38704
IIA, 8.2.6. Effects on algal growth and growth rate	OECD 201,EPA J 123-2,EU C.3	*Navicula pelliculosa*	static	96 h	EbC50/ErC50	> 84.2	84.2		Sowig P., Weller O., Gosch H. (1999aj): Document No. C001109
IIA, 8.2.8 Effects on aquatic plants	US-EPA, 123-2, ASTM E1415-91	*Lemna gibba*	static	14 d	NOEC/ErC50	0.00874	0.0176		Morrow J. E., Ward G. S. (1993a): Document No. A49587
IIA, 8.2.8 Effects on aquatic plants	OECD draft guideline, June 1998, US-EPA J 123-2, ASTM E 1415-19	*Lemna gibba*	static	7 d	NOEC EbC50 / ErC50	NOEC is well below 0.0092 mg/L	< 0.0092 / <0.0092	percentage of inhibition: 55 % (growth rate), 53 % (biomass)	Sowig P. (2002ag): Document No. C025093

* No replicates were used for testing and the concentration of amidosulfuron was measured only for nominal test concentrations of 1, 10 and 100 mg ai/L. The mean measured concentrations of the test substance were below 80 % of nominal concentrations, therefore it is not acceptable to use nominal concentrations (as it was done by the notifier). Since no measured values were available for the test concentrations of 5 and 50 mg ai/L the nominal values were extrapolated to values comparable to the mean measured values of the other test concentrations.

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Acute toxicity to fish (refer to Annex point IIA 8.2.1)

Reference: Fischer R. (1987af): The effect of Hoe 075032 – substance, technical (Identification code: Hoe 075032 OH ZC98 0001) to *Salmo gairdneri* (rainbow trout) in a static acute toxicity test (Sg365/b, method BBA). Document No. A35829

Test guideline: EPA-660/3-75-009 (1975), BBA Leaflet no. 33 (1975)

Material and methods:

The toxicity of amidosulfuron (purity 97.7 %, batch no. H225/1/2) to rainbow trout (*Oncorhynchus mykiss*, former *Salmo gairdneri*) was tested under static conditions for 96 hours. Ten fish with an average length of 4.8 cm were tested at each concentration, solvent control and control. The test vessels had a volume of 50 L. The fish loading was 0.96 cm/L or 0.25 g fish/L. The nominal concentrations were 32, 100, 320 and 1000 mg ai/L. Mortality and abnormal behaviour were recorded every 24 hours. Dimethylsulphoxide (DMSO) was used as a solvent at a concentration of 0.5 mL/L. Test conditions: Temperature, 16 ± 1 °C; photoperiod, 16 h light / 8 h dark, pH, 7.1 – 8; total hardness (as $CaCO_3$) 283 mg/L; dissolved O_2, 6.5 – 10.7 mg/L

Findings:

The visual limit of solubility of the ai was exceeded at a concentration of 320 mg ai/L. No dead individuals were observed in the control, solvent control and in the test concentrations of 32 and 100 mg ai/L. 3 fish died in the test concentration of 320 mg ai/L and one fish was found to be dead at the highest test concentration of 1000 mg ai/L. Abnormal swimming behaviour (as an indication of intoxication) was observed at concentrations of 320 and 1000 mg ai/L. Based on the test results the LC50 could not be calculated. The LC50 was assumed as > 320 mg ai/L.

Conclusion: LC50 > 320 mg ai/L, NOEC = 100 mg ai/L

Comment (RMS): The concentration of the ai was not measured. No replicates of the concentrations were tested. However, the study was accepted and a new study with *Oncorhynchus mykiss* is not considered to be necessary because of the following reasons: Fish are not the most sensible group of organisms. Studies with the formulated ai and *Oncorhynchus mykiss* were conducted and the toxicity of the formulated product is within the same range as the unformulated ai.

Reference: Fischer R. (1987ah): The effect of Hoe 075032 – substance, technical (Identification code: Hoe 075032 OH ZC960001) to *Lepomis macrochirus* (bluegill sunfish) in a static acute toxicity test (method EPA). Document No. A37697

Test guideline: EPA-660/3-75-009 (1975)

Material and methods:

The toxicity of amidosulfuron (purity 95.7 %, batch no. H225/5+6) to bluegill sunfish (*Lepomis macrochirus*) was tested under static conditions for 96 hours. Five fish with an average length and weight of 4.7 cm and 2.5 g (mean from 10 measurements) were placed in test vessels with a volume of 50 litres. The fish loading was 0.25 g/L or 0.47 cm/L. The test was conducted with six replicates of a test concentration of 100 mg ai/L and with an untreated control (two test vessels with 5 fish

each). Test conditions: Temperature, 22 ± 1 °C, photoperiod, 16 h light / 8 h dark, pH, 7 – 7.6; dissolved O_2, 7.4 – 9 mg/L; total hardness (as $CaCO_3$), 41.2 – 42.5

Findings:

No mortality or signs of intoxications were observed at the tested concentration of 100 mg ai/L.

Conclusion: 96 h LC_{50} > 100 mg ai/L, 96 h NOEC = 100 mg/L

Comment (RMS): The test concentrations were not measured.

Reference: Fischer R., Schulze E. F. (1988a): The effect of Hoe 075032 – substance, technical (Identification code: Hoe 075032 OH ZC96 0001) to *Lepomis macrochirus* (bluegill sunfish) in a static acute toxicity test (method EPA). Document No. A38908

Test guideline: EPA 660/3-75-009 (1975)

Material and methods:

The toxicity of amidosulfuron (purity 95.7 %, batch no. H225/5+6) to bluegill sunfish (*Lepomis macrochirus*) was tested under static conditions for 96 hours. Ten fish each were exposed to concentrations of 10, 18, 32, 56 mg ai/L. The highest concentration of 100 mg ai/L was tested with 30 fish in 3 replicates. No replicates were tested at the other concentrations. The test solutions were prepared by adding NaOH up to a pH of 10. After dispensing the test substance the test solution was adjusted to a pH of 7 with concentrated HCl. Therefore an untreated and an "adjusted" control were tested. The concentration of the test substance was analysed by means of HPLC at 0, 48 and 96 hours. Stainless steel tanks containing 150 L of test water served as test vessels. The average fish weight and length was 2.9 g and 4.8 cm (mean of 10 individuals). Test conditions: Temperature, 22 ± 1 °C, photoperiod, 16 h light / 8 h dark, pH, 7.1 – 7.8; total hardness (as $CaCO_3$), 43.2 – 45.2 mg/L; dissolved O_2, 7.4 – 8.9 mg/L

Findings:

The measured values of the test substance concentration were in the range of 80.8 – 102.9 %, except for the nominal concentration of 100 mg ai/L where concentration less than 80 % were measured at 48 hours. Since the measured concentrations of the ai were again within the range of 80 and 120 % of nominal at the end of test nominal values were used for reporting. No mortality or signs of intoxication were observed at the tested concentrations up to 100 mg ai/L.

Conclusion: 96 h LC_{50} > 100 mg ai/L, 96 h NOEC = 100 mg/L

Comment (RMS): The study was considered to be acceptable.

Reference: Boeri R.L. (1989f): Static acute toxicity of sample number Hoe 075032 to the sheepshead minnow, *Cyprinodon variegatus*. Document No. A40984

Test guideline: EPA 540/9-85-009 (1985)

Material and methods:

The toxicity of amidosulfuron (Hoe 075032 OH ZC94 0001, batch no. 1/87 + 1/88, purity = 94 %) was tested under static conditions for 96 hours. Twenty fish were randomly distributed among two replicates of each treatment level of 14, 24, 38, 56, 94 mg ai/L, solvent control and control. Glass aquaria served as test vessels containing 10 L of test solution. The mean fish length and weight was 1.6 cm and 0.0608 g. The fish loading was 0.061 g/L. Filtered natural seawater was used as dilution

water. Test conditions: Temperature, 21 – 22 °C; photoperiod, 16 h light / 8 h dark, pH, 7.2 – 7.9; dissolved O_2, 5.6 – 7.2 mg/L; salinity, 2 %;

Findings:

Precipitation was observed at the test concentrations of 65 mg ai/L and 94 mg ai/L. Test concentrations were not measured, therefore results were based on nominal concentrations. No mortality occurred at the tested concentrations.

Conclusion: 96 h LC50 > 94 mg ai/L, 96 h NOEC = 94 mg/L

Comment (RMS): The test concentrations were not measured and precipitation was observed at the two highest tested nominal concentrations of 56 mg ai/L and 94 mg ai/L at least at the beginning of the test. Nevertheless, since the results were in agreement with the results of the other fish studies the study was accepted and no new study is considered to be necessary.

General comment to the fish studies: The test concentrations were not measured in three out of four tests.

