Committee for Risk Assessment

RAC

Annex 1

Background document

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

mandipropamid

EC number: -
CAS number: 374726-62-2

CLH-O-0000003601-83-01/A1

Adopted

08 March 2013

CONTENTS

Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Mandipropamid***
EC number:	**-**
CAS number:	374726-62-2
Annex VI Index number:	**-**
Degree of purity:	≥93 %
Impurities:	***No relevant impurities***

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 entry	No entry
Current proposal for consideration by RAC	Aquatic acute 1 – H400 Aquatic chronic 2 – H411	N; R50/53
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Aquatic acute 1 – H400 Aquatic chronic 2 – H411	N; R50/53

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

2.14.	Oxidising solids	-			Data conclusive, but not sufficient for classification
2.15.	Organic peroxides	-			Data conclusive, but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	-			Data conclusive, but not sufficient for classification
3.1.	Acute toxicity - oral	No classification	-	-	conclusive, but not sufficient for classification
	Acute toxicity - dermal	No classification	-	-	conclusive, but not sufficient for classification
	Acute toxicity - inhalation	No classification	-	-	conclusive, but not sufficient for classification
3.2.	Skin corrosion / irritation	No classification	-	-	conclusive, but not sufficient for classification
3.3.	Serious eye damage / eye irritation	No classification	-	-	conclusive, but not sufficient for classification
3.4.	Respiratory sensitisation	No classification	-	-	conclusive, but not sufficient for classification
3.4.	Skin sensitisation	No classification	-	-	conclusive, but not sufficient for classification
3.5.	Germ cell mutagenicity	No classification	-	-	conclusive, but not sufficient for classification
3.6.	Carcinogenicity	No classification	-	-	conclusive, but not sufficient for classification
3.7.	Reproductive toxicity	No classification	-	-	conclusive, but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure	No classification	-	-	conclusive, but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	No classification	-	-	conclusive, but not sufficient for classification
3.10.	Aspiration hazard	No	-	-	conclusive, but not sufficient for

		classification			classification
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1, H400 Aquatic Chronic 2, H411	1		
5.1.	Hazardous to the ozone layer				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

H411 Toxic to aquatic life with long lasting effects

Precautionary statements:

P101 If medical advice is needed, have product container or label at hand.

P102 Keep out of reach of children.

P270 Do not eat, drink or smoke when using this product.

P273 Avoid release to the environment

P391 Collect spillage

P501 Dispose of contents/container to ….

Suppl. Hazard:

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	-			Data conclusive, but not sufficient for classification
Oxidising properties	-			Data conclusive, but not sufficient for classification
Flammability	-			Data conclusive, but not sufficient for classification
Other physico-chemical properties *[Add rows when relevant]*	-			-
Thermal stability	-			Data conclusive, but not sufficient for classification
Acute toxicity	No classification	-	-	conclusive, but not sufficient for classification
Acute toxicity – irreversible damage after single exposure	No classification	-	-	conclusive, but not sufficient for classification
Repeated dose toxicity	No classification	-	-	conclusive, but not sufficient for classification
Irritation / Corrosion	No classification	-	-	conclusive, but not sufficient for classification
Sensitisation	No classification	-	-	conclusive, but not sufficient for classification
Carcinogenicity	No classification	-	-	conclusive, but not sufficient for classification
Mutagenicity – Genetic toxicity	No classification	-	-	conclusive, but not sufficient for classification
Toxicity to reproduction – fertility	No classification	-	-	conclusive, but not sufficient for classification
Toxicity to reproduction – development	No classification	-	-	conclusive, but not sufficient for classification

Toxicity to reproduction – breastfed babies. Effects on or via lactation	No classification	-	-	conclusive, but not sufficient for classification
Environment	N R50/53			

1) Including SCLs

2) Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: N Dangerous for the Environment

R-phrases: R50/53 Very toxic to aquatic organisms, may cause long-term adverse effect in the aquatic environment.

S-phrases: S2 Keep out of the reach of children

S13 Keep away from food, drink and animal feeding stuffs

S20/21 When using do not eat, drink or smoke

S56 Dispose of this material and its container to hazardous or special waste collection point.

S57 Use appropriate container to avoid environmental contamination.

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 sheets.

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Mandipropamid is a new mandelamide fungicide. The compound was applied as new active substance under Council Directive 91/414/EEC, with Austria as Rapporteur Member State. In accordance with Article 36(2) of the CLP Regulation, mandipropamid 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 mandipropamid under Directive 91/414/EEC. This assessment (DAR) was based on one full data package submitted by one company.

Mandipropamid 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.

2.2 Short summary of the scientific justification for the CLH proposal

No classification and labelling has been proposed regarding physical and chemical properties by Austria as Rapporteur Member State for mandipropamid

Regarding classification criteria for Mandipropamid for **aquatic environment hazards acute category 1** (very toxic to aquatic organisms) is proposed.

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

DSD: N, R50/53 (DSD)
CLP: Aquatic Acute 1, H400, M=1; Aquatic Chronic 2, H411

Aquatic Acute classification is based on:

- EC50 value for *Crassostrea virginica* = 0.97 mg/L (Palmer et al 2005c), resulting in N, R50 (DSD) and Aquatic Acute 1, H400, M =1 (CLP)

Aquatic chronic classification is based on:

- Mandipropamid is not considered as ready biodegradable/rapid degradable. Therefore a R53 (DSD) classification is proposed.
- chronic aquatic toxicity studies
  Based on the non rapid degradability and on the toxicity to Daphnia (Grade 2003) with a NOEC= 0.28 mg/L. a classification with Aquatic Chronic 2, H411 (CLP) is proposed.

2.3 Current harmonised classification and labelling

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

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

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

2.4 Current self-classification and labelling

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

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

2.4.2 Current self-classification and labelling based on DSD criteria

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

No need for justification (mandipropamid is a pesticide)

Part B.

SCIENTIFIC EVALUATION OF THE DATA

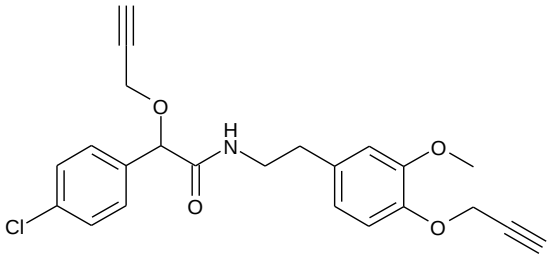
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	---
EC name:	Mandipropamid
CAS number (EC inventory):	---
CAS number:	374726-62-2
CAS name:	Benzeneacetamide, 4-chloro-N-[2-[3-methoxy-4-(2-propyn-1-yloxy)phenyl]ethyl]-α-(2-propyn-1-yloxy)-
IUPAC name:	2-(4-chlorophenyl)-N-{2-[3-methoxy-4-(prop-2-yn-1-yloxy)phenyl]ethyl}-2-(prop-2-yn-1-yloxy)acetamide
CLP Annex VI Index number:	---
Molecular formula:	$C_{23}H_{22}ClNO_4$
Molecular weight range:	411.9 g/mol

Structural formula:



1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Mandipropamid	94.7 %	95.7 %	97.3 %

Current Annex VI entry: No entry available.

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
-			

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
-				

1.2.1 Composition of test material

Human health hazard assessment: purity of tested technical material in the range from 96.5% to 98.5%.

Environmental hazard assessment: purity of tested technical material in the range from 96.1% to 99.5%

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Study	Method	Material	Results	Conclusion/Comment	Reference
B.2.1.1 Melting point, freezing point or solidification point (IIA 2.1.1)	OECD 102 capillary method with photocell detection GLP	pure substance 990 g/kg	96.4° C to 97.3 °C	Acceptable EEC/A1 is based on OECD 102	Das R., (2002a) (NOA446510/ 0024)
B.2.1.2 Boiling point (IIA 2.1.2)	OECD 103 DSC GLP	pure substance 990 g/kg	Thermal decomposition starts at about 200 °C	Acceptable EEC/A2 is based on OECD 103	Das R., (2003a) (NOA446510/ 0038)
B.2.1.3 Temperature of decomposition or sublimation (IIA 2.1.3)	OECD 103 DSC GLP	pure substance 990 g/kg	Thermal decomposition starts at about 200 °C	Acceptable EEC/A2 is based on OECD 103	Das R., (2003a) (NOA446510/ 0038)
	OECD 113 DSC and TGA GLP	tech. substance 952 g/kg	Stable in nitrogen or air, no thermal decomposition or weight loss attributable to reaction/decomposition at room temperature	Acceptable	Vehling H., (2005) (NOA446510/ 0401)
B.2.1.4 Relative density (IIA 2.2)	OECD 109 pycnometer -air comparison GLP	pure substance 990 g/kg	1.24×10^3 kg/m^3 at 22 °C corresponds to a relative density = 1.24	Acceptable EEC/A3 is based on OECD 109	Füldner H., (2003) (NOA446510/ 0031)
B.2.1.5 Vapour pressure (IIA 2.3.1)	OECD 104 gas saturation GLP	pure substance 990 g/kg	$< 9.4 \times 10^{-7}$ Pa at 20 °C $< 9.4 \times 10^{-7}$ Pa at 25 °C $< 9.4 \times 10^{-7}$ Pa at 50 °C	Acceptable EEC/A4 is based on OECD 104	Geoffroy A.,(2003) (NOA446510/ 0064) Das R., (2006d) (Doc. 10115200)

Study	Method	Material	Results	Conclusion/Comment	Reference
			HPLC was used for the determination of the concentration of mandipropamid condensed in the U-tube, based on the method of analysis used for the determination of active substance in technical grade material. The reference solutions were prepared with different concentrations in order to take into account the expected concentrations of mandipropamid in the test solutions.		
B.2.1.6 Volatility, Henry's law constant (IIA 2.3.2)	calculation	–	< 9.2 x 10^{-5} Pa m³ / mol at 25 °C: <u>values used for calculation:</u> vapour pressure at 25 °C : < 9.4 x 10^{-7} Pa water solubility at 25 °C : 4.2 mg/L	Acceptable	Baker S., (2005) (NOA446510/ 0445)
B.2.1.7 Appearance: physical state (IIA 2.4.1)	Visual assessment GLP	pure substance 990 g/kg	light beige powder	Acceptable	Das R., (2002b) (NOA446510/ 0025)
	Visual assessment GLP	tech. substance 952 g/kg	light beige fine powder	Acceptable	Das R., (2005a) (NOA446510/ 0376)
B.2.1.9 Appearance: odour (IIA 2.4.2)	Organoleptic GLP	pure substance 990 g/kg	odourless	Acceptable	Das R., (2002b) (NOA446510/ 0025)
	Organoleptic GLP	tech. substance 952 g/kg	odourless	Acceptable	Das R., (2005a) (NOA446510/ 0376)
B.2.1.10 Spectra of the active substance (IIA 2.5.1)	GLP	pure substance 990 g/kg	**UV/VIS** **Solution c = 1.287 mg/100 mL** / **Wave-length [nm]** / **ε [L/mol x cm]**	Acceptable	Oggenfuss P., (2004) (NOA446510/ 0082)