5.4.1.2 Long-term toxicity to fish

Chronic toxicity to fish (refer to Annex point IIA 8.2.2)

Prolonged toxicity (21 day exposure) to fish (refer to Annex point IIA 8.2.2.1)

Reference: Fischer R. (1991d): Hoe 075032 – substance technical (Hoe 075032 00 ZC94 0001) Effect to *Salmo gairdneri* (rainbow trout) in a 21-day prolonged toxicity test (method OECD). Document No. A45487

Test guideline: OECD 204 (1984)

Material and methods:

The toxicity of amidosulfuron (purity 93.8 %, batch no. 1/87 + 1/88) to rainbow trout (*Oncorhynchus mykiss*) was tested under flow through conditions for 21 days. Ten fish with an average weight and length of 4.81 g and 6.53 cm (mean of all tested individuals) were exposed to nominal concentrations of 1, 5, 10, 50, 100 mg ai/L, solvent control (Tween 80) and control. No replicates were used. Fish were fed daily with 0.92 – 1.01 g dry food per tank. Stainless steal tanks filled with 50 L of test medium served as test vessels. The biological loading was 0.97 g/L and 1.29 cm/L, respectively. The concentration of amidosulfuron at nominal concentrations of 1, 10 and 100 mg ai/L was measured on days 0, 4, 11 and 18 by means of HPLC. Mortality and growth served as the criterion of effect. Mortality and signs of intoxication (abnormal swimming behaviour) were recorded every 24 hours. Test conditions: Temperature, 13.8 – 15.3; photoperiod, 16 h light/8 h dark; pH, 7.4 – 8; dissolved O_2, 8.7 – 12.8; total hardness (as $CaCO_3$), 301 – 352 mg/L

Findings:

The measured values of the test substance were in 5 cases out of 12 considerably below 80 % of nominal concentrations. The test results were reported as nominal concentrations in the test protocol. However, we consider mean measured concentrations as the appropriate values because of the low measured concentrations. The mean measured concentrations were 92.5, 64.1 and 68.9 % of nominal concentrations of 1, 10 and 100 mg ai/L. The mean percentage of the three mean measured values was 75.18 % of nominal values. This mean percentage of 75.18 % was used to extrapolate from the nominal values of 5 and 50 mg ai/L to possible mean measured values of 3.75 and 37.59 mg ai/L. Fish exposed to the solvent control showed slower movement than the untreated control group. No other visual signs of intoxication or abnormal swimming behaviour were

observed in the treated or in the untreated control groups. One fish died in the test concentration of 6.41 mg ai/L. This was regarded as not being related to the test substance since no mortality was observed in the higher test concentrations. Effects on the growth of the test fish were observed. The increase in size and weight declined with increasing concentration of the test substance. Even a loss in weight was observed at a concentration of 37.59 mg ai/L and higher. At a concentration of 37.59 mg ai/L the difference to the controls was significant (level of significance $p < 0.05$). Therefore the 21-d NOEC was 6.41 mg ai/L

Conclusion: 21 d NOEC = 6.41 mg ai/L

Comment (RMS): No replicates were used for testing and the concentration of amidosulfuron was measured only for nominal test concentrations of 1, 10 and 100 mg ai/L. The mean measured concentrations of the test substance were below 80 % of nominal concentrations, therefore it is not acceptable to use nominal concentrations (as it was done by the notifier). Since no measured values were available for the test concentrations of 5 and 50 mg ai/L we have extrapolated the nominal values to values comparable to the mean measured values of the other test concentrations. The study was accepted by the RMS because the results were plausible with respect to the results of the acute tests and the moderate acute toxicity of amidosulfuron to fish. No new chronic fish study was demanded in order to avoid unnecessary testing.

Fish early life stage toxicity test (refer to Annex point IIA 8.2.2.2)

A fish early life stage toxicity test is not required because the bioconcentration potential is low (log P_{ow} = 1.63) and the acute toxicity is low (96 h LC_{50} > 100 mg ai/L).

Fish life cycle test (refer to Annex point IIA 8.2.2.3)

A fish full life cycle test is not required because the bioconcentration potential is low (log P_{ow} = 1.63), the acute toxicity is low (96 h LC_{50} > 100 mg ai/L) and no hints do exist that amidosulfuron could act as an endocrine disruptor affecting the reproduction of fish.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates (refer to Annex point IIA 8.2.4)

Reference: Fischer R., Schulze E. F. (1988b): The effect of Hoe 075032 – substance technical (Identification code: Hoe 075032 OH ZC96 0001) to *Daphnia magna* (waterflea) in a static acute toxicity test (method OECD). Document No. A38705

Test guideline: OECD 202(1984)

Material and methods:

Young daphnids (less than 24 hours old) were exposed to amidosulfuron (purity 95.7 %, batch no. H 225/5+6) under static conditions for 48 hours. The nominal concentrations of the test substance were 5.6, 10, 18, 32, 56 and 100 mg ai/L. Two replicates per test concentration were tested. 10 individuals were used per replicate. 300 mL glass jars filled with 200 mL test solution were used as test vessels. The pH was adjusted to 10 with NaOH in order to enhance the solubility of the test substance and afterwards the test medium was adjusted to pH 7 with HCl. Therefore an untreated

and an adjusted control were tested. Test conditions: Temperature, 20 ± 1 °C; photoperiod, 16 h light / 8 h dark; pH, 7.7 – 7.8; dissolved O_2, 8.3 – 9.1 mg/L, total hardness (as $CaCO_3$), 218 mg/L.

Findings:

The concentration of ai was not measured in the test systems. Results were reported as nominal concentrations. No mortality was observed in the controls and up to a concentration of 18 mg ai/L. 10 % and 40 % of animals died at test concentrations of 32 and 56 mg ai/L. After 48 hours all animals were found dead at a concentration of 100 mg ai/L. The LC_{50} value was calculated by probit method to be 112 mg ai/L for 24 hours and 55 mg ai/L for 48 hours. The appropriate 95 % confidence limits were calculated as 89 – 233 mg ai/L and 47 – 65 mg ai/L, respectively.

Conclusion: 48 h LC_{50} = 55 mg ai/L, 48 h NOEC = 18 mg ai/L

Comment (RMS): The concentration of the ai in the test solution was not measured.

Reference: Fischer R. (1987ag): The effect of Hoe 075032 – substance technical (Identification code: Hoe 075032 OH ZC96 0001) to *Daphnia magna* (waterflea) in a static acute toxicity test (method EPA). Document No. A37699

Test guideline: EPA-660/3-75-009(1975)

Material and methods:

Young daphnids (less than 24 hours old) were exposed to amidosulfuron (purity 95.7 %, batch no. H 225/5+6) under static conditions for 48 hours. The nominal concentrations of the test substance were 10, 18, 32, 56 and 100 mg ai/L. Two replicates per test concentration were tested. 10 individuals were used per replicate. 300 mL glass jars filled with 200 mL test solution were used as test vessels. The pH was adjusted to 10 with NaOH in order to enhance the solubility of the test substance and afterwards the test medium was adjusted to pH 7 with HCl. Therefore an untreated and an adjusted control were tested. Test conditions: Temperature, 20 ± 1 °C; photoperiod, 16 h light / 8 h dark; pH, 7.4 – 7.8; dissolved O_2, 8.3 – 8.7 mg/L, total hardness (as $CaCO_3$), 44.5 mg/L.

Findings:

The concentration of ai was not measured in the test systems. Results were reported as nominal concentrations. No mortality was observed in the controls and at a concentration of 10 mg ai/L. 25 % and 30 % of animals died at test concentrations of 18 and 32 mg ai/L. After 48 hours all animals were found dead at concentrations of 56 and 100 mg ai/L. The LC50 value was calculated to be 65 mg ai/L for 24 hours and 36 mg ai/L for 48 hours. The appropriate 95 % confidence limits were calculated as 56 – 100 mg ai/L and 18 – 56 mg ai/L, respectively.

Conclusion: 48 h LC50 = 36 mg ai/L, 48 h NOEC = 10 mg ai/L

Comment (RMS): The concentration of the ai in the test solution was not measured.

5.4.2.2 Long-term toxicity to aquatic invertebrates

Chronic toxicity to aquatic invertebrates (refer to Annex point IIA 8.2.5)

Reference: Heusel R. (1991cz): Hoe 075032 – substance, technical (Hoe 075032 00 ZC94 0001) Effect to *Daphnia magna* (waterflea) in a 21-day reproduction test (method OECD). Document No. A46125

Test guideline: OECD 202 (1984)

Material and methods:

The effects of amidosulfuron (purity 93.8 %, batch no. 1/87 + 1/88) on the reproduction of *Daphnia magna* was tested under semi static conditions for 21 days. Daphnids were fed three times a week with a mixture of algae and fish food and transferred to a freshly prepared test medium. A dilution series of 0.1, 0.32, 1, 3.2 and 10 mg ai/L was prepared for testing. 40 daphnids (< 24 hours old) were tested at each concentration and control. Four replicates were tested per concentration and control. Each 500 mL test vessel contained 400 mL test solution and 10 daphnids. Physical and chemical parameter were determined in one beaker of each concentration from the freshly prepared and aged test solution. The concentration of amidosulfuron was analysed in freshly prepared and aged test solutions by means of HPLC. The NOEC was calculated by analysis of variance and Duncan´s Multiple Range Test and the EC_{50} was calculated by probit method. Test conditions: Temperature, 20 ± 1 °C; photoperiod, 16 h light / 8 h dark; pH, 7.5 – 8.1; dissolved O_2, 4.9 – 9.1 mg/L; total hardness (as $CaCO_3$), 191 - 222 mg/L (measured only in freshly prepared test solutions).

Findings:

The measured concentrations of the ai were greater than 80 % of the nominal value. Therefore test results were reported on the basis of nominal values. All animals died at the highest test concentration of 10 mg ai/L within 7 days of exposure. Immobilization of adult individuals and delayed brood was observed at a concentration of 3.7 mg ai/L. Release of brood started at day 9 at concentrations below 3.2 mg ai/L and in controls. The number of life juveniles was not significantly different from the controls up to a concentration of 1 mg/L.

The mortality and reproduction results were as follows:

Table 51: The mortality and reproduction results

Treatment level mg/L	Mean number of survived adults	Mean sum of alive larvae per survived female
0 (control)	10	118.6
0.1	10	115.5
0.32	10	115.5
1	9	103.8
3.2	6.25*	68.7*

* ..... indicates significant differences from control ($p < 0.05$)

The 21 d NOEC was 1 mg ai/L and the 21 d EC_{50} was calculated to be 3.2 mg ai/L (95 % confidence limits = 2.5 – 3.2 mg ai/L)

Conclusion: 21 d NOEC = 1 mg ai/L, 21 d EC_{50} = 3.2 mg ai/L

Comment (RMS): The study was considered to be acceptable.

5.4.3 Algae and aquatic plants

Effects on algal growth and growth rate (refer to Annex point IIA 8.2.6)

Reference: Fischer R., Schulze E. F. (1988c): The Effect of Hoe 075032 – substance technical (Identification code: Hoe 075032 OH ZC96 0001) to *Scenedesmus subspicatus* CHODAT (green alga) in a growth inhibition test (method OECD). Document No. A38704

Test guideline: OECD 201 (1984)

Material and methods:

The effects of amidosulfuron (purity 95.7 %, batch no. H 225/5+6) on the growth of *Scenedesmus subspicatus* were determined in a 72 h test under static conditions. The medium for pre- and test culture of the green alga was according to the medium suggested in guideline OECD 201. Two dilution series of amidosulfuron were tested: 0.1, 0.32, 1, 3.2, 10, 32, 100 mg ai/L and 0.032, 0.1, 0.32, 1, 3.2, 10, 32, 100, 320, 1000 mg ai/L. Three replicates were used per treatment level and six replicates were used for the untreated control. The test was conducted with 300 mL glass flasks containing 100 mL of test medium and an initial cell density of 1000 cells/mL. The test vessels were constantly shaked and constantly illuminated by wide spectrum fluorescent lamps of the universal white-type L25 and a light intensity of 4000 lux. At test days 1, 2 and 3 the cell concentrations were determined for each flask. Test conditions: Temperature, 24.2 – 25.3 °C (test 1), 24.7 – 26.2 °C (test 2); pH, 7.8 – 8.3 (test 1), 7.7 – 8 (test 2);

Findings:

The concentration of the test substance was not measured. Results were based on nominal values. The first test resulted in low growth inhibition at the highest concentration and an equivocal concentration-effect relationship. Therefore the results of the second test were used for the calculation of the E_bC_{50} value. Growth inhibition was observed at concentrations at and above 10 mg ai/L. The 72 h E_bC_{50} was calculated by approximate E_bC_{50} and binominal test to be 47 mg ai/L (95 % confidence limits = 32 – 100). No significant effects on growth were found up to a concentration of 3.2 mg ai/L.

Conclusion: 72 h E_bC_{50} = 47 mg ai/L, 72 h NOEC = 3.2 mg ai/L

Comment (RMS): The concentration of the test substance was not measured. Since algae did not represent the most critical endpoint the study was accepted and no new study with green algae is required.

Reference: Sowig P., Weller O., Gosch H. (1999aj): Amidosulfuron (pro. approved ISO) substance, technical – Code: AE F075032 00 1D99 0004 – Algal growth inhibition – *Navicula pelliculosa*. Document No. C001109

Test guideline: OECD 201, EPA J 123-2, EU C.3

Material and methods:

The effects of amidosulfuron (purity 99.4 %) on the growth of *Navicula pelliculosa* were determined in a 96 h test under static conditions. The medium for pre- and test culture of the alga was in compliance with the limits set in the OECD and EPA guidelines. A dilution series of the following nominal values was tested: 10, 18, 32, 56, 100 mg ai/L. Three replicates were used per treatment level and six replicates were used for the untreated control. The test was conducted with 300 mL glass flasks containing 100 mL of test medium and an initial cell density of 10000 cells/mL. The test vessels were constantly shaked and illuminated by wide spectrum fluorescent

lamps of the universal white-type L25 and a light intensity of 63 µE*m^{-2}*s^{-1}. After 24, 48, 72 and 96 hours the cell concentrations were determined for each flask using a light microscope and a counting chamber. The concentration of amidosulfuron was analysed at the beginning and at the end of test by means of HPLC. The NOEC was statistically determined by analysis of variance, general linerar models with Duncan´s multiple range test. Test conditions: Temperature, 25 ± 1 °C; pH, 7.1 – 8.3; dissolved O_2, 7.5 – 9.4 mg/L; total hardness in mmol/L (Ca^{2+} + Mg^{2+}), 0.29 (measured at start of testing).

Findings:

The mean measured values were in the range of 80.1 – 98.3 % of nominal values. In one case the measured concentration was below 80 % of the nominal concentration. Therefore the results were based on mean measured concentrations of 7.85, 15.25, 29.66, 48.5 and 84.2 mg ai/L. Growth inhibition was more pronounced after 72 h than after 96 hours of exposure. The corresponding 72 h and 96 h E_bC_{50} / E_rC_{50} were determined as > 84.2 mg ai/L. Statistically significant inhibition of growth was not observed at a significance level of p = 0.05). Therefore the NOEC was determined as 84.2 mg ai/L.

Conclusion: 72 h E_bC_{50} / E_rC_{50} > 84.2 mg, 72 h NOEC = 84.2 mg ai/L

Comment (RMS): The study was considered to be acceptable.

Effects on aquatic plants (refer to Annex point IIA 8.2.8)

Reference: Morrow J. E., Ward G. S. (1993a): Technical Hoe 075032 (Hoe 075032 00 ZD99 0001): Acute toxicity to duckweed, *Lemna gibba* G3, under static test conditions. Document No. A49587

Test guideline: US-EPA, 123-2, ASTM E1415-91

Material and methods:

The effects of amidosulfuron (AE F075032, purity 98.7 %, batch no.H 225/1+2) to the growth of *Lemna gibba* were examined under static conditions for 14 days. Lemna cultures with an initial frond number of 15 were exposed to nominal concentrations of 5.4, 9, 15, 25, 42 and 70 µg ai/L, control and solvent control (dimethylformamid). Three replicates were used per concentration, control and solvent control. The test containers were continuously illuminated with a mean light intensity of 69.9 and 80.4 µE*m^{-2}*s^{-1}. Duckweed growth was measured by making frond counts on days 3, 6, 9, 12 and 14. The base water for the test medium was deionized filtered water enriched with nutrients as described by ASTM. The test media (and all test concentrations) were renewed after 7 days. The EC_{50} values were calculated by probit analysis and the NOEC was determined by analysis of variance and Dunnett test. The concentration of the test substance was measured on days 0, 7 (new and old medium) and 14 by means of HPLC. Test conditions: Temperature, 22.1 – 26.4 °C; pH, 7.4 – 10.1

Findings:

Mean measured concentrations were in the range of 91 – 103 % of nominal. The test results were reported on the basis of nominal values. The mean number of fronds in the control increased from 15 to 182 after 14 days of growth. A dose dependant reduction of growth was observed with increasing concentration of amidosulfuron from a mean measured concentration of 8.74 up to 65.5 µg ai/L. The ErC_{50} was calculated to be 17.6 µg ai/L with 95 % confidence limits of 15.3 – 20.3. The NOEC was 8.74 µg ai/L.

Conclusion: 14 d ErC_{50} = 17.6 µg ai/L, 14 d NOEC = 8.74 µg ai/L

Comment (RMS): The study was considered to be acceptable.

Reference: Sowig P. (2002ag): Duckweed (*Lemna gibba* G3) growth inhibition test with recovery phase AE F075032; substance technical. Document No. C025093

Test guideline: OECD draft guideline, June 1998, US-EPA J 123-2, ASTM E 1415-19

Material and methods:

The effects of amidosulfuron (AE F075032 00 1D99 0013, purity 99.4 %, batch no.H 225/1+2) to the growth of *Lemna gibba* and the potential recovery after the treatment were examined under semistatic conditions. Lemna cultures with an initial frond number of 12 per replicate were exposed to nominal concentrations of 10, 18, 32, 56 and 100 µg ai/L and control. The plants were cultured and tested in 20X-AAP nutrient medium which was in compliance with the limits set in the ASTM and EPA guideline. The test media (and all test concentrations) were renewed after 3 and 5 days. The test was conducted in 300 mL Erlenmayer-flasks which were filled with 150 mL medium. Six replicates were used per concentration and control. The test vessels were continuously illuminated with a mean light intensity of 100 - 106 $E*m^{-2}*s^{-1}$. Duckweed growth was measured by making frond counts on days 0, 3, 5, 7 (treatment phase) and on days 7, 10, 12, 14 (recovery phase). Dry weights were determined on days 0, 7 (treatment phase) and on days 7, 14 (recovery phase). The E_bC_{50}/E_rC_{50} values were calculated by binomial probability, moving average and probit method. The NOEC was verified by analysis of variance with DUNCAN´s Multiple Range Test. The concentration of amidosulfuron was analysed at days 0, 3 and 5 from fresh prepared solutions and at days 3, 5, 7 from aged test solutions by means of HPLC. Test conditions: Temperature, 23 – 24 °C; pH, 7.7 – 9 (treatment phase), 7.4 – 9 (recovery phase); dissolved O_2, 6.8 – 8.7 mg/L (treatment phase), 8.3 – 9 mg/L (recovery phase); conductivity, 1542 – 1587 µS/cm (treatment phase), 1535 – 1593 µS/cm (recovery phase); total hardness (Ca^{2+} + Mg^{2+}), 2.5 mmol/L; acid binding capacity (in mmol HCl/L), 2.9

Findings:

Since the time weighted average concentrations during the 7 day treatment period were between 72.5 and 91.96 % of nominal values, the following time weighted average values were used for the calculation of the biological endpoints: 9.2, 13.05, 25.63, 45.97 and 79.17 µg ai/L. At day 10 (day 3 of recovery phase) the test substance concentrations were below the limit of detection in the highest nominal test concentration of 100 µg ai/L. After the 7 day treatment phase the growth inhibition (biomass and growth rate) was > 50% in the lowest test concentration and rose with increasing dose up to 79.55 % (growth rate) and 67.39 % (biomass) in the highest test concentration. The E_bC_{50}/E_rC_{50} was not calculated because no value of less than 50 % growth inhibition was observed. During the recovery phase a growth inhibition of 0.98 % (growth rate) and 6.82 % (biomass) was observed at the lowest test concentration. Growth inhibition rose with increasing concentration of amidosulfuron up to 21.38 % (growth rate), 26.06 % (biomass) in the highest tested concentration. The 7 d E_bC_{50}/E_rC_{50} values were < 9.2 µg ai/L and the 7 d NOECs based on growth rate and on biomass were < 9.2 µg ai/L. For the recovery phase the 7 d E_bC_{50}/E_rC_{50} values were > 79.17 µg ai/L and the 7 d NOECs based on growth rate and on biomass was 9.2 µg ai/L (growth rate) and 13.05 µg ai/L (biomass).