Study	Method	Material	Results			Conclusion/Comment	Reference
			neutral (methanol)	223 276	20144 2724		
			acidic (methanol/1 N HCl (90+10)	223 276	20313 2845		
			basic (methanol / 1 N NaOH (90+10)	223 276	19414 2864		
			The given data in respect to the **IR**, **NMR** and **MS** spectra were found to be in agreement with the proposed chemical structure.				
B.2.1.10.1 Optical purity						Not relevant	
B.2.1.11 Spectra of relevant impurities (IIA 2.5.2)			Not required as no impurities of toxicological or ecotoxicological concern were identified			Acceptable	Tier II
B.2.1.12 Solubility in water (IIA 2.6)	OECD 105 flask method GLP	pure substance 990 g/kg	4.2 mg/L in pure water at 25 °C HPLC was used for the determination of the concentration of mandipropamid, based on the method of analysis used for the determination of active substance in technical grade material. The reference solutions were prepared with different concentrations in order to take into account the expected concentrations of mandipropamid in the test solutions.			Acceptable EEC/A6 is based on OECD 105 Although column elution method is required for substances which water solubility is < 10^{-2} g/L the notifier justifies the use of the flask method that the evaporation of organic solvent was not	Das R., (2003b) (NOA446510/0026) Das R., (2006a) (Doc. 10115199)

Study	Method	Material	Results	Conclusion/Comment	Reference
				complete and the crystal structure of mandipropamid may be altered during the deposition onto the carrier material of the column. Effect of pH is not required since there is no dissociation in water in the environmentally relevant pH-range (see B.2.1.18)	
		Metabolite CGA 380775 (CA 3584) pure substance 982 g/kg	The solubility in aqueous buffered solutions at 25 °C has been determined to be: 230 mg/L pH 5.0 230 mg/L pH 7.0 280 mg/L pH 9.0	Acceptable	Das R., (2004a) (CGA380775/0001)
		Metabolite CGA 380778 (R 730383) pure substance 980 g/kg	The solubility in pure water at 25 °C is 100 mg/L	Acceptable	Das R., (2004b) (CGA380778/0001)
		Metabolite SYN 500003 (R 740990, CA 4013)	The solubility in aqueous buffered solutions at 25 °C has been determined to be: 45 g/L pH 5.0 170 g/L pH 7.0 170 g/L pH 9.3	Acceptable	Das R., (2004c) (SYN500003/0001)

Study	Method	Material	Results	Conclusion/Comment	Reference
		pure substance 990 g/kg			
		Metabolite SYN 504851 (R 740991) pure substance 970 g/kg	The solubility in aqueous buffered solutions at 25 °C has been determined to be: > 500 g/L pH 4.8 > 500 g/L pH 7.0 and 9.0	Acceptable	Das R., (2005b) (SYN504851/0005)
		Metabolite SYN 535839 pure substance 960 g/kg	The solubility in pure water at 25 °C is 26 mg/L	Acceptable	Das R., (2004d) (SYN535839/0001)
		Metabolite SYN 536638 (R 290539) pure substance 980 g/kg	The solubility in pure water at 25 °C is 14 mg/L	Acceptable	Das R., 2005c (SYN536638/0001)
		Metabolite NOA 458422 (CA 4011) pure substance 990 g/kg	The solubility in aqueous buffered solutions at 25 °C has been determined to be: 51 mg/L pH 5.0 51 mg/L pH 7.0 49 mg/L pH 9.0	Acceptable	Das R., (2005d) (CA4011/0005)
B.2.1.13 Solubility in organic solvents	CIPAC MT 157.3 GLP	tech. substance 952 g/kg	The solubility in different solvents at 25 °C was determined to be: acetone 300 g/L	Acceptable	Das R., (2005e) (NOA446510/ 0375) Das R., (2006b)

Study	Method	Material	Results	Conclusion/Comment	Reference
(IIA 2.7)			dichloromethane 400 g/L ethyl acetate 120 g/L hexane 42mg/L methanol 66 g/L octanol 4.8g/L toluene 29 g/L HPLC was used for the determination of the concentration of mandipropamid, based on the method of analysis used for the determination of active substance in technical grade material. The reference solutions were prepared with different concentrations in order to take into account the expected concentrations of mandipropamid in the test solutions.		(Doc. 10115182)
B.2.1.14 Partition coefficient *n*-octanol/water (IIA 2.8.1)	OEDC 107 (shake flask method) GLP	pure substance 990 g/kg	The octanol/water partition coefficient (Pow) at 25 °C in pure water was determined to be: Pow = 1600 (± 42) log Pow = 3.2 HPLC was used for the determination of the concentration of mandipropamid, based on the method of analysis used for the determination of active substance in technical grade material. The reference solutions were prepared with different concentrations in order to take into account the expected concentrations of mandipropamid in the test solutions.	Acceptable EEC/A8 is based on OECD 107	Das R., (2003c) (NOA446510/ 0027) Das R., (2006c) (Doc. 10115098)
		Metabolite	The octanol/water partition coefficient	Acceptable	Das R., (2005f)

Study	Method	Material	Results	Conclusion/Comment	Reference
		CGA 380775 (CA 3584) pure substance 982 g/kg	(Pow) at 25 °C was determined to be: Pow = 120 (± 3.1) log Pow = 2.1 at pH 5.0 Pow = 120 (± 3.0) log Pow = 2.1 at pH 7.0 Pow = 100 (± 1.5) log Pow = 2.0 at pH 9.0		(CGA380775/0003)
		Metabolite CGA 380778 (R 730383) pure substance 980 g/kg	The octanol/water partition coefficient (Pow) at 25 °C was determined to be: Pow = 360 (± 11)log Pow = 2.6	Acceptable	Das R., (2004e) (CGA380778/0002)
		Metabolite SYN 500003 (R 740990, CA 4013) pure substance 990 g/kg	The octanol/water partition coefficient (Pow) at 25 °C was determined to be: Pow = 1.8 (± 0.051) log Pow = 0.27 at pH 5.0 Pow = 0.057 (± 0.0020) log Pow = -1.2 at pH 6.8 Pow = 0.026 (± 0.00089) log Pow = -1.6 at pH 9.0	Acceptable	Das R., (2005g) (SYN500003/0006)
		Metabolite SYN 504851 (R 740991) pure substance 970 g/kg	The octanol/water partition coefficient (Pow) at 25 °C was determined to be: Pow = 4.9 (± 0.053) log Pow = 0.69 at pH 5.0 Pow = 0.14 (± 0.0083) log Pow = -0.86 at pH 6.8 Pow = 0.055 (± 0.0011) log Pow = -1.3 at pH 9.0	Acceptable	Das R., (2005h) (SYN504851/0008)

Study	Method	Material	Results	Conclusion/Comment	Reference
		Metabolite SYN 535839 pure substance 960 g/kg	The octanol/water partition coefficient (Pow) at 25 °C was determined to be: Pow = 9000 (± 400) log Pow = 4.0	Acceptable	Das R., (2004f) (SYN535839/0002)
		Metabolite SYN 536638 (R 290539) pure substance 980 g/kg	The octanol/water partition coefficient (Pow) at 25 °C was determined to be: Pow = 4000 (± 59) log Pow = 3.6	Acceptable	Das R., (2005i) (SYN536638/0002)
		Metabolite NOA 458422 (CA 4011) pure substance 990 g/kg	The octanol/water partition coefficient (Pow) at 25 °C was determined to be: Pow = 600 (± 18) log Pow = 2.8 at pH 5.0 Pow = 550 (± 6.7) log Pow = 2.7 at pH 7.0 Pow = 560 (± 25) log Pow = 2.8 at pH 9.1	Acceptable	Das R., (2005j) (CA4011/0007)
Effect of pH (4-10) on the n-octanol/water partition co-efficient (IIA 2.8.2)			Not relevant as the active substance shows no pH dependency	(see B.2.1.18)	
B.2.1.15 Hydrolysis rate (IIA 2.9.1)	OECD 111 GLP	^{14}C labelled NOA 446510, 989 g/kg radio-	The hydrolytic behaviour of NOA 446510 was investigated in diluted aqueous buffer solutions at pH 4, 7 and 9 using ^{14}C labelled active substance. The recovery for all samples was between	Acceptable For details see B.8.4 Fate and behaviour	Buckel T., (2002) (NOA446510/ 0018)

Study	Method	Material	Results	Conclusion/Comment	Reference
		chemical purity	92.7 and 105.7% of the applied radioactivity. No degradation of the test substance was observed under all conditions. Therefore, NOA 446510 is hydrolytically stable at pH 4, 7 and 9.		
B.2.1.16 Direct phototrans-formation (IIA 2.9.2)	OECD, Proposal "Phototrans-formation of Chemicals in Water – Direct and Indirect Photolysis" Draft, Aug. 2000 GLP	^{14}C labelled NOA 446510 1980 Bq μg^{-1} radio-chemical purity: >99%	The photolytic degradation was evaluated in sterile buffer solution at pH 7, under a xenon arc light, at 25°C using ^{14}C-labelled test substance at a concentration of 1 µg mL^{-1}. The samples were irradiated for periods up to the equivalent of 17 days summer sunlight. Duplicate "dark" control samples were also prepared and maintained at 25 °C and analysed at the same time period as the irradiated samples. The estimated half-life was 34 hours of continuous irradiation. At least 16 degradates were formed, none of which represented >5% of the applied radioactivity at any point during the study. With further irradiation these degradates were broken down further to at least 10 highly polar degradates. The mean mass balance from irradiated samples was 102.9% of the applied radioactivity, of which up to 16.2% was characterised as $^{14}CO_2$.	Acceptable For details see B.8.4 Fate and behaviour	Hand L and Towers J., (2003) (NOA446510/ 0041)
B.2.1.17 Quantum yield (IIA 2.9.3)	OECD, Proposal "Phototrans-formation of Chemicals in Water – Direct and Indirect	pure substance 990 g/kg	The quantum yield of direct photolysis was found to be Φ = 0.37, at 300 nm wavelength of applied light. Photolytic half-life in shallow waters was estimated for geographic latitudes of 30°N, 40°N and 50°N for all seasons.	Acceptable For details see B.8.4 Fate and behaviour	Schmidt E., (2004) (NOA446510/ 0118)