Conclusion: The 7 d E_bC_{50}/E_rC_{50} were < 9.2 µg ai/L. However, the percentages of inhibition were 55.03 % (growth rate) and 53.01 % (biomass) at the concentration of 9.2 µg ai/L. Therefore EC_{50} values were assumed to be not far below this dosage.

Comment (RMS): The study was considered to be acceptable.

5.4.4 Other aquatic organisms (including sediment) (refer to Annex point IIA 8.2.4)

Reference: Boeri R. L. (1989e): Static acute toxicity of sample number Hoe 075032 to the mysid, *Mysidopsis bahia*. Document No. A40985

Test guideline: EPA 540/9-85-010(1985)

Material and methods:

The acute toxicity of amidosulfuron (purity 94 %, batch no. 1/87 + 1/88) to *Mysidopsis bahia* was tested under static conditions for 96 hours. The nominal concentrations of the test substance were 14, 24, 38. 56 and 94 mg ai/L. Twenty juvenile mysids (less than 96 hours after release) were randomly distributed among two replicates of each test concentration, control and solvent control. Filtered sea water, diluted to 2 % salinity with deionized water was used as dilution water. Dimethyl formamid (DMF) served as a solvent. The mean weight of shrimps was 1.1 mg and the mean length was 4.4 mm. The biologicals loading of the 2 L vessels filled with 1 L test solution was 0.0011 g/L. Test condtions: Temperature, 23 °C; photoperiod, 16 h light / 8h dark; pH, 7.5 – 8; dissolved O_2, 5 – 8.3 mg/L; salinity 2 %

Findings:

Precipitation of the test substance was observed in the test vessels containing 56 and 94 mg ai/L. The concentration of the test substance was not measured and the test results were based on nominal concentrations. On individual died in the solvent control and one was found dead at a concentration of 38 mg ai/L after 24 hours. No further animals died at the tested concentration of 38 mg ai/L and at concentrations up to 56 mg ai/L until the end of test after 96 hours. Therefore the mortality observed at the concentration of 38 mg ai/L was considered not being related to the test substance. 95 % of the mysids died at the highest test concentration of 94 mg ai/L within 96 hours. The 96 h LC_{50} value was calculated by non linear interpolation method to be 75 mg ai/L (95 % confidence limits = 56 – 94 mg/L)

Conclusion: 96 h LC_{50} = 75 mg ai/L, 96 h NOEC = 56 mg ai/L

Comment (RMS): The concentration of the test substance was not measured.

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

Data element: Degradation (evidence of rapid degradation)				
	Test guideline / design	pH	GLP (y/n)	Reliability *
Biotic degradation (% degradation in 28 davs (or, if absent, half- life in water (d)):				
Degradation is depending on concentration of active substance: 10 mg a.i./L: 80 %degradation in 28 davs 20 mg a.i./L: 32 % degradation in 28 davs Amidosulfuron is not considered as readily biodegradable since the pass level of 60% of ThCO2 was not reached within 10 day window	OECD 301B	7.5	y	
water/sediment system Water: DT50: 73 d (S1), 10 d (S2) Whole system: DT50: 91 d (S1), 16 d (S2) geomean (S1/S2) = 38.1 d Mineralisation : 18.78 % CO2 in (S1) 25.2 % CO2 in (S2)	aerobic water-sediment study SETAC guideline, part 1, 8.2 of march 1995 to satisfy the data requirements of EU Directive 95/36/EC, Annex 1, section 7, part 7.2.1.3.2 of July 1995		y	
Abiotic degradation (Hvdrolvsis) (half- life (d)): Amidosulfuron is hydrolytically stable at an environmentally relevant pH value DT50 at pH 6 = 237.1 d. DT50 at pH 7 =>365 d.	No Guideline		n	
Conclusion: the criteria for rapid degradation are not fulfilled because **Amidosulfuron is hydrolytically stable at an environmentally relevant pH value** **the pass level of 60% of ThCO2 was not reached within 10 day window in a ready biodegradability test** **$DT_{50\ WHOLE\ SYSTEM}$ in aerobic water-sediment system is > 16 d (geomean (S1 and S2) = 38.1 d)** **(As DT50 = > 16 d, occuring metabolites in the aerobic water-sediment system are not relevant for classification and labelling and will not be considered).** **Mineralisation in aerobic water-sediment system is 18.78 % CO2 in (S 1) and 25.2 % CO2 in (S 2), therefore ultimate degradation (full mineralisation) can be excluded.**				

Data element: Evironmental Distribution (not relevant for classification and labelling)				
	Test guideline / design	pH	GLP (y/n)	Reliability
Rate of degradation under aerobic conditions DT50 (1st order kinetics) 3 – 29 days (mean 19.2) DT90 10 – 97 days (mean 63.7 days).				
rate of degradation under anaerobic conditions DT50 >300 d.				
Adsorption/Desorption $K_{F,OC}$ values were calculated to be in the range of 5.7 to 83.3 L/kg with an arithmetic mean of 36.4 L/kg, indicating high mobility.				
Volatilisation Henry´s constant of 1.6 x 10^{-6} Pa m^3/mol (20° C) Vapour pressure of 1.3 x 10^{-5} Pa (20° C)				

Physical-chemical properties important for evaluation of aquatic hazards for the purpose of classification

				Test guideline / design	pH	GLP (y/n)	Reliability *
Water solubility (Sw): 3070 mg/L				EEC/A6 Flask method	7	y	
Log octanol/water partition coefficient (Log Kow):				Flask method	4 7 9	y	
pH	4.0 (23 °C)	**7.0 (22 °C)**	9.0 (23 °C)				
Log P_{ow}	1.07	**-1.56**	-2.21				
P_{ow}	11.7	**0.027**	0.006				

Comments: The substance is readily soluble. Log K_{ow} < 4 (-1.56; pH=7), indicate low potential for bioaccumulation,.

Data element: Acute (short-term) aquatic toxicity
Generally expressed in terms of LC_{50} or EC_{50} (mg/L)

	L(E)C_{50} [mg/L]	Test guideline / design	GLP (y/n)	Reliability *
Fish (96 hr LC_{50}):				
Oncorhynchus mykiss	> 320	EPA-660/3-75-009 (1975), BBA Leaflet no. 33 (1975)	y	
Lepomis macrochirus	> 100	EPA-660/3-75-009	y	
Lepomis macrochirus	> 100	EPA-660/3-75-009	y	
Cyprinodon variegatus	> 94	EPA 540/9-85-009 (1985)	y	
Crustacea (48 hr EC_{50}):				
Daphnia magna	55	OECD 202(1984)	y	
Daphnia magna	36	EPA-660/3-75-009(1975)	y	
Algae/aquatic plants (72 or 96 hr E_rC_{50}):				
Scenedesmus subspicatus	47	OECD 201 (1984)	y	
Navicula pelliculosa	>84.2	OECD 201,EPA J 123-2,EU C.3	y	
Lemna gibba	0.0176	US-EPA, 123-2, ASTM E1415-91	y	
Lemna gibba	**<0.0092** (Sowig (2002ag), refer to DAR Annex point IIA, 8.2.8 Effects on aquatic plants)	OECD draft guideline, June 1998, US-EPA J 123-2, ASTM E 1415-19	y	

Conclusion:
The 7 d E_rC_{50} used for classification was < 9.2 µg ai/L (Sowig (2002ag) refer to DAR, Annex point IIA, 8.2.8 Effects on aquatic plants). However, the percentages of inhibition were 55.03 % (growth rate) at the concentration of 9.2 µg ai/L. Therefore EC_{50} value was assumed to be not far below this dosage.
Acute aquatic toxicity (based on the lowest of the available toxicity value <0.0092 mg/L) is between 0.001 and 0.01 mg/L. This corresponds to a M-factor of 100.

Data element: Chronic (long-term) aquatic toxicity Generally expressed in terms of NOEC (mg/L)				
	NOEC [mg/L]	Test guideline / design	GLP (y/n)	Reliability *
Fish (21 d NOEC):				
Oncorhynchus mykiss	6.41	OECD 204 (1984)	y	
Crustacea (21 d NOEC):				
Daphnia magna	3.2	OECD 202 (1984)	y	
Algae/aquatic plants (NOEC):				
Scenedesmus subspicatus	3.2 (72 h)	OECD 201 (1984)	y	
Navicula pelliculosa	84.2 (72 h)	OECD 201,EPA J 123-2,EU C.3	y	
Lemna gibba	**0.00874 (14 d)** (Morrow (1993a), refer to DAR Annex point IIA, 8.2.8 Effects on aquatic plants))	US-EPA, 123-2, ASTM E1415-91	y	
Conclusion: **Chronic aquatic toxicity (based on the lowest of the available toxicity values) is between 0.001 and 0.01 mg/L. This corresponds to M-factor of 10 (no rapid degradation).**				

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

In acute aquatic toxicity studies, ErC50 value for aquatic plants were obtained at amidosulfuron concentrations between 0.001 and 0.01 mg/L (<0.0092 mg/L; Sowig). Amidosulfuron is not readily biodegradable.

Amidosulfuron therefore fulfills the criteria for classification following Directive 67/548/EEC and should be classified Dangerous for the Environment with the following risk and safety phrases:

N Dangerous for the Environment

R50 Very toxic to aquatic organisms

R53 May cause long term effects in the environment

S60 This material and its container must be disposed of as hazardous waste

S61 Avoid release to the environment. Refer to special instructions/Safety Data Sheet

Conclusion of environmental classification according to Regulation EC 1272/2008

In acute aquatic toxicity studies, ErC50 value for aquatic plants were obtained at amidosulfuron concentrations between 0.001 and 0.01 mg/L (<0.0092 mg/L; Sowig (2002ag), refer to DAR Annex point IIA, 8.2.8 Effects on aquatic plants). This corresponds to a **M-factor of 100** and results in a **Aquatic Acute 1 H400 'Very toxic to aquatic life'** classification .

The low Log Kow = -1.56 (at pH=7), indicates a low potential for bioaccumulation.

Amidosulfuron and is **not rapidly degradable** as:

a) Amidosulfuron is hydrolytically stable at an environmentally relevant pH value,

b) the pass level of 60% of theoretical formation of CO2 was not reached within the 10 days window in a modified Sturm test in accordance with the OECD 301 B guideline

c) the DT50 whole system obtained in an aerobic simulation study in water/sediment systems was 91 d (S1) and 16 d (S2) respectively,

thus the **criteria for rapid degradation are not fulfilled**

The lowest chronic toxicity value was the $NOEC_{growthrate}$ = **0.00874** mg/L **(**Morrow (1993a), refer to DAR Annex point IIA, 8.2.8 Effects on aquatic plants) determined with *Lemna Gibba*. As the NOEC-value is between 0.001 and 0.01 mg/L and Amidosulfuron does not fulfill the criteria for rapid degradation, classification as **Aquatic Chronic 1 H410 'Very toxic to aquatic life with long lasting effects'** with a **M-factor of 10** according to Regulation EC 1272/2008 will be proposed.

Amidosulfuron therefore fulfills the criteria for classification as aquatic environmental hazard based on the CLP Regulation.

Amidosulfuron should be classified:

Aquatic Acute 1	H400	'Very toxic to aquatic life'
Aquatic Chronic 1	H410	'Very toxic to aquatic life with long lasting effects'
Signal Word:		'Warning' and environmental warning label.

A M-factor (acute) of 100 is applicable based on 0.001 <$L(E)C_{50}$ ≤0.01 mg/l

A M-factor (chronic) of 10 is applicable based on 0.001 <NOEC ≤0.01 mg/l (no rapid degradation)

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

Amidosulfuron has a log Kow of -1.07, **indicating a low potential for bioaccumulation.**

Criteria for rapid degradation are not fulfilled as:

a) Amidosulfuron is hydrolytically stable at an environmentally relevant pH value,

b) the pass level of 60% of theoretical formation of CO_2 was not reached within the 10 days window in a modified Sturm test in accordance with the OECD 301 B guideline

c) the DT50 whole system obtained in an aerobic simulation study in water/sediment systems was 91 d (S1) and 16 d (S2) respectively,

Amidosulfuron is a very high acute toxic towards aquatic plants with an ErC50 of < 9.2 µg a.i./L for *Lemna gibba*. This corresponds to a **M-factor of 100** and results in an **Aquatic Acute 1, H400, 'Very toxic to aquatic life'** classification.

The lowest chronic toxicity value was the $NOEC_{growthrate}$ = **0.00874** mg/L, determined with *Lemna gibba*. Amidosulfuron **does not fulfill the criteria for rapid degradatio**n, therefore classification as **Aquatic Chronic 1, H410, 'Very toxic to aquatic life with long lasting effects' with a M-factor of 10** will be proposed.

RAC evaluation of hazardous to the aquatic environment

Summary of dossier submitter's proposal

The dossier submitter proposed to classify amidosulfuron as hazardous to the aquatic environment, Acute category 1 - H400 and Chronic category 1 - H410, with M-factors 100 and 10 respectively, according to the Regulation (EC) 1272/2008 (CLP), and R50/53 (and SCLs corresponding to the acute M-factor of 100), according to Directive 67/548/EEC (DSD).

The proposal for the classification for acute aquatic hazard is based on the ecotoxicological test results from three species of fish, two species of crustaceans, two species of algae, and from two tests with the duckweed *Lemna gibba*, one with a treatment period of 14 days, the other with a treatment period of 7 days, displayed in table 50. These tests show that *Lemna gibba* is several orders of magnitude more sensitive than all other taxonomic groups tested. The EC50 values for this species are far below 1 mg/L thus fulfilling the criterion for classification for acute aquatic hazard in the category 1 (CLP) and R50 (DSD). Based on the 7d *Lemna gibba* study the dossier submitter concluded that the EC50 lies between 0.001 and 0.01 mg/L (55% inhibition at 9.2 µg/L), and proposed an acute M-factor (according to CLP) of 100.

The dossier submitter's proposal for the classification for long term aquatic hazard is based on the following additional argumentations.

Amidosulfuron is not prone to photolysis and is hydrolytically stable under pH conditions relevant for the environment. It is not readily biodegradable. In simulation tests its degradation half-time of 38 days in two water-sediment systems was well above the classification criterion of 16 days, while only around 20% mineralisation after 180 days did not indicate ultimate degradation.

Thus, based on this information the dossier submitter concluded that amidosulfuron is not rapidly degradable.

With logPow = -1.56 (pH 7; 1.07 at pH 4) amidosulfuron shows no indication of bioaccumulation potential meeting the classification criteria (BCF > 500 under CLP and BCF > 100 under DSD).

The dossier submitter proposed therefore to classify for long term aquatic hazard as R53 according to DSD.

Regarding the classification for long term aquatic hazard according to CLP, the dossier submitter proposed to base the classification on the lowest of the available toxicity values, which the dossier submitter considered to be the NOEC of 8.74 µg/L of the 14 days *Lemna gibba* study.

This finding would determine a classification for aquatic chronic category 1, accompanied by an M-factor of 10.

After the public consultation, the dossier submitter has resubmitted a new version of the CLH report, which implements some minor corrections and editorial changes pointed out during public consultation. This report is provided at the end of the response to comments (RCOM) document in the Annex 2.

Comments received during public consultation

During the public consultation, comments on hazards to the aquatic environment were received from six Member States.

The comments did not question the proposal of classification as aquatic acute 1 and chronic 1. Likewise, regarding the proposed acute M-factor of 100 (and corresponding SCL under DSD criteria), only supportive comments were submitted. However, the proposed chronic M-factor of 10 was questioned by comments from one Member State. This Member State argued that in the 7 days

study on *Lemna gibba* the NOEC should be well below the value of 9.2 µg/L and recommends that the chronic M-factor be modified from 10 to 100 based on 7 days acute toxicity data and on the non rapid degradation of the substance.

The other Member States generally supported the dossier submitter's proposal but indicated some minor corrections (mainly related to labelling) and editorial changes.

For the full set of comments and responses, see the response to comments document (RCOM) in the Annex 2.

Detailed description on relevant arguments and information received during the public consultation

Not needed.

Outcome of RAC assessment - comparison with criteria and justification

RAC supports the proposal from the dossier submitter to classify amidosulfuron as hazardous to the aquatic environment, Acute category 1 with M-factor 100.

Concerning the long term aquatic hazard, RAC supports the classification as hazardous to the aquatic environment, Chronic category 1. However, RAC does not support the proposed M-factor of 10 and proposes instead a value of 100.

RAC considered both available key studies on duckweed species *Lemna gibba* as not relevant or inconclusive for chronic classification (see extended analysis, below).

RAC concludes that, in the absence of conclusive data on chronic toxicity for the most sensitive taxonomic group, the surrogate approach according CLP guidance Annex I, Table 4.1.0 (b) (iii) should be applied. The key information for this approach is 1) the conclusion that amidosulfuron is not rapidly degradable, and 2) the EC50 for *Lemna gibba*.

RAC supports the conclusion of the dossier submitter that the EC50 for *Lemna gibba* is comprised between 0.001 and 0.01 mg/L.

On this basis, the aquatic hazard of amidosulfuron should be classified according CLP criteria with

H400, Category Acute 1, M = 100

H410, Category Chronic 1, M = 100

and according DSD criteria with

N; R50/53 and applying specific concentration limits (SCL) as follows:

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

Extended analysis of the key studies provided by the dossier submitter

Comments from one Member State during public consultation questioned the basis for the chronic M-factor of 10 proposed by the dossier submitter. Since sufficient details were not provided in the CLH report, both the experimental observations presented and the corresponding comments gave RAC sufficient reason to consult the original full study reports for the two key studies with the duckweed species *Lemna gibba*.

The study cited as Morrow and Ward (1993a) has been conducted according to USEPA and ASTM guideline for 14d with *Lemna gibba,* the only ones which were available at that time. Starting with

15 fronds, growth was recorded as frond counts on days 3, 6, 9, 12, and 14. At first glance, the control, solvent control and all treatment levels showed only limited growth during the first 9 days: in the control and solvent control, frond numbers were only 3.8-fold and 3.7-fold respectively after 6d and 4.3-fold and 4.1-fold respectively after 9d. Then growth rates increased in all treatments and reached in the control and in the solvent control 12-fold and 10.7-fold frond numbers after 14d. However, the current OECD 221 Guideline requires more than 7-fold frond numbers after only 7 days for valid tests. In principle, sufficient exponential growth is essential for biologically meaningful tests measuring growth inhibition. As the clearly limited growth during the first 9 days was also common to all treatments, RAC considers the study not relevant for classification purposes.