Study	Method	Material	Results	Conclusion/Comment	Reference
	Photolysis" Draft, Aug. 2000 GLP		Summer half-lives between 30 and 60 days were calculated for 30°N and 50°N respectively.		
B.2.1.18 Dissociation constant (pKa) (IIA 2.9.4)	OECD 112 spectrophotometric titration GLP	pure substance 990 g/kg	No pKa was found at various pH values in the range of 1.0 to 12.0 of a solution of NOA 446510 in water.	Acceptable	Martin N., (2003) (NOA446510/ 0029)
		Metabolite CGA 380775 (CA 3584) pure substance 982 g/kg	pKa = 10.34 at 20 °C	Acceptable	Martin N., (2004a) (CGA380775/0002)
		Metabolite CGA 380778 (R 730383) pure substance 980 g/kg	pKa = 11.64 at 20 °C	Acceptable	Martin N., (2004b) (CGA380778/0004)
		Metabolite SYN 500003 (R 740990, CA 4013) pure substance 990 g/kg	pKa = 2.76 at 20 °C	Acceptable	Martin N., (2004c) (SYN500003/0002)
		Metabolite SYN 504851 (R 740991)	pKa = 2.91 at 20 °C	Acceptable	Richner D., (2005a) (SYN504851/0004)

Study	Method	Material	Results	Conclusion/Comment	Reference
		pure substance 970 g/kg			
		Metabolite SYN 535839 pure substance 960 g/kg	No pKa was found in the pH range of 1.0 to 12.0	Acceptable	Martin N., (2004d) (SYN535839/0003)
		Metabolite SYN 536638 (R 290539) pure substance 980 g/kg	No pKa was found in the pH range of 1.0 to 12.0	Acceptable	Martin N., (2005) (SYN536638/0003)
		Metabolite NOA 458422 (CA 4011) pure substance 990 g/kg	pKa = 10.37 at 20 °C	Acceptable	Richner D., (2005b) (CA4011/0006)
B.2.1.19 Stability in air, photochemical oxidative degradation (IIA 2.10)	Calculation with Atmospheric Oxidation Program based on Atkinson method		The atmospheric oxidation of NOA 446510 by hydroxyl radicals was estimated by calculation according to Atkinson. The estimated half-life is 1.4 hours.	Acceptable	Widmer H., (2003) (NOA446510/0035)
B.2.1.20 Flammability (IIA 2.11)	EEC A10 GLP	tech. substance 952 g/kg	Preliminary Test: the test substance melted and charred but did not ignite	Acceptable Not classified as highly flammable in terms of its burning	Jackson W.A., (2005a) (NOA446510/0405)

Study	Method	Material	Results	Conclusion/Comment	Reference
			According to EEC A10 a full test is not required	characteristics	
B.2.1.21 Auto-flammability (IIA 2.11.2)	EEC A16 GLP	tech. substance 952 g/kg	No ignition was detected below the melting point	Acceptable Compound is not considered as auto-flammable under the test conditions	Jackson W.A., (2005b) (NOA446510/ 0403)
B.2.1.22 Flash point (IIA 2.12)			Not relevant NOA 446510 is a solid with a melting point > 40 °C		
B.2.1.23 Explosive properties (IIA 2.13)	EEC A14 GLP	tech. substance 952 g/kg	The substance did not explode when exposed to heat, mechanical shock or friction	Acceptable Compound is not considered as explosive under the test conditions of EEC/A14 Although dust explosion does not cover this annex point, the MSDS for mandipropamid technical indicates that the compound is capable of forming flammable dust clouds in air, which can produce a dust cloud explosion, if ignited.	Jackson W.A., (2005c) (NOA446510/ 0404)
B.2.1.24 Surface tension (IIA 2.14)	OECD 115 GLP	tech. substance 952 g/kg	σ = 72.8 mN / m 90 % of the saturation concentration at 20 °C	Acceptable Mandipropamid is not regarded as surface active.	Richner D., (2005c) (NOA446510/ 0426)
B.2.1.25	EC A17	tech.	Not an oxidising substance.	Compound is not	Jackson W.A.,

Study	Method	Material	Results	Conclusion/Comment	Reference
Oxidizing properties (IIA 2.15)	GLP	substance 952 g/kg	The maximum overall burning rate is 2.4 mm/s for the 5% test substance mixture. This is lower than the max. burning rate of the reference mixture (3.4 mm/s) containing of 60% $Ba(NO_3)_2$/Cellulose.	considered as oxidizing under the test conditions	(2005d) (NOA446510/ 0402)
B.2.1.2.26 pH (IIA 2.16)				This is not an EC data requirement	
Storage stability (IIA 2.17.1)				This is not an EC data requirement	
Stability (temperature, metals) (IIA 2.17.2)				This is not an EC data requirement	
Other/special studies (IIA 2.18)				This is not an EC data requirement	

According to Directive 91/414/EEC, granulometry is not required for active substances. Thus, no study considering this end-point has been provided.

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for Classification and Labelling.

2.2 Identified uses

Mandipropamid is a new mandelamide fungicide agriculture for foliar application on vegetables and grapes.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

No classification required.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Absorption: The percentage absorption of radioactivity over 48 hours after dosing was calculated from the amounts found in urine, bile, cage wash and carcass of bile duct cannulated rats. The extent of absorption was similar in both sexes, but more extensive at the low dose level (3 mg/kg bw) than at the high dose level (300 mg/kg bw). At the low dose level, absorption was 74 % in males and 67 % in females. At the high dose level, absorption was 30 % in males and 45 % in females.

Distribution: Following a single oral dose of either 3 or 300 mg/kg of the test substance to both male and female rats, tissue concentrations were considered to be low in all cases and were also consistently lower in female tissues than in male tissues. The highest residues were present in the liver and kidneys 8 hours after application, however, these values declined rapidly. The half life of elimination in the tissues investigated was approximately 24 hours or lower. When repeated doses of 3 mg/kg were administered to male rats, levels of radioactivity found in tissues were also generally low. Tissue accumulation profiles for liver and kidneys indicate that the concentration reached a plateau by 4 days. Elimination from these organs was rapid after termination of dosing. No potential for bioaccumulation was identified.

Excretion: In non-cannulated low dose rats, about 70 % of test substance were excreted within 48 hours, with males excreting most of the radioactivity by faeces and females excreting roughly half of the radioactivity by faeces and the other half by urine. In the high dose animals when absorption was saturated, large proportions of test substance were found in the faeces (about 80 % after 48 hours) while only 2-10 % were found in urine in both sexes. Excretion was almost complete within 7 days of dosing, by which time all excised tissue and carcass residues were very low (<0.5 % of the administered dose). Biliary elimination was important at both dose levels and in both sexes, accounting for 73 % and 55 % of a 3 mg/kg dose and 28 % and 22 % of a 300 mg/kg dose in males and females, respectively. Residues in expired air were near to or below the limit of detection.

Metabolism: The principle steps in metabolism involved loss of one or both propargyl groups, followed by glucuronidation and O-demethylation to produce 6 major metabolites. There were no sex or dose related differences in the qualitative metabolic profile. However, a sex difference was observed in the major route of excretion and relative proportions of metabolites excreted via certain routes. In females, the major route of excretion was via the urine, and NOA 458422 glucuronide was identified as the major urinary metabolite. In males, the major route of excretion was via the faeces, with NOA 458422 being the major metabolite. The substance was extensively metabolised at the low dose level of 3 mg/kg, with 21 % and 12 % of the parent found in the faeces of non-cannulated males and females, respectively. In bile duct-cannulated rats, the amount of unchanged parent compound was 13 % in males and

22 % in females. At the high dose level, where absorption of a gavage dose was less extensive, a high proportion of the parent compound was detected unchanged in the faeces (>70 %). This was considered to represent the unabsorbed dose, since no unchanged parent was detected in the bile. Similarily, no unchanged parent was present in urine. Repeated daily dosing, investigated in the male rat only, had no effect on the metabolism of mandipropamid, and similar metabolite profiles were obtained 24 hours after the first and fourteenth consecutive daily doses.

4.1.2 Human information

No data available.

4.1.3 Summary and discussion on toxicokinetics

Absorption, distribution, excretion and metabolism (toxicokinetics) (Annex IIA, point 5.1)

Rate and extent of oral absorption ‡	70 % absorbed (rat study, 3 mg/kg bw), based on excretion via urine and bile
Distribution ‡	Uniformly distributed; highest levels found in liver and kidney
Potential for accumulation ‡	no evidence for bioaccumulation
Rate and extent of excretion ‡	rapid, mainly via faeces (70–80% within 48 hours)
Metabolism in animals ‡	loss of one or both propargyl groups, followed by glucuronidation and O-demethylation
Toxicologically relevant compounds ‡ (animals and plants)	Mandipropamid
Toxicologically relevant compounds ‡ (environment)	Mandipropamid

4.2 Acute toxicity

Table 11: Summary table of relevant acute toxicity studies

Type of Study	Species	Vehicle	Results	Reference
Acute Oral	rat	corn oil	LD_{50} > 5000mg/kg bw	Moore G (2004)
Acute Dermal	rat	corn oil	LD_{50} > 5050mg/kg bw	Kuhn J (2005)
Acute Inhalation	rat	clean dry air	LC_{50} > 5.19 mg/l/4h	Kilgour J (2003)
Skin Irritation	rabbit	moistened with deionized water	Not irritant	Johnson I (2004a)
Eye Irritation	rabbit	test substance was used as supplied	Not Irritant	Johnson I (2004b)
Skin sensitisation (LLNA)	mouse	dimethylformamide (DMF)	Not a sensitiser	Johnson I (2004c)

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

After oral application to female rats, the acute oral LD_{50} of mandipropamid techn. was greater than 5000 mg/kg/bw. All animals survived and gained bodyweight during the 14 days following dosing. Apart from ano-genital staining noted for one rat five hours post-dosing, all animals appeared active and healthy over the 14-day observation period. There were no other signs of gross toxicity or abnormal behaviour. No gross abnormalities were noted at examination *post mortem*.