The second study cited as Sowig (2002ag) has been conducted according to the 1998 draft of current OECD TG 221 for 7d with *Lemna gibba*. Starting with 12 fronds, growth was recorded as frond counts on days 3, 5, and 7. Control growth was constantly exponential with ca. 15-fold frond numbers at day 7, thus clearly fulfilling current validity requirements. The following table provides an overview of the growth rate inhibition for all treatment levels after 7d:

amidosulfuron [µg/L] (twa)	0	9.2	13.1	25.6	46.0	79.2
growth rate inhibition [%]	-	55.0	61.8	74.8	76.6	79.6

These figures indicate a very shallow concentration-response relationship and that the real effect threshold expressed as NOEC, EC10 or similar should be well below the lowest treatment level of 9.2 µg/L. This study results in no clear NOEC, as the lowest test concentration of 9.2 µg/L (measured, time-weighted average – twa) already caused 55% growth rate inhibition. While RAC agrees to the dossier submitter's conclusion that the EC50 can be assumed close to 9 µg/L, extrapolation towards the effect threshold region of the concentration-response would be highly speculative. Thus RAC considered this second key study as inconclusive for the purpose of aquatic chronic classification according CLP guidance Annex I, Table 4.1.0 (b) (i), including a corresponding chronic M-factor. The study is however considered reliable and its EC50 close to 9 µg/L should be used as basis for both acute classification and for applying the surrogate approach according CLP guidance Annex I, Table 4.1.0 (b) (iii) for chronic classification.

Classification categories	aquatic environmental hazard **acute category 1** aquatic environmental hazard **chronic category 1**	
GHS Pictogram		
Signal Word	Warning	
Hazard Statement	H400	'Very toxic to aquatic life',
	H410	'Very toxic to aquatic life with long lasting effects'
	EUH401	'To avoid risks to human health and the environment, comply with the instructions for use'
M-factor (acute)	100	

M-factor (chronic)	10	
Precautionary statements — Prevention	P273	Avoid release to the environment
	P391	Collect spillage
	P501	Dispose of contents/container to ….

6 OTHER INFORMATION

7 REFERENCES

7.1 Physico-chemical properties

Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Bogdoll B.	2005d	1. Amendment Hoe 075032 Solubility in organic solvents (Loeslichkeit in organischen Loesungsmitteln) Code: Hoe 075032 OH ZB99 0001 Generated by: Bayer CropScience GmbH, DEU; Document No: C046705 GLP / GEP Yes unpublished	Y	BCS
Bogdoll B., Lemke G.	2005a	Henry's law constant of amidosulfuron at pH4, pH7 and pH9 Generated by: Bayer CropScience GmbH, DEU; Document No: C048205 GLP / GEP No unpublished	Y	BCS
Bogdoll B., Lemke G.	2005a	Henry's law constant of amidosulfuron at pH4, pH7 and pH9 Generated by: Bayer CropScience GmbH, DEU; Document No: C048205 GLP / GEP No unpublished	Y	BCS
Franke J.	2001a	Surface tension Amidosulfuron substance, technical Code: AE F075032 00 1D99 0013 Generated by: Siemens Axiva GmbH & Co. KG, DEU; Sicherheitstechnik, Frankfurt Document No: C018325 GLP / GEP Yes unpublished	Y	BCS
Franke J.	2001b	Relative density Amidosulfuron substance, technical Code: AE F075032 00 1D99 0013 Generated by: Siemens Axiva GmbH & Co. KG, DEU; Sicherheitstechnik, Frankfurt Document No: C018324 GLP / GEP Yes unpublished	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Franke J.	2005a	Auto-flammability (Solids - determination of relative self-ignition temperature) 1st amendment to report SI045-98 Amidosulfuron; substance, technical AE F075032 00 1D99 0004 Generated by: Siemens AG, Frankfurt, DEU; Document No: C046700 GLP / GEP Yes unpublished	Y	BCS
Gildemeister H., Rockmann S.	1989a	Hoe 075032-^{14}C Photodegradation in water Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A40662 GLP / GEP Yes unpublished	Y	BCS
Goerlitz G.	1992o	Hoe 075032, Dissociation constant (pKA) Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A48868 GLP / GEP No unpublished	Y	BCS
Goerlitz G., Eyrich U.	1987aj	Loeslichkeit in organischen Loesungsmitteln Hoe 075032 Generated by: Hoechst AG; GBC-Analytisches Laboratorium Document No: A35798 GLP / GEP Yes unpublished	Y	BCS
Goerlitz G., Eyrich U.	1987as	Solubility in water Generated by: Hoechst AG; GBC-Analytisches Laboratorium Document No: A35801 GLP / GEP Yes unpublished	Y	BCS
Grewer	1987a	Determination of vapour pressure as a function of temperature of Hoe 075032 0H ZB99 0001 Generated by: Hoechst AG; Angewandte Physik Document No: A40555 GLP / GEP No unpublished	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Helgers A	2005c	GLP certificates for testing facilities, where studies were carried out, that were submitted in frame of the EU-dossier Response to the Rapporteur Member State Austria in preparation of the Draft Assessment Report (DAR) Amidosulfuron (AE F075032) Generated by: Bayer CopScience AG, Monheim, DEU; Document No: C048119 unpublished	Y	BCS
Hoffmann H.	1998m	Amidosulfuron; substance, technical AE F075032 00 1D99 0004 Flammability (solids) Generated by: Aventis Research & Technologies Gmbh & Co KG; Document No: C001016 GLP / GEP Yes unpublished	Y	BCS
Hoffmann H.	1998n	Amidosulfuron; substance, technical AE F075032 00 1D99 0004 Auto-flammability (solids-determination of relative self-ignition temperature) Generated by: Aventis Research & Technologies GmbH & Co KG; Document No: C001017 GLP / GEP Yes unpublished	Y	BCS
Hoffmann H.	1998o	Amidosulfuron; substance, technical AE F075032 00 1D99 0004 Explosive properties Generated by: Aventis Research & Technologies GmbH & Co KG; Document No: C001018 GLP / GEP Yes unpublished	Y	BCS
Klais O., Rexer K.	1994ac	Hoe 075032 substance, technical (code: Hoe 075032 00 ZD93 0001) Determination of oxidising properties Generated by: Hoechst Schering AgrEvo GmbH; Research Formulations Frankfurt Document No: A52702 GLP / GEP No unpublished	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Kocur J.	1989a	Hoe 075032 substance, technical Colour Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A40679 GLP / GEP No unpublished	Y	BCS
Kocur J.	1989c	Hoe 075032 substance, technical Odour Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A41148 GLP / GEP No unpublished	Y	BCS
Kocur J.	1989d	Hoe 075032 substance, technical Physical form Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A40686 GLP / GEP No unpublished	Y	BCS
Kocur J., Rexer K.	1989c	Hoe 075032 substance, pure Colour Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A41818 GLP / GEP No unpublished	Y	BCS
Kocur J., Rexer K.	1989d	Hoe 075032 substance, pure Odour Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A41819 GLP / GEP No unpublished	Y	BCS
Kocur J., Rexer K.	1989e	Hoe 075032 substance, pure Physical form Generated by: Hoechst AG; GB C / Forschung Formulierung Document No: A41822 GLP / GEP No unpublished	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Muehlberger B., Eyrich U.	2004a	AE F075032 UV / VIS spectral data and molar extinction coefficient Code: AE F075032 00 1D99 0013 Generated by: Bayer CropScience GmbH, Frankfurt, DEU; Document No: C045777 GLP / GEP Yes unpublished	Y	BCS
Muehlberger B., Lemke G.	2004c	AE F075032, amidosulfuron Water solubility at pH4, pH7 and pH9 (flask method) Generated by: Bayer CropScience, Frankfurt, DEU; Document No: C045907 GLP / GEP Yes unpublished	Y	BCS
Muehlberger B., Wiche A.	2004a	AE F075032 (amidosulfuron) Partition coefficient 1-octanol / water Code: AE F075032 (amidosulfuron) Generated by: Bayer CropScience GmbH, DEU; Product Technology - Analytics Frankfurt Bayer CropScience GmbH, DEU; Product Technology - Analytics Frankfurt Document No: C044973 GLP / GEP Yes unpublished	Y	BCS
Rose	1993b	Assessment of the reactivity of organic molecules with OH-radicals of the troposphere by the method of Atkinson (1988) Generated by: Hoechst AG; Abteilung Umweltschutz Document No: C002027 GLP / GEP No unpublished	Y	BCS
Sarafin R., Winterscheidt G.	1989a	Mass-spectrum Generated by: Hoechst AG; GBC-Analytisches Laboratorium Document No: A39855 GLP / GEP No unpublished	Y	BCS
Sarafin R., Zeisberger E.	1989a	Infrared (IR) absorption-spectrum Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A40147 GLP / GEP No unpublished	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Schollmeier M.	1993a	Structure elucidation of a hydrolysis degradate of the sulfonylurea Amidosulfuron (Hoe 075032) Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A51873 GLP / GEP No unpublished	Y	BCS
Schollmeier M., Britten I.	1992a	Hoe 075032 Determination of Abiotic Hydrolysis as a Function of pH (Hoe 075032 00 ZB98 0001) Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A47707 GLP / GEP Yes unpublished	Y	BCS
Schollmeier M., Eyrich U.	1992i	Hoe 075032 Determination of Abiotic Hydrolysis as a Function of pH (Hoe 075032 00 ZB98 0001) Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A48869 GLP / GEP Yes unpublished	Y	BCS
Schumann C.	1989a	NMR-spectroscopic data Generated by: Hoechst AG; GBC-Analytisches Laboratorium Document No: A39960 GLP / GEP No unpublished	Y	BCS
Smeykal H.	2004e	Melting point Boiling point Thermal stability Amidosulfuron Code: AE F075032 00 1D99 0013 Generated by: Siemens AG, Frankfurt, Germany; Bayer CropScience GmbH, DEU; Product Technology - Analytics Frankfurt Document No: C045781 GLP / GEP Yes unpublished	Y	BCS

7.2 Human health hazard assessment

Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Allday; D.E.	1988a	Metabolism and pharmacokinetics in male and female rats after a single oral administration of 500 mg/kg body weight Hoechst Pharmaceutical Research Laboratories, Buckingshamshire, UK, Report No. DA1D040489 GLP not published	Y	BCS
Allday; D.E.	1988b	Metabolism and pharmacokinetics in male rats following oral administration of testsubstance at a concentration of 10 000 ppm in food Hoechst Pharmaceutical Research Laboratories, Buckingshamshire, UK, Report No. DA1D260589 GLP not published	Y	BCS
Allday; D.E.	1990	Metabolism and pharmacokinetics in male and female rats after a single intravenous administration of 10 mg/kg body weight Hoechst Pharmaceutical Research Laboratories, Buckingshamshire, UK, Report No. DA1D040790 GLP not published	Y	BCS
Allen, T. R.; Braunhofer, P. G.; Frei, T.; Luetkemeier, H.; Biedermann, K.; Springall, C. J.	1993	52-week oral toxicity (feeding) study with Hoe 075032 substance technical (Code: Hoe 075032 OH ZC97 0001) in the dog RCC Research and Consulting Company LTD., Switzerland RCC Project No. 310375 GLP not published	Y	BCS
Baeder, Ch.	1988a	Hoe 075032 – substance technical (Code: Hoe 075032 0H ZC97 0001): Testing for embryotoxicity in the Wistar rat after oral administration (Limit test) Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 89.0318 GLP not published	Y	BCS

Author(s)	Year	Title Source (where different from company) Company, Report No GLP or GEP status (where relevant), Published or not	Data Protection Claimed Y/N-R/NR	Owner
Baeder, Ch.	1988b	Hoe 075032 – substance technical (Code: Hoe 075032 0H ZC97 0001): Testing for embryotoxicity in the Himalayan rabbit after oral administration (Limit test) Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 89.0319 GLP not published	Y	BCS
Baeder, Ch.	1990	Hoe 075032 - substance technical (Code: Hoe 075032 00 ZC94 0001): Testing for embryotoxicity and effects on post-natal development in Wistar rats after oral administration (Limit test) Pharma Development Toxicology, Hoechst AG, Report No. 91.0382 GLP not published	Y	BCS
Brunk, R.	1988	Hoe 075032 – technical substance (Code: Hoe 075032 OH ZC97 0001). Testing for toxicity by repeated oral administration to Beagle dogs for 1 month (Range-finding-Test) Pharma Research Toxicology and Pathology, Hoechst AG, Study No. 88.1275 GLP not published	Y	BCS
Brunk, R.	1989	Hoe 075032 – technical substance (Code: Hoe 075032 OH ZC97 0001). Testing for toxicity by repeated oral administration to Beagle dogs (3-month feeding study) Pharma Research Toxicology and Pathology, Hoechst AG, Study No. 87.1462 GLP not published	Y	BCS
Diehl, K.-H.; Leist, K.-H.	1987e	Hoe 075032 – substance technical: Testing for acute intraperitoneal toxicity in the male and female Wistar rat Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.1895 GLP not published	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Diehl, K.-H.; Leist, K.-H.	1987a	Hoe 075032 – substance technical: Testing for acute oral toxicity in the male and female Wistar rat Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.1897 GLP not published	Y	BCS
Diehl, K.-H.; Leist, K.-H.	1988a	Hoe 075032 – active ingredient technical: Testing for acute oral toxicity in the male and female NMRI mouse Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.0477 GLP not published	Y	BCS
Diehl, K.-H.; Leist, K.-H.	1988b	Hoe 075032 – substance technical: Testing for acute dermal toxicity in the male and female Wistar rat Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.1896 GLP not published	Y	BCS
Diehl, K.-H.; Leist, K.-H.	1987b	Hoe 075032 – substance technical: Testing for primary dermal irritation in the rabbit Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.1889 GLP not published	Y	BCS
Diehl, K.-H.; Leist, K.-H.	1987c	Hoe 075032 – substance technical: Testing for primary eye irritation in the rabbit Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.1898 GLP not published	Y	BCS
Diehl, K.-H.; Leist, K.-H.	1987d	Hoe 075032 – substance technical: Testing for sensitising properties in the Pirbright-White guinea pig in a maximisation test Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.0476 GLP not published	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Diehl, K.-H.; Leist, K.-H.	1988c	Hoe 075032 – substance technical (Code: Hoe 075032 OH ZC97 0001). Subchronic oral toxicity – dose range finding – (28-day feeding study) in the wistar rat Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 87.1457 GLP not published	Y	BCS
Diehl, K.-H.; Leist, K.-H.	1988d	Hoe 075032 – substance technical (Code: Hoe 075032 OH ZC97 0001). Subchronic oral toxicity – dose range finding – (28-day feeding study) in the NMRI mouse Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 87.1456 GLP not published	Y	BCS
Dotti, A.; Kinder, J.; Biedermann, K.; Springall, C.J.	1992b	Hoe 075032 – substance technical (Code: Hoe 075032 00 ZC95 0001): Two-generation reproduction study in the rat RCC, Research and Consulting Company, AG, Switzerland, Report No. 243268 GLP not published	Y	BCS
Dotti, A.; Probst, D.; Luetkemeier, H; Schlotke, B.; Biedermann, K.	1992a	Hoe 075032 – substance technical (Code: Hoe 075032 00 ZC96 0002): combined chronic toxicity/oncogenicity (feeding) study in the rat RCC, Research and Consulting Company Ltd, CH, RCC Project No. 238768 GLP not published	Y	BCS
Ehling, G.	2004a	Inhouse historical control data, Wistar rat, for study report no. 89.0318 (Baeder, Ch., 1988): Hoe 075032 (Amidosulfuron) rat embryotoxicity study on finding: individual scull bones – slight or non-ossification Aventis Pharma Deutschland GmbH, Report no. C 048111 not published	Y	AVN-DE

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Ehling, G.	2004b	Inhouse historical control data, Himalayan rabbit, for study report no. 89.0319 (Baeder, Ch., 1988): Hoe 075032 (Amidosulfuron) rabbit embryotoxicity study on finding: at 13th thoracic vertebra – short or normally long – uni- or bilateral Aventis Pharma Deutschland GmbH, Report No. C048110 not published	Y	AVN-DE
Gutierrez, L.	2002	Amidosulfuron (^{14}C-AE F075032): repeat oral low dose ADME study in the rat Bayer CropScience, France; Report No. SA 02220 GLP not published	Y	BCS
Heidemann, A.	1989	Hoe 075032 – substance technical (Code: Hoe 075032 0H ZC94 0001) Chromosome aberration assay in human lymphocytes in vitro CCR Cytotest Cell Research GmbH & Co. KG, CCR Project No. 134605 GLP not published	Y	BCS
Hofmann, T; Bube, A.	1992	Hoe 075032; substance technical. Code: Hoe 075032 OH ZC97 0001. Testing for subchronic inhalation toxicity (21 applications within 29days) in male and female Wistar rats Pharma Development Toxicology, Hoechst AG, Report No. 91.0129 GLP not published	Y	BCS
Hofmann, T.; Jung, R.	1988	Hoe 075032 – active ingredient technical: Testing for acute dust inhalation toxicity in the male and female SPF Wistar rat 4-hour LC_{50} Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.0044 GLP not published	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Johnson, C.	1987	Metabolism and pharmacokinetics in male and female rats after a single oral administration of 10 mg/kg body weight Hoechst Pharmaceutical Research Laboratories, Buckingshamshire, UK, Report No. CJ1D280188 GLP not published	Y	BCS
Müller, W.	1988a	Hoe 075032 – substance technical (Code: Hoe 075032 0H ZC97 0001) Study of the mutagenic potential in strains of Salmonella typhimurium (Ames test) and Escherichia coli Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 87.1825 GLP not published	Y	BCS
Müller, W.	1988b	Hoe 075032 – substance technical (Code: Hoe 075032 0H ZC97 0001) Detection of gene mutations in somatic cells in culture: HGPRT-test with V79 cells Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.1636 GLP not published	Y	BCS
Müller, W.	1988c	Evaluation of Hoe 075032 – substance technical (Code: Hoe 075032 0H ZC97 0001) in the unscheduled DNA synthesis test in mammalian cells in vitro Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.0365 GLP not published	Y	BCS
Müller, W.	1987	Hoe 075032 – substance technical (Code: Hoe 075032 0H ZC96 0001): micronucleus test in male and female NMRI mice after oral administration Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 87.1807 GLP not published	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Pelcot, C.	2003	Skin sensitization test in guinea pigs (According to Magnusson and Kligman) CIT, BP 563, France Report No. 21760 TSG GLP not published	Y	BCS
Schollmeier, U.; Leist, K.-H.	1989a	Hoe 075032 – substance technical (Code: Hoe 075032 OH ZC97 0001). Subchronic oral toxicity (13-week feeding study) in the Wistar rat Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.1387 GLP not published	Y	BCS
Schollmeier, U.; Leist, K.-H.	1989b	Hoe 075032 – substance technical (Code: Hoe 075032 OH ZC97 0001). Subchronic oral toxicity (13-week feeding study) in the NMRI mice Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 88.1386 GLP not published	Y	BCS
Schollmeier, U.; Leist, K.-H.	1989c	Hoe 075032; substance technical. Code: Hoe 075032 00 ZC97 0001. Cumulative dermal toxicity (5 treatments in 8 days) in the male and female Wistar rat Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 89.0252 GLP not published	Y	BCS
Schollmeier, U.; Leist, K.-H.	1990	Hoe 075032; substance technical. Code: Hoe 075032 0H ZC97 0001. Subchronic dermal toxicity (21 treatments in 30 days) in the Wistar rat Pharma Research Toxicology and Pathology, Hoechst AG, Report No. 90.1139 GLP not published	Y	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Tennekes, H.; Janiak, T.; Stucki, H. P.; Probst, D.; Luetkemeier, H.; Vogel, O.; Armstrong, J. M.; Heusner, W.; Biedermann, K.	1992	Hoe 075032 – substance technical (Code: Hoe 075032 00 ZC96 0002): oncogenicity (feeding) study in mice RCC, Research and Consulting Company Ltd, CH, RCC Project No. 238770 GLP not published	Y	BCS
Till, C.P	1988	Metabolism and pharmacokinetics in male and female rats after a single oral administration of 100 mg/kg body weight Hoechst Pharmaceutical Research Laboratories, Buckingshamshire, UK, Report No. CT1D220788 GLP not published	Y	BCS
Till, C.P	1992	Metabolism in rats following single oral administration of test substance at a dose level of 500 mg/kg body weight Hoechst Pharmaceutical Research Laboratories, Buckingshamshire, UK, Report No. CT1D021092 GLP not published	Y	BCS