4.2.1.2 Acute toxicity: inhalation

Nose-only exposure for 4 hours to a particulate concentration of 5.19 mg//l resulted in no deaths and signs of mild irritation to the respiratory tract from which the animals made a rapid recovery. It is concluded that the LC_{50} of mandipropamid exceeds 5.19 mg//l. During and immediately following exposure, abnormalities generally associated with restraint (wet fur, stains around the nose) were observed in all animals. Other signs noted were slight salivation and signs of respiratory tract irritation (increased breathing depth and abnormal respiratory noise).
All female animals had completely recovered by day 2 and in males only abnormal respiratory noise remained in 2 males on day 2 and in one male on day 3. All animals had fully recovered by day 4 of the study.

There were not treatment-related findings at necropsy.

4.2.1.3 Acute toxicity: dermal

The acute dermal LD_{50} of mandipropamid techn. to male and female rats was greater than 5050 mg/kg bodyweight. There were no signs of systemic toxicity or skin irritation. All animals showed normal weight gain during the study. There were no treatment-related findings at examination *post mortem.*

4.2.1.4 Acute toxicity: other routes

No information on other routes.

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

Mandipropamid is of low acute oral, dermal and inhalative toxicity in rats (rat oral LD_{50} > 5000 mg/kg bw, dermal LD_{50} > 5050 mg/kg bw, LC_{50} > 5.19 mg/L air/4h.

4.2.4 Comparison with criteria

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

4.2.5 Conclusions on classification and labelling

No classification and labelling is proposed regarding acute toxicity.

RAC evaluation of acute toxicity
Summary of the Dossier submitter's proposal The Dossier Submitter (DS) did not propose any acute toxicity classification for mandipropamid. The DS's assessment and conclusion on acute toxicity was based on three studies (oral, dermal and inhalation) in rats. In female rats, the acute oral LD_{50} for mandipropamid (technical grade) was greater than 5000 mg/kg/bw. No death was reported. No effect on behaviour was observed nor gross abnormalities after examination *post mortem*. All animals gained bodyweight during the observation period of 14 days. Only an anogenital staining was found in one rat (5 hours post dosing period). The acute inhalation toxicity exposure was performed as a nose-only exposure for four hours. No death was reported and the LC_{50} was stated to be greater than 5.19 mg/l. No treatment-related effects were observed at necropsy. Signs of respiratory tract irritation were observed during and immediately following exposure (slight to mild: increased

breathing depth and abnormal respiratory noise) but animals recovered rapidly (full recovery by day 4).

The acute dermal LD_{50} in rats was greater than 5050 mg/kg/bw. There were no signs of systemic toxicity or dermal irritation. All animals showed normal weight gain (no death reported) and no treatment-related findings were reported at necropsy.

According to the DS, no classification and labelling is warranted regarding acute toxicity.

Comments received during public consultation
Two Member States (MSs) agreed with the DS's proposal that classification is not warranted for acute toxicity.

Assessment and comparison with the classification criteria
In rats, the oral LD_{50} for mandipropamid is greater than 5000 mg/kg/bw, the inhalation LC_{50} is greater than 5.19 mg/L and the dermal LD_{50} is above 5050 mg/kg/bw.
All the reported LD_{50} and LC_{50} are above the CLP criteria value for classification (2000 mg/kg/bw for the oral and dermal route, 5mg/L for the inhalation route). The RAC agrees that classification for acute toxicity is not warranted for mandipropamid according to CLP or DSD.

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

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

No specific, non-lethal, target organ toxicity after single exposure was observed in acute toxicity studies. 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.

4.3.2 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 regarding specific target organ toxicity after single exposure.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)
Summary of the Dossier submitter's proposal The DS did not propose STOT-SE classification for mandipropamid. After a single exposure, no specific non-lethal target organ toxicity was observed in acute toxicity tests. No human data is available in supporting classification for the hazard class. **Comments received during public consultation**

Three MS agreed with the DS's proposal that classification is not warranted for STOT-SE.

Assessment and comparison with the classification criteria
No effects or toxicological changes were reported to support classification for specific target organ toxicity after single exposure. The RAC agrees with the DS's proposal that classification is not warranted for specific target organ toxicity after single exposure according to CLP or DSD.

4.4 Irritation

4.4.1 Skin irritation

Table 12: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
Dermal irritation study	Rabbit (New Zealand White albino)	slight erythema and slight desquamation in one animal for 4 days.	Johnson, I.R.; 2004

4.4.1.1 Non-human information

Two male and one female rabbits were dermally exposed for four hours to 500 mg of mandipropamid techn. There were no signs of ill-health in any animal during the study. Very slight erythema was seen in one animal for 4 days. Slight desquamation was also seen in the same animal on day 4 only. There were no other signs of skin irritation. All signs of irritation had completely resolved within 7 days of application.

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, mandipropamid is not irritant to the intact shaved rabbit skin.

4.4.1.4 Comparison with criteria

Estimated skin irritation scores are below the criteria for 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 mandipropamid regarding skin irritation.

RAC evaluation of skin corrosion/irritation
Summary of the Dossier submitter's proposal The DS did not propose classification for skin corrosion/irritation. The conclusion was based on one skin irritation study in rabbits in which rabbits were dermally exposed for 4 hours to 500 mg of mandipropamid. Only slight effects were observed in one animal on the fourth day after the exposure and the effects disappeared by the seventh day. **Comments received during public consultation** Two MS agreed with the DS's proposal that classification is not warranted for skin corrosion/irritation. **Assessment and comparison with the classification criteria** Estimated skin irritation scores from the irritation study are below the values set in the criteria for classification and labelling. It can also be mentioned that in a repeated dermal toxicity study, only a slight skin irritation was reported at the application site. The RAC agrees with the DS's proposal that classification and labelling is not warranted for skin corrosion/irritation according to CLP or DSD.

4.4.2 Eye irritation

Table 13: Summary table of relevant eye irritation studies

Method	Results	Remarks	Reference
Eye irritation study	Rabbit (New Zealand White albino)	Slight iritis, redness and chemosis	Johnson, I.R.; 2004

4.4.2.1 Non-human information

Two male and one female rabbits received approximately 100mg mandipropamid techn. into the conjunctival sac of the left eye. There were no signs of ill health in any animal during the study. Application into the eye caused practically no or slight initial pain (class 1-2 on a 0-5 scale). There were no corneal effects. Slight iritis was seen in two animals approximately 1 hour after application. Conjunctival effects were seen in all animals and consisted of slight or moderate redness and slight or mild chemosis for up to 4 days, and a slight discharge approximately 1 hour after application. Additional signs of irritation comprised lachrymatory discharge and dried secretion around the periorbital skin. All signs of irritation had completely resolved within 7 days of application.

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 rabbit eye irritation study, mandipropamid is not irritant.

4.4.2.4 Comparison with criteria

Estimated eye irritation scores (24 – 72 hours) are below the criteria for 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 mandipropamid regarding eye irritation.

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

There is no specific information regarding the ability of mandipropamid to cause irritation to the respiratory tract during the acute inhalation toxicity study.

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 classification is proposed for respiratory tract irritation.

4.4.3.4 Comparison with criteria

4.4.3.5 Conclusions on classification and labelling

4.5 Corrosivity

Based on the data from the skin and eye irritation studies it can be concluded that mandipropamid is not corrosive.

4.6 Sensitisation

4.6.1 Skin sensititsation

Table 15: Summary table of relevant skin sensitisation studies

Method	Results	Remarks	Reference
Local Lymph Node Assay	Not sensitising		Johnson, I.R.; 2005

4.6.1.1 Non-human information

Mandipropamid techn. was assessed for its skin sensitisation potential using the mouse Local Lymph Node Assay (LLNA). Under the conditions of this test, application of mandipropamid at concentrations of 10%, 25% or 50% w/v in DMF resulted in a less than 3-fold isotope incorporation at all three concentrations. Mandipropamid is therefore unlikely to be a sensitiser.

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 the skin sensitisation study (mouse Local Lymph Node Assay), mandipropamid is not sensitising. According to classification criteria, classification and labelling is not warranted.

4.6.1.4 Comparison with criteria

Effects observed in the skin sensitisation study in an mouse Local Lymph Node Assay 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 mandipropamid regarding skin sensitisation.

RAC evaluation of skin sensitisation
Summary of the Dossier submitter's proposal Mandipropamid was tested in an LLNA study at concentrations of 10, 25 or 50% w/v in DMF. At all the concentrations tested, the stimulation index was less than 3 and it was so concluded that mandipropamid is not a skin sensitizer. **Comments received during public consultation** Two MS agreed with the DS's proposal that classification is not warranted for skin

sensitisation.

Assessment and comparison with the classification criteria
The results of the reported study are considered negative since the stimulation index was less than 3 at all tested concentrations when compared to the control. Thus, the RAC agrees with the DS's proposal that mandipropamid does not fulfil the criteria for classification according to CLP or DSD as skin sensitizer.

4.6.2 Respiratory sensitisation

No data on respiratory sensitisation available.

4.7 Repeated dose toxicity

Table 17: Summary table of relevant repeated dose toxicity studies

• Method	• Dose levels	• NOAEL	• Remarks (Relevant effects at the LOAEL)	• Reference
Wistar rats, 90 days oral	0, 100, 500, 3000, 5000 ppm/diet (equivalent to 0, 8.2, 41.1, 260 and 435 mg/kg bw (♂); 0, 8.9, 44.7, 260 and 443 mg/kg bw (♀)	500 ppm (41.1mg/kg bw ♂; 44.7 mg/kg bw ♀)	-bodyweight ↓ -bodyweight gain ↓ -haematological and clinical chemical findings -liver weight ↑ -periportal hypertrophy/eosinophilia -kidney weight ↑ tubular basophilia	Pinto P; 2005a
Beagle dogs, 90 days oral	0, 5, 25, 100, 400 mg/kg bw/d (capsule)	25 mg/kg bw/d	-haematological and clinical chemical findings -liver weight ↑ -porphyrin deposition	Brammer A; 2005a
Beagle dogs, 1 year oral	0, 5, 40, 400 mg/kg bw/d (capsule)	5 mg/kg bw/d	-bodyweight ↓ -haematological and clinical chemical findings -liver weight ↑ -porphyrin deposition	Brammer A; 2005b
Wistar rats, 28 days dermal	0, 250, 500, 1000 mg/kg bw/d	1000 mg/kg bw/d	No toxicologically significant changes at the highest dose tested	Lees D; 2005

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

The short-term toxicity of mandipropamid has been tested in a 90-day oral toxicity study in rats. Mandipropamid has also been tested in 90-day and 1 year oral toxicity studies in dogs via capsule administration.