7.3 Environmental hazard assessment

7.3.1 Fate and Behaviour in the environment

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Dorn R.	2001	Degradation and metabolism of amidosulfuron (AE F075032) in one soil under standard conditions Generated by: SLFA Neustadt, DEU; Document No: C012457 GLP / GEP Yes unpublished	Yes	BCS
Erzgraeber B.	2001	Kinetic evaluation of the aerobic soil metabolism of AE F075032 in different soils using TopFit 2.0 Code: AE F075032, AE F101630, AE F128870 Generated by: Aventis CropScience GmbH, DEU; Environmental Risk Assessment, Frankfurt Document No: C014079 GLP / GEP No unpublished	Yes	BCS
Gildemeister H.	1992	Hoe 075032-14C Anaerobic soil Metabolism Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie Document No: A48777 GLP / GEP Yes unpublished	Yes	BCS
Gildemeister H.	1993	Hoe 075032-14C, Degradation kinetics in soil SLV under aerobic conditions Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A49610 GLP / GEP Yes unpublished	Yes	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Gildemeister H.	1993	Hoe 075032-14C, Degradation kinetics in a silt and a loam soil under aerobic conditions Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A49611 GLP / GEP Yes unpublished	Yes	BCS
Gildemeister H., Jordan H.-J.	1989	Hoe 075032-14C Photodegradation on Soil Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A40582 GLP / GEP Yes unpublished	Yes	BCS
Gildemeister H., Rockmann S.	1989a	Hoe 075032-14C Photodegradation in water Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A40662 GLP / GEP Yes unpublished	Yes	BCS
Goerlitz G.	1990	Hoe 075032 Adsorption/Desorption in the System Soil/Water Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A44733 GLP / GEP Yes unpublished	Yes	BCS
Knoch E.	2000a	Degradability and fate of amidosulfuron in the aquatic environment (water / sediment system) Generated by: Institut Fresenius Chem.und Biolog. Lab. GmbH; Isotope Laboratory Document No: C009793 GLP / GEP Yes unpublished	Yes	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Moendel M.	2001a	Adsorption/desorption of amidosulfuron (AE F075032) in three different soils Generated by: SLFA Neustadt, DEU; Document No: C012456 GLP / GEP Yes unpublished	Yes	BCS
Noack M., Wolf U., Noack U.	1991c	Biological degradability of Hoe 075032 in a modified Sturm test in accordance with the OECD Guideline 301 B for Testing Chemicals of 19 September 1984 Generated by: Dr.U.Noack-Laboratorium fuer Angewandte Biologie; Document No: A54662 GLP / GEP Yes unpublished	Yes	BCS
Purghart V.	2003	Amidosulfuron (AE F075032): Soil photolysis Generated by: Springborn Smithers Laboratories (Europe) AG, CHE; Document No: C031983 GLP / GEP Yes unpublished	Yes	BCS
Rose	1993	Assessment of the reactivity of organic molecules with OH-radicals of the troposphere by the method of Atkinson (1988) Generated by: Hoechst AG; Abteilung Umweltschutz Document No: C002027 GLP / GEP No unpublished	Yes	BCS
Schollmeier M., Britten I.	1992a	Hoe 075032 Determination of Abiotic Hydrolysis as a Function of pH (Hoe 075032 00 ZB98 0001) Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A47707 GLP / GEP Yes unpublished	Yes	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Schollmeier M., Eyrich U.	1992	Hoe 075032 Determination of Abiotic Hydrolysis as a Function of pH (Hoe 075032 00 ZB98 0001) Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A48869 GLP / GEP Yes unpublished	Yes	BCS
Sochor H.	1999	Amidosulfuron water dispersible granula 750 g/kg (Code: AE F075032 00 WG75 A109) Investigation of the dissipation of AE F075032 00 WG75 A109 in soil under field conditions Generated by: Hoechst Schering AgrEvo GmbH; Rueckstaende und Verbrauchersicherheit, Frankfurt Document No: C003109 GLP / GEP Yes unpublished	Yes	BCS
Till C.P.	1989	Hoe 075032-14-C Kinetics and Metabolism in soil under aerobic conditions at an application rate of 0.06 mg kg-1 (Part I) Generated by: Hoechst UK; Document No: A40368 GLP / GEP Yes unpublished	Yes	BCS
Till C.P.	1991	Hoe 075032-14-C Kinetics and Metabolism in Sandy Clay Loam SCL(F) under aerobic conditions at an application rate of 0.06 mg kg-1 Generated by: Hoechst UK; Document No: A46505 GLP / GEP Yes unpublished	Yes	BCS
Till C.P.	1991	Hoe 075032-14-C Kinetics and metabolism in loamy sand LS 2.2 under aerobic conditions at 10° C and at an application rate of 0.06 mg kg-1 Generated by: Hoechst UK; Document No: A46546 GLP / GEP Yes unpublished	Yes	BCS

7.3.2 Aquatic Toxicity

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Boeri Robert L.	1989f	Static acute toxicity of sample number Hoe 075032 to the sheepshead minnow, *Cyprinodon variegatus* Generated by: Enseco, USA; Document No: A40984 GLP / GEP Yes unpublished	Yes	BCS
Fischer R.	1987af	The Effect of Hoe 075032 - substance, technical (Identification code : Hoe 075032 OH ZC98 0001) to *Salmo gairdneri* (Rainbow trout) in a Static-Acute Toxicity Test (Sg365/b, method BBA) Generated by: Hoechst AG; Pflanzenschutz Forschung Biologie Document No: A35829 GLP / GEP Yes unpublished	Yes	BCS
Fischer R.	1991d	Hoe 075032 - substance, technical (Hoe 075032 00 ZC94 0001) Effect to *Salmo gairdneri* (Rainbow trout) in a 21-day Prolonged Toxicity Test (method OECD) Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A45487 GLP / GEP Yes unpublished	Yes	BCS
Fischer R.	1987ag	The Effect of Hoe 075032 - substance, technical (Identification code : Hoe 075032 OH ZC96 0001) to *Daphnia magna* (Waterflea) in a Static-Acute Toxicity Test (method EPA) Generated by: Hoechst AG; Pflanzenschutz Forschung Biologie Document No: A37699 GLP / GEP Yes unpublished	Yes	BCS
Fischer R., Schulze E.-F.	1988a	The Effect of Hoe 075032 - substance, technical (Identification code : Hoe 075032 OH ZC96 0001) to *Lepomis macrochirus* (Bluegill sunfish) in a Static-Acute Toxicity Test (method EPA) Generated by: Hoechst AG; Pflanzenschutz Forschung Biologie Document No: A38908 GLP / GEP Yes unpublished	Yes	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Fischer R., Schulze E.-F.	1988b	The Effect of Hoe 075032 - substance, technical (Identification code : Hoe 075032 OH ZC96 0001) to *Daphnia magna* (Waterflea) in a Static-Acute Toxicity Test (method OECD) Generated by: Hoechst AG; Pflanzenschutz Forschung Biologie Document No: A38705 GLP / GEP Yes unpublished	Yes	BCS
Fischer R., Schulze E.-F.	1988c	The Effect of Hoe 075032 - substance, technical (Identification code : Hoe 075032 OH ZC96 0001) to *Scenedesmus subspicatus* CHODAT (Green alga) in a Growth Inhibition Test (method OECD) Generated by: Hoechst AG; Pflanzenschutz Forschung Biologie Document No: A38704 GLP / GEP Yes unpublished	Yes	BCS
Heusel R.	1991cz	Hoe 075032 - substance, technical (Hoe 075032 00 ZC94 0001) Effect to *Daphnia magna* (Waterflea) in a 21-day Reproduction Test (method OECD) Generated by: Hoechst AG; GB C / Produktentwicklung Oekologie 1 Document No: A46125 GLP / GEP Yes unpublished	Yes	BCS
Morrow J. E., Ward G. S.	1993a	Technical Hoe 075032 (Hoe 075032 00 ZD99 0001) Acute toxicity to duckweed (*Lemna gibba*) G3, under Static test conditions Generated by: Toxikon Environmental Sciences; Document No: A49587 GLP / GEP Yes unpublished	Yes	BCS
Sowig P.	2002ag	Duckweed (*Lemna gibba* G3) growth inhibition test with recovery phase AE F075032 substance, technical Code: AE F075032 00 1D99 0013 Generated by: Bayer CropScience GmbH, DEU; Ecotoxicology, Frankfurt Document No: C025093 GLP / GEP Yes unpublished	Yes	BCS

Author(s)	**Year**	**Title** **Source (where different from company)** **Company, Report No** **GLP or GEP status (where relevant),** **Published or not**	**Data Protection Claimed** **Y/N-R/NR**	**Owner**
Sowig P., Weller O., Gosch H.	1999aj	Amidosulfuron (prov. approved ISO) substance, technical Code: AE F075032 00 1 D99 0004 Algal growth inhibition - *Navicula pelliculosa* Generated by: Hoechst Schering AgrEvo GmbH; Entwicklung Umweltforschung, Frankfurt Document No: C001109 GLP / GEP Yes unpublished	Yes	BCS