In a 90 day dietary toxicity study in rats, toxicity was demonstrated at the two highest dose levels (3000 and 5000 ppm), manifest as reduced bodyweight in males. The bodyweights at these two dose levels continued to diverge from the control group throughout the study. At

3000 and 5000 ppm there were decreases in a number of red blood cell parameters, indicating red blood cells as a target. Also at these dose levels there were elevations in plasma albumin, total protein, cholesterol and γ-glutamyl transferase and increased liver weights with associated histopathological change (increased periportal hypertrophy/eosinophilia), indicating the liver to be a target organ. At 500 ppm, relative liver weight in males was slightly higher than controls. Increased kidney weight (3000 and 5000 ppm) and increased incidence of tubular basophilia (5000 ppm) were also noted in males. The NOAEL was considered to be 500 ppm, equivalent to 41.1 mg/kg bw/d for males and 44.7 mg/kg bw/d for females.

In a 90 day study in dogs, oral administration of mandipropamid resulted in clear evidence of liver toxicity in animals dosed at 400 and 100 mg/kg bw/d. Liver toxicity was characterised by increased liver weight, marked elevations in liver enzymes (alkaline phosphatase and alanine aminotransferase) and porphyrin deposition within the liver. Other treatment related effects included reductions in white blood cell count and neutrophil count (females at 400 mg/kg bw/d), increases in plasma cholesterol (both sexes at 100 and 400 mg/kg bw/d) and decreases in plasma aspartate aminotransferase activity (both sexes at 400 and males at 100 mg/kg bw/d). The NOAEL of mandipropamid in this study was considered to be 25 mg/kg bw/d.

In a 1 year study in dogs, oral administration of mandipropamid resulted in clear evidence of toxicity in dogs dosed at 400 and 40 mg/kg bw/d. Effects included reduced bodyweights at 400 mg/kg bw/d and liver toxicity at both dose levels, characterised by increased liver weight, marked elevations in liver enzymes (alkaline phosphatase and alanine aminotransferase) and porphyrin deposition within the liver. Other treatment related effects included reductions in MCV and MCH (both sexes at 400 mg/kg bw/d), increases in platelets (males at 40 and 400 mg/kg bw/d) and decreased activated partial thromboplastin time (males at 400 mg/kg bw/d). The NOAEL of mandipropamid in this study was considered to be 5 mg/kg bw/d.

4.7.1.2 Repeated dose toxicity: inhalation

No data available.

4.7.1.3 Repeated dose toxicity: dermal

The short-term toxicity of mandipropamid has been tested in a 28 day percutaneous toxicity study in rats. Dermal administration of mandipropamid at dose levels up to 1000 mg/kg bw/day for 21 days in a 28 day period to male and female rats produced no evidence of systemic toxicity. There was an increased incidence of signs of slight skin irritation at 250, 500 and 1000 mg/kg/day, including erythema, oedema and desquamation at the application site.

4.7.1.4 Repeated dose toxicity: other routes

No data available.

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 data available.

4.7.1.7 Summary and discussion of repeated dose toxicity

Repeat dose toxicity studies in mice, rats and dogs confirmed the liver as target organ of mandipropamid.

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

Effects observed in the subchronic studies in rat, mouse and dog do not trigger the criteria for classification and labelling for repeated dose toxicity.

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

Effects observed in the subchronic studies in rat, mouse and dog do not trigger the criteria for classification and labelling for repeated dose toxicity.

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 studies in rat, mouse and dog do not trigger the criteria for classification and labelling for repeated dose toxicity.

RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)
Summary of the Dossier submitter's proposal The DS did not propose any classification for repeated dose toxicity (DSD) or specific target organ toxicity after repeated exposure (CLP). <u>*Short-terms oral studies (90-days in rat and dog, 1 year in dog)*</u> Short term toxicity of mandipropamid was tested in a 90-day oral toxicity study in rats exposed via diet at 100, 500, 3000 and 5000 ppm, e.g. 0, 8.2/8.9, 41.1/44.7, 260/260, 435/443 mg/kg bw M/F, respectively (Pinto, 2005a). Liver was identified as the main target organ with: • Increased relative liver weight from 3000 ppm in both sexes (24.6 and 33.5% in males and 15.2 and 29.5% in females at 3000 and 5000 ppm, respectively) and also slightly in males at 500 ppm (8.0%). • Clinical chemistry from 3000 ppm: o in both sexes: plasma albumin (up to 7.6%), protein (up to 5.4%, statistically significant in females only at 5000 ppm) and o in females: cholesterol (up to 15.7%) and γ-glutamyl transferase. • Histopathological changes from 3000 ppm with an increased incidence of portal hypertrophy, eosinophilia (only at 5000 ppm in males); Other treatment-related effects also included: • Decrease in bodyweight and bodyweight gain in males: at 3000 ppm (11% and

16%, respectively) and 5000 ppm (8% and 11%, respectively)
- Haematological effects at 3000 and 5000 ppm with: decrease in red blood cells parameters with haemoglobin (max 7%), haematocrit (max 5.9%), mean cell volume or MCV (max 4.9%), mean cell haemoglobin (max 6.1%) and mean cell haemoglobin concentration (max 1.6%); MCV was also very slightly lowered (1.9%) in females at 500 ppm;
- Kidney in males: decrease in relative weight from 3000 ppm (6 and 9%) and a tubular basophilia from 500 ppm (higher incidence with historical control groups only significant at 5000 ppm – no detailed data).

The dose of 500 ppm (41.1 mg/kg bw in males and 44.7 mg/kg bw in females) is then considered as NOAEL in this 90-day rat study, the LOAEL being 3000 ppm (260 mg/kg bw in males and females).

Mandipropamid was tested in a 90-day oral toxicity in groups of 4 dogs exposed via gelatine capsules at 5, 25, 100 and 400 mg/kg bw (Brammer, 2005).
Liver was identified as the main target organ with:
- Increased relative liver weight at 400 mg/kg bw in both sexes (16% M -17% F) and also in males at 100 mg/kg bw (19.0%).
- Clinical chemistry in both sexes:
  - Marked elevation of ALT at 400 mg/kg bw (up to 132.9 vs 39.3 IU/l in F, week 13) and AP from 100 mg/kg bw (up to 560 vs 263 IU/l in M at 400 mg/kg, week 13) with increasing value with time
  - Increased cholesterol in both sexes from 100 mg/kg bw (up to 42% in F at 400 mg/kg bw)
- Histopathological changes with a brown pigmentation of hepatocytes and Kupffer cells: all animals of both sexes at 400 mg/kg bw and 1/4 M and 2/4 F at 100 mg/kg bw.

Other treatment related effects included haematological effects in females at 400 mg/kg with decreases in white blood cells and neutrophil count. No change in red blood cell parameters was identified.

The NOAEL for this 90-day dog study was 25 mg/kg bw, with a LOAEL at 100 mg/kg bw.

Mandipropamid was tested in a 1 year oral toxicity in groups of 4 dogs exposed via gelatine capsules at 5, 40 and 400 mg/kg bw (Brammer, 2005).
Liver was identified as the main target organ with:
- Increased relative liver weight at 400 mg/kg bw in males (20%).
- Clinical chemistry in both sexes:
  - Marked elevation of ALT at 400 mg/kg bw (209.3 vs. 38.4 IU/l in M, week 52) and AP from 40 mg/kg bw (up to 590 vs 158 IU/l in F at 400 mg/kg bw, week 52)
- Histopathological changes with a pigmentation in both sexes: 3/4 M and 3/4 F at 400 mg/kg bw and 2/4 M and 1/4 F at 40 mg/kg bw.

Other treatment related effects included:
- Decreases in bodyweight and bodyweight gain at 400 mg/kg bw in both sexes at some points of the study (week 4-12 for males with max of 6% and week 11-18 for females, max of 8%).
- Haematological effects: decrease in mean cell volume or MCV (max 4.6%), mean cell haemoglobin or MCH (max 5.5%) in both sexes at 400 mg/kg, increase in platelets (males from 40 mg/kg bw), decreased partial thromboplastin time (males at 400 mg/kg bw).

The NOAEL for mandipropamid in this 1 year dog study was 5 mg/kg with a LOAEL of 40 mg/kg bw.

Long-term oral studies (rat, mice)

Mandipropamid was tested in a combined chronic/carcinogenic study in groups of 64 rats exposed for 2 years at doses of 50, 250 and 1000 ppm in diet for 2 years (eq. to 3/3.5, 15.2/17.6 and 61.3/69.7 mg/kg bw in males and females, respectively). Interim sacrifice kill was scheduled after week 52 for 12M and 12F of each group.

Liver effects observed, at the top dose of 1000 ppm, were similar to the effects in the 90-day studies:

- Increase in liver weight at interim kill (week 53): in both sexes at 1000 ppm (10% in M, 14% in F) and in females at 250 ppm (10%). Liver weight was also increased at week 105 in females at 1000 ppm (12%);
- Clinical chemistry at 1000 mg/kg bw: plasma albumin increased (7%) in males up to week 53; γ-glutamyl transferase increased in males from week 53 (16.7 IU/l vs 10.1 IU/l at week 105).
- Histopathological changes at week 53: increase in the incidence periportal eosinophilia in both sexes at 1000 ppm and at 250 ppm in females. This change was not seen at week 105.

Effects on kidney were also reported in males at 1000 ppm:

- Macroscopic findings (enlargement, discoloration, roughened surface and combination) with incidences as follows

Macroscopic kidneys findings

	Mandipropamid			
Findings	0	50	250	1000
Enlarged	2	4	4	6
Pale	4	5	5	5
Roughened surface	5	4	8	13
Pale/roughened surface+/-cysts	9	12	9	14
Cyst/s (single or multiple within organ)	3	3	4	7
TOTAL	23	28	30	45
Animals on Study	64	64	64	64

- Histological changes: increase in the severity of chronic progressive nephropathy (CPN) associated with an increased incidence of an osteo-renal syndrome.

Microscopic findings in kidney of males

Microscopic findings in kidney of males	Dose group level (ppm)			
	0	50	250	1000
Total number of animals with marked chronic progressive nephropathy (CPN)	15	17	18	24
Number of individual animals with the full osteo-renal syndrome (CPN plus bone changes plus parathyroid hyperplasia)	3	3	1	11

A slight increase in kidney weights in females at 250 and 1000 ppm was also observed (7% max) but at week 53 only.

Other treatment related effects included:

- Decrease in bodyweight and in bodyweight gain in males during the first 3 months (4%) and on most occasions between weeks 67 and 103 (max 7%),
- Haematological findings in both sexes: decrease in mean cell volume (max 3.9%) and mean cell haemoglobin (up to 5.1%)

The NOAEL in this long-term study in rats is set at 250 ppm (15.2 mg/kg bw in males, 17.6 mg/kg bw in females), with a LOAEL of 1000 ppm (61.3 mg/kg bw in males and 69.7 mg/kg bw in females)

Mandipropamid was tested in a carcinogenic study in mice exposed by diet at doses of 100, 500 and 2000 ppm for 80 weeks (10.6/13.2, 55.2/67.8 and 222.7/284.6 mg/kg bw in males and females, respectively). Liver as a target organ is confirmed in this study with an increase in the liver weight observed at the top dose of 2000 ppm in both sexes (15% in males, 8.9% in females) and slight in males at 500 ppm (11.7%). A slight decrease in bodyweight and bodyweight gain were reported in both sexes (max 6%, not statistically significant) at 2000 ppm. Other treatment related effects at the top dose of 2000 ppm were a decrease in spleen weights in both sexes (17% in M, 10% in F) as well as an increase in kidney weights in females (7.7%). These were not considered as significant since not supported by microscopic findings.

The NOAEL in this long-term study in mice was identified at 500 ppm (55.2 mg/kg bw M, 67.8 mg/kg bw F) with a LOAEL at 2000 ppm (222.7/284.6 mg/kg bw).

Short-term dermal study
No toxicity was reported in the 28-day study in rats exposed to mandipropamid by dermal route up to 1000 mg/kg bw. Only slight irritation was observed at the application site.

Other studies (neurotoxicity)
Mandipropamid was assessed for potential neurotoxicity in an acute and a subchronic neurotoxicity study in the rat and no neurotoxicpotential was observed. No effect on functional observation battery test was reported in the 2 year chronic/carcinogenicity study in rats.

Conclusion of DS
According to the DS, no classification and labelling is proposed regarding repeated toxicity.

Comments received during public consultation
Two MS agreed with the DS's proposal that classification is not warranted for STOT-RE/repeated dose toxicity.

Assessment and comparison with the classification criteria
The RAC agreed with the DS that no classification for STOT-RE/repeated dose toxicity is needed but assessed in more detail the effects on liver and kidneys in coming to this conclusion.

Some liver effects were reported in the different repeated oral toxicity studies conducted in several species and several exposure durations (90-day study in rats and dogs, 1 year study in dogs, 2 years in rats and mice). The effects were observed mostly above or close to the guidance value ranges (10 < CLP value ≤ 100 mg/kg bw in a 90-day oral study).

- LOAEL of 260 mg/kg bw in 90-day study in rats
- LOAEL of 100 mg/kg in 90-day study in dogs
- LOAEL of 40 mg/kg bw in 1 year study in dogs
- LOAEL of 61.3 mg/kg bw in long-term study in rats
- LOAEL of 222.7 mg/kg bw in long-term study in mice

Moreover, the observed effects consisted of: a slight increase in liver weight, increased metabolic activity, and some histopathological changes mainly considered as adaptative (periportal hypertrophy, eosinophilia).

For the dermal route, the NOAEL and LOAEL (28-days rat study) were > 1000 mg/kg bw,

i.e. above the criteria for classification (60 < CLP criteria values for category 2 ≤ 600 mg/kg bw).

According to the CLP Regulation, classification in Category 2 for STOT-RE is applicable, when significant toxic effects observed in repeated-dose study conducted in experimental animals are seen to occur within the guidance value ranges.

The RAC agreed with the DS that the reported effects of mandipropamid in liver, because of their nature and the dose at which they occurred, do not warrant a classification as STOT-RE 2 according to CLP or Xn;R48 according to DSD.

The RAC also assessed the kidney effects because of the chronic progressive nephropathy (CPN) observed in the long-term study in rat. An increase of macroscopic findings in the kidneys was reported at the top dose of 61.3 mg/kg/bw in males (e.g. enlarged, pale, cysts) with an incidence of 45/64 vs 23/64 in the controls. An increase in the incidence and severity of CPN is mentioned (no details), associated with an increase in the number of animals with a marked CPN (24/64 vs 15/64 e.g. 38% vs 23%), as well as an increase in the number of animals with full osteo-renal syndrome (CPN associated with bone changes and parathyroid hyperplasia: 11/64 vs 3/64 in controls). The increase is however above the cut-off value (12.5 mg/kg/bw for a Category 2). CPN is a common pathology in aging rats although no historical control data was provided. Moreover, the majority of animals remained unaffected and no change in chemistry that could be related to renal function impairment was reported (e.g, no change in proteinuria). The CPN pathology seems to occur in male but was not observed in either female rats, or in the long-term study in mice.

The available supporting studies do not provide enough background to consider the kidney as a target organ. In the 2-generation study in rats, kidney weights were increased in the F0 and F1 males and females but only at the top dose of 1500 ppm (120 mg/kg bw), with a maximal change of 10% and no associated histological changes. t can also be mentioned that no effects were reported in dogs (90-days and 1 year studies) and in developmental studies in rats or rabbits (only macroscopic examination in parents was available following the protocol of such studies), bearing in mind that these are all rather short-term studies. Therefore, the RAC concludes that the observed effects in kidneys are not enough to justify classification.

In conclusion, the RAC agrees with the DS that the reported effects of mandipropamid in liver and kidney do not warrant a classification as STOT-RE 2 according to CLP or Xn;R48 according to DSD.

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

Effects observed in the subchronic studies in rat, mouse and dog do not trigger the criteria for classification and labelling for repeated dose toxicity.

4.9 Germ cell mutagenicity (Mutagenicity)

The mutagenicity of mandipropamid has been adequately investigated *in vitro* and *in vivo*.

Table 18: Summary table of relevant in vitro and in vivo mutagenicity studies

Type of Study	Test system	Dose levels	Results	Reference
In vitro studies				

Bacterial reverse mutation	*Salmonella typhimurium* (TA1535, TA1537, TA98 and TA100) and two strains of *Escherichia coli* (WP2P and WP2P*uvrA*)	100 to 5000 µg/plate	Negative	Callander R (2005)
In vitro cytogenetics	human lymphocytes	2.5 to 100 µg/ml	Negative	Fox V (2002)
Mammalian cell gene mutation (mouse lymphoma)	L5178Y mouse lymphoma cells	1-4119µg/ml	Negative	Clay P (2002)
In vivo studies				
Rat bone marrow micronucleus	bone marrow of male rats	2000mg/kg	Negative	Fox V (2005)
Unscheduled DNA synthesis – rat liver	liver of male rats	2000 mg/kg	Negative	Clay (2005)

4.9.1 Non-human information

4.9.1.1 In vitro data

In vitro, mandipropamid was negative in both bacterial (Ames test) and mammalian cells (L5178Y $TK^{+/-}$ mouse lymphoma) for gene mutation. The L5178Y $TK^{+/-}$ assay was also negative for clastogenicity. In the *in vitro* cytogenetic assay using primary human lymphocyte cultures, mandipropamid was examined for evidence of chromosomal damage up to dose levels limited by cytotoxicity to the cells (100µg/ml). Mandipropamid showed no evidence of induced chromosomes aberrations in this assay either in the presence or absence of S9-mix.

4.9.1.2 In vivo data

In vivo, mandipropamid was found to be non-clastogenic in the rat bone marrow micronucleus assay at the limit dose of 2000mg/kg. There was also no evidence for any induction of DNA damage or repair in the rat liver by mandipropamid using the UDS assay.

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 data available.

4.9.4 Summary and discussion of mutagenicity

Mandipropamid has been examined in a range of *in vitro* and *in vivo* genotoxicity assays, including endpoints of gene mutation, chromosomal damage and DNA repair.

All the results were negative, showing that mandipropamid has no genotoxic potential *in vitro* and *in vivo.*

4.9.5 Comparison with criteria

Effects observed in the *in vitro* and *in vivo* mutagenicity studies do not trigger the criteria for classification and labelling for mutagenicity.

4.9.6 Conclusions on classification and labelling

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

RAC evaluation of germ cell mutagenicity
Summary of the Dossier submitter's proposal *In vitro*, mandipropamid was negative for gene mutation in bacterial (Ames test) and mammalian cells (L5178 mouse lymphoma cells, TK). The *in vitro* cytogenetic assay on human lymphocytes was also negative. *In vivo*, mandipopamid did not show evidence of clastogenic properties in a bone marrow micronucleus assay and no induction of DNA damage or repair in a UDS assay. **Comments received during public consultation** Two MS agreed with the DS's proposal that classification is not warranted. **Assessment and comparison with the classification criteria** Mandipropamid was negative in genotoxicity assays *in vitro* and *in vivo*. The RAC agrees that classification is not justified according to CLP or DSD.

4.10 Carcinogenicity

Table 19: Summary table of relevant carcinogenicity studies

Method	Dose levels	NOAEL	Remarks (Relevant effects at the LOAEL)	Reference
Wistar rats, 2 years oral	0, 50, 250, 1000 ppm/diet (equivalent to 0, 3, 15.2 and 61.3 mg/kg bw (♂) and 0, 3.5, 17.6 and 69.7 mg/kg bw (♀)	250 ppm (15.2 mg/kg bw ♂; 17.6 mg/kg bw ♀)	-bodyweight ↓ -bodyweight gain ↓ -haematological and clinical chemical findings -liver weight ↑ -periportal hypertrophy/eosinophilia -chronic progressive nephropathy; osteo-renal syndrome	Pinto P; 2005b
C57BL/10J$_f$CD-1 mice, 80 weeks oral	0, 100, 500, 2000 ppm/diet (equivalent to 0, 10.6, 55.2 and 222.7 mg/kg bw (♂) and 0, 13.2, 67.8 and 284.6 mg/kg bw (♀)	500 ppm (55.2 mg/kg bw ♂; 67.8 mg/kg bw ♀)	-bodyweight ↓ -bodyweight gain ↓ -liver weight ↑	Milburn G.; 2005a

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

The chronic toxicity and carcinogenic potential of mandipropamid was investigated in rats when administered orally in the diet for a period of up to 105 weeks. The highest dose of 1000 ppm, equivalent to 61.3 mg/kg bw for males and 69.7 mg/kg bw for females, caused decreases in mean cell volume (MCV) and mean cell haemoglobin (MCH) in both male and female rats, indicating red blood cells as a target.

Some clinical chemistry parameters were affected at this dose level too.

Increased liver weights were observed at 1000 ppm. Histopathologically, an increase in the incidence of periportal eosinophilia in the liver in both sexes at a dose level of 1000 ppm and in females also at $\geq$ 250 ppm was observed at week 53. This confirms the liver as a target organ.

In the kidneys of males, chronic progressive nephropathy associated with an increased incidence of an osteo-renal syndrome was observed at 1000 ppm.

Mandipropamid was not carcinogenic in the rat. There were no treatment-related increases in the incidence of tumours and no trend towards increased numbers of tumours with dose. The NOAEL for mandipropamid was considered to be 250 ppm (15.2 mg/kg bw/day in males and 17.6 mg/kg bw/day in females), based on low body weight, liver and kidney toxicity and changes in red blood and clinical chemistry parameters in the 1000 ppm groups.

The carcinogenic potential of mandipropamid in mice was investigated when administered orally via the diet for at least 80 weeks.

There was a treatment-related reduction in bodyweight and bodyweight gain in both sexes at the highest dose level of 2000 ppm, equivalent to 222.7 mg/kg bw for males and 284.6 mg/kg bw for females.
Increases in liver weights at 2000 ppm in both sexes and at 500 ppm in males confirmed the liver as target organ of mandipropamid.

There were no treatment-related increases in the incidence of tumours and no trend towards increased number of tumours with dose.

500 ppm, equivalent to 55.2 mg/kg bw for males and 67.8 mg/kg bw for females can be considered as NOAEL for mandipropamid in this study.

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 data available.

4.10.4 Summary and discussion of carcinogenicity

Based on the results of two submitted studies in rats and mice, mandipropamid can be regarded to have no oncogenic potential.

4.10.5 Comparison with criteria

No oncogenic effects were observed in studies conducted with mandipropamid, neither in rat nor in mouse carcinogenicity studies (according to both DSD and CLP).

4.10.6 Conclusions on classification and labelling

Mandipropamid can be regarded to have no oncogenic potential.

RAC evaluation of carcinogenicity
Summary of the Dossier submitter's proposal Mandipropamid was investigated for carcinogenicity in rats exposed orally in the diet for 105 weeks at doses up to 1000 ppm (eg. 61.3 mg/kg bw males and 69.7 mg/kg bw females). Carcinogenicity was also investigated in orally exposed mice for 80 weeks at doses up to 2000 ppm (eg. 222.7 mg/kg bw males and 284.6 mg/kg bw females). There were no treatment related increases in the incidence of tumours and no trends towards increased numbers of tumours in both studies. **Comments received during public consultation** Two MS agreed with the DS's proposal that classification is not warranted. **Additional key elements** Detailed information from the DAR report enabled to confirm the suitability of the studies for classification purposes (guideline, protocol, results). **Assessment and comparison with the classification criteria** No carcinogenic effect was observed in the rat oral study nor in the mice oral study. However, some non-neoplasic effects were observed in the rat chronic/carcinogenicity study, reported in STOT-RE section. The RAC agrees with the DS's proposal that carcinogenicity classification for mandipropamid is not warranted according to CLP or DSD.

4.11 Toxicity for reproduction

Table 20: Summary table of relevant reproductive toxicity studies

Study; Reference	Dose levels	NOAEL	Relevant effects
Multigeneration, rats Milburn G.; 2005b	0, 50, 250, 1500 ppm/diet (equivalent to 0, 4, 20 and 120 mg/kg bw	parental: 250 ppm (20 mg/kg bw) reproductive: 1500 ppm (120 mg/kg bw) developmental: 250 ppm (20 mg/kg bw)	Parental and offspring: -bodyweight ↓ -liver weight ↑
Developmental toxicity, rats Moxon M.; 2005a	0, 50, 200, 1000 mg/kg bw	maternal: 200 mg/kg bw developmental: 1000 mg/kg bw	maternal: plasma total protein ↓, total bilirubin ↓ albumin/globulin ratio ↑ developmental: no effects
Developmental toxicity, rabbits Moxon M.; 2005b	0, 50, 250, 1000 mg/kg bw	maternal: 1000 mg/kg bw developmental: 1000 mg/kg bw	maternal: no effects developmental: no effects

4.11.1 Effects on fertility

4.11.1.1 Non-human information

Effects on fertility were investigated in a multigeneration study in rats. Dietary administration of mandipropamid at a dose level of 1500 ppm for two successive generations did result in decreased bodyweights in F1 males during the pre-mating period. F0 and F1 females in the 1500 ppm group producing F1A and F2A litters respectively had slightly lower bodyweights on days 15 and/or 22 post partum, but these differences were no longer evident on day 29.

Bodyweight of F1A and F2B pups in the 1500 ppm group was reduced from day 15 onwards, but there were no effects on bodyweight in F2A pups.

The liver was identified as the target organ, increases in liver weight were seen in both sexes, both generations, in parents and in pups. The effects were confined to the 1500 ppm dose group.

There were no effects on implantation data or reproductive performance and no microscopic changes were observed in the reproductive system that could be related to mandipropamid.

The parental NOAEL for systemic toxicity can be considered at 250 ppm, equivalent to approximately 20 mg/kg bw/d. For pup developmental effects the NOAEL can be considered at

250 ppm also. The NOAEL for effects on reproduction was considered to be 1500 ppm, equivalent to approximately 120 mg/kg bw/d.

4.11.1.2 Human information

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

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

Developmental toxicity tests of mandipropamid were performed in rats and rabbits.

Mandipropamid administered at a dose level of 50, 200 or 1000 mg/kg/day had no effect on the clinical condition of rats, on maternal bodyweight or food consumption and no treatment-related findings were observed at examination post mortem. Plasma total protein and total bilirubin were lower and albumin/globulin ratio higher in the rats given 1000 mg/kg/day. The maternal NOAEL can be considered at 200 mg/kg/day.

There was no effect of mandipropamid on the number, growth or survival of the foetuses in utero. There was no effect of mandipropamid on foetal development. Although major observations affecting the sternum were seen only in foetuses in the mandipropamid treated groups the incidence of foetuses affected was very small and not dose-related. Also, there were no minor changes in the appearance or ossification of the sternebrae to indicate that mandipropamid adversely affected this area of the skeleton and there was no evidence for an effect of mandipropamid on other ossification centres of the skeleton. The low incidence of major observations affecting the sternum was therefore considered to be incidental to treatment with mandipropamid. The NOAEL for developmental effects can be set at 1000 mg/kg bw/d.

In rabbits, there were no adverse effects of 50, 250 or 1000 mg/kg/day mandipropamid on the clinical condition, bodyweight or food consumption of the pregnant female rabbits. Therefore the NOAEL for maternal toxicity can be considered at 1000 mg/kg bw/d.

No effect on the number, growth, survival or development of the foetuses in utero has been observed.

The group mean values of foetuses with an incompletely ossified odontoid and incompletely ossified 5th sternebra observed in the intermediate and high dose groups were within the historical controls means. Therefore these differences are considered not to be related to treatment.

The NOAEL for developmental toxicity can be considered at 1000 mg/kg bw/d.

4.11.2.2 Human information

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

4.11.3 Other relevant information

No data available.

4.11.4 Summary and discussion of reproductive toxicity

Dietary administration of mandipropamid at a dose level of 1500 ppm for two successive generations did result in decreased bodyweights in F1 males during the pre-mating period. F0 and F1 females in the 1500 ppm group producing F1A and F2A litters respectively had slightly lower bodyweights on days 15 and/or 22 post-partum, but these differences were no longer evident on day 29.

Bodyweight of F1A and F2B pups in the 1500 ppm group was reduced from day 15 onwards, but there were no effects on bodyweight in F2A pups.

The liver was identified as the target organ, increases in liver weight were seen in both sexes, both generations, in parents and in pups. The effects were confined to the 1500 ppm dose group.

There were no effects on implantation data or reproductive performance and no microscopic changes were observed in the reproductive system that could be related to mandipropamid.

The parental NOAEL for systemic toxicity can be considered at 250 ppm, equivalent to approximately 20 mg/kg bw/d. For pup developmental effects the NOAEL can be considered at 250 ppm also. The NOAEL for effects on reproduction was considered to be 1500 ppm, equivalent to approximately 120 mg/kg bw/d.

In a teratogenicity study in rats, mandipropamid administered at dose levels of 1000 mg/kg/day had effects on plasma total protein and total bilirubin levels and the albumin/globulin ratio. The maternal NOAEL can be considered at 200 mg/kg/day.

Although major observations affecting the sternum were seen only in foetuses in the mandipropamid treated groups the incidence of foetuses affected was very small and not dose-related. Also, there were no minor changes in the appearance or ossification of the sternebrae to indicate that mandipropamid adversely affected this area of the skeleton and there was no evidence for an effect of mandipropamid on other ossification centres of the skeleton. The low incidence of major observations affecting the sternum was therefore considered to be incidental to treatment with mandipropamid. The NOAEL for developmental effects can be set at 1000 mg/kg bw/d.

In a teratogenicity study in rabbits, there were no adverse effects of 50, 250 or 1000 mg/kg/day mandipropamid on the clinical condition, bodyweight or food consumption of the pregnant female rabbits. Therefore the NOAEL for maternal toxicity can be considered at 1000 mg/kg bw/d.

The group mean values of foetuses with an incompletely ossified odontoid and incompletely ossified 5th sternebra observed in the intermediate and high dose groups were within the historical controls means. Therefore these differences are considered not to be related to treatment.

The NOAEL for developmental toxicity can be considered at 1000 mg/kg bw/d.

4.11.5 Comparison with criteria

No effects on fertility or development were observed in studies conducted with mandipropamid, neither in a rat multigeneration study, nor in rat and rabbit developmental studies (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 mandipropamid, therefore, no classification is proposed.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The DS did not propose any reproductive toxicity classification for mandipropamid, based on a two-generations study in rats and two developmental studies, one in rabbits and one in rats.

Two-generations study

Mandipropamid was tested in a two generation study in rats at doses in the diet of 50, 250 and 1500 ppm.

At 1500 ppm, effects on bodyweight were observed:

- Decrease in F1 males during pre-mating period: from week 1 (8.4%) and for the majority of the period (until week 9) and increase in F1 females from week 4 (up to 6%).
- Slightly lower (around 3.5%) in F0 and F1 females on days 15 and/or day 22 post-partum but no longer evident on day 29
- Decrease in the pup weight in both sexes in F1A and F2B from day 15 and up to 14%, but no effects were reported in F2A pups.

At 1500 ppm, an increase in liver weight (up to 19%) was observed in both sexes and in both generations (parents and pups).

There were no effects on implantation data or reproductive performance and no microscopic changes related to treatment. The NOAEL for systemic parental toxicity and development was determined at 250 ppm (20 mg/kg bw). The NOAEL for reproduction was identified at the top dose of 1500 ppm in the diet (120 mg/kg bw).

Developmental toxicity in rats

Mandipropamid was tested for teratogenicity in groups of 24 female rats at doses of 50, 200 or 1000 mg/kg bw on days 5-21 of gestation (Moxon, 2005). No effect on clinical condition, maternal bodyweight or food consumption and no treatment related findings were reported at post-mortem examination. At 1000 mg/kg bw, plasma total protein (48.1 vs 52.4) and total bilirubin (2.66 vs 3.46 e.g 23%) were lower and albumin/globulin ratio was higher (1.28 vs 1.19). Total bilirubin was also slightly lower at 200 mg/kg (2.94 vs 3.46 mg/kg e.g 15%).

The maternal NOAEL is considered to be 200 mg/kg bw.

No effects were reported on number, growth, survival or development of foetuses *in utero*.

At foetal examination, major skeletal observations on sternum in foetuses treated with mandipropamid were reported as cleft sternebrae, cleft sternal cartilage and cleft xiphoid cartilage.

Summary of skeletal sternal observations and associated effects

Mandipropamid (mg/kg bw) (Moxon ME, 2005)			
0	50	200	1000

Total litters (viable)	23	24	23	24
Live fetuses / dam	12.0	10.8	11.9	12.3
Live fetuses -total	275	259	274	294
number of fetuses (litters) affected	0 (0)	3 (3)	2 (2)	3(3)
% per fetuses - calculated	0,0	1,2	0,7	1,0
% (data)	0 - 1.2%			

Detailed available information on major sternal observations: number of foetuses (%) and number of litters (%)

	Mandipropamid (mg/kg bw) (Moxon ME, 2005)				HCD data (10 studies between 1996-2003)
	0	50	200	1000	%
Total litters (viable)	23	24	23	24	
Live fetuses / dam	12.0	10.8	11.9	12.3	
Live fetuses - total	275	259	274	294	
Cleft sternebrae					
sternebra 5 – fetuses (%)	0	2 (0.8)	0	0	0.0 - 0.6
litters (%)	0	2 (8.3)	0	0	
sternebra 6 – fetuses (%)	0	3 (1.2)	0	0	0.0 - 0.4
litters (%)	0	3 (12.5)	0	0	
all sternebrae – fetuses (%)	0	0	0	1 (0,3)	0.0
litters (%)	0	0	0	1 (4,2)	
Cleft sternal cartilage					
between 2 and 1 – fetuses (%)	0	0	1 (0.4)	1(0.3)	0.0 - 0.4
litters (%)	0	0	1 (4.3)	1 (4.3)	
between 3 and 2 – fetuses (%)	0	0	1 (0.4)	0	0.0
litters (%)	0	0	1 (4.3)	0	
between 4 and 3 – fetuses (%)	0	3 (1.2)	1 (0.4)	0	0.0 - 0.4
litters (%)	0	3 (12.5)	1 (4.3)	0	
between 5 and 4 – fetuses (%)	0	2 (0.8)	1 (0.4)	0	0.0 - 0.4
litters (%)	0	2 (8.3)	1 (4.3)	0	

between 6 and 5 – fetuses (%)	0	1 (0.4)	1 (0.4)	0	0.0
litters (%)		1 (4.2)	1 (4.3)	0	
Xiphoid cartilage cleft					
Fetuses (%)	0	2 (0.8)	2 (0.7)	2 (0.7)	0.0
litters (%)	0	2 (8.3)	2 (8.7)	2 (8.3)	

However, the incidence of foetuses affected was very small and not dose related. Also, no effect was observed in the appearance or ossification of sternebrae, which would indicate that mandipropamid adversely affects this area of the skeleton while there was no evidence for an effect on other areas of the skeleton. The low incidence of the major observations affecting the sternum is considered to be incidental.

Some minor skeletal observations (rib 13 shortened, odontoid bipartite ossification) were observed with statistically significance in the 200 mg/kg bw (incidence of 64.9% vs 55.1%, e.g 177/274 vs 150/275) but not in the 1000 mg/kg bw group (48.7%, e.g. 154/294). Some minor external and visceral observations were statistically significantly higher in the 1000 mg/kg bw group (liver cysts, slightly reduced kidneys, slightly dilated ureters, kinked ureters).

Detailed information on minor external and visceral observations: number of foetuses (%) and number of litters (%)

	Mandipropamid (mg/kg bw) (Moxon ME, 2005)			
	0	50	200	1000
Liver cysts - fetuses (%)	1 (0.4)	1 (0.4)	0	4 (1.4)
Litters (%)	1 (4.3)	1 (4.2)	0	2 (8.3)
Kidney reduced slight - fetuses (%)	0	0	0	1 (0.3)
Litters (%)	0	0	0	1 (4.2)
Ureter dilated slight - fetuses (%)	1 (0.4)	2 (0.8)	1 (0.4)	5 (1.7)
Litters (%)	1 (4.3)	2 (8.3)	1 (4.3)	4 (16.7)
Ureter kinked - fetuses (%)	4 (1.5)	4 (1.5)	9 (3.3)	11 (3.7)
Litters (%)	4 (17.4)	3 (12.5)	5 (21.7)	8 (33.3)

The NOAEL for development is 1000 mg/kg bw.

Developmental toxicity in rabbits

Mandipropamid was tested for teratogenicity in groups of 4 female rabbits exposed at 50, 250, 1000 mg/kg bw on days 5-29 of gestation (Moxon, 2005). No effects were observed on parental generation: clinical observations, bodyweight or food consumption. The NOAEL for maternal toxicity is 1000 mg/kg bw. In relation to development, there were no effects on number, growth, survival or development of foetuses *in utero*. Upon foetal skeletal examination, no major effect of the treatment was observed (type or incidence). The frequency of minor observations was increased in all treated groups but with no dose-relation. The frequency of variant was increased at the high dose of 1000 mg/kg bw.

Percentages of skeletal observations

	Mandipropamid (mg/kg bw) (Moxon ME, 2005)			
	0	50	200	1000
Total litters (viable)	22	22	22	24

Live fetuses / dam	7,95	8,23	8,27	8
Live fetuses - total calculated	174,9	181,06	181,94	192
skeletal major observations – fetuses (%) litters	(1.1) 2/22	(1.9) 4/22	(0.9) 2/22	(1.4) 3/24
skeletal minor observations – fetuses (%) litters	(27.3) 19/22	**(47.0) 20/22**	**(45.5) 21/22**	**(41.5) 23/24**
skeletal variant – fetuses (%) litters	(61.7) 22/22	(72.9) 22/22	(67.3) 22/22	**(79.7) 24/24**

Note : Figures in bold with statistical significance

Consideration of the specific observations reveals some minor skeletal effects or variations in particular:

- Increased incidence of incomplete ossification of odontoid (4.4% and 5.7% foetuses affected at 250 and 1000 mg/kg bw, respectively vs 0.6% for control). A dose relationship is reported and the % of litters affected at 1000 mg/kg bw is also higher (33.3% vs 4.5% for controls) but the frequency of affected foetuses is within the historical control values (0.0% - 8.0 % foetuses in 10 studies between 1995-2003)
- Increased incidence of incomplete ossification observed for 5th sternebrae at 250 and 1000 mg/kg bw (22.0 and 20.8 respectively vs 12.6% for control) within the historical control means (9.3% - 38% in 10 studies between 1995 and 2003).
- Some other minor/variant skeletal effects were reported with no dose relation and within historical range, e.g increased unossified 5th sternebrae in all treated groups (17.7%, 13.7% and 15.6% at 50, 250 and 1000 mg/kg bw, respectively, vs 10% in control) and within historical range (5.7-16.9%).
- All effects are reported in the table below.

Detailed on specific skeletal observations

	Mandipropamid (mg/kg bw) (Moxon ME, 2005)				HCD
	0	50	200	1000	%
Total litters (viable)	22	22	22	24	
Live fetuses / dam	7,95	8,23	8,27	8	
Live fetuses - total calculated	174,9	181,06	181,94	192	
skeletal minor observations					
Ondontoid incompletly ossified - fetuses (%)	1 (0.6)	4 (2.2)	**8 (4.4)**	**11 (5.7)**	0.0 - 8.0
litters (%)	1 (4.5)	4 (18.2)	6 (27.3)	**8 (33.3)**	
Sternebra 5 not ossified - fetuses (%)	10 (5.7)	**32 (17.7)**	**25 (13.7)**	**30 (15.6)**	5.7 - 16.9
litters (%)	6 (27.3)	12 (54.5)	12 (54.5)	**13 (54.2)**	
skeletal variant					
Sternebra 5 incompletly ossified - fetuses (%)	22 (12.6)	29 (16.0)	**40 (22.0)**	**40 (20.8)**	9.3 - 38.0
litters (%)	11 (50.0)	15 (68.2)	**15 (68.2)**	**14 (58.3)**	
Rib 7 costal cartilage shortened - fetuses (%)	7 (4.0)	**33 (18.2)**	**18 (9.9)**	**31 (16.1)**	0.0 - 14.0

litters (%)	6 (27.3)	**15 (68.2)**	9 (40.9)	11 (45.8)	
Rib 13 attached to vertebral column - long length - fetuses (%)	35 (20.0)	**53 (29.3)**	43 (23.6)	52 (27.1)	20.0 - 54.5
litters (%)	14 (63.6)	16 (72.7)	19 (86.4)	18 (75.0)	
27 Pre-pelvic vertebrae bilateral - fetuses (%)	4 (2.3)	**25 (13.8)**	**15 (8.2)**	12 (6.3)	2.3 - 34.4
litters (%)	4 (18.2)	**12 (54.5)**	9 (40.9)	7 (29.2)	

Note : Figures in bold are statistically significant

The skeletal effects were minor or variants, within historical control,without dose-relation and are not considered as treatment related. The NOAEL for development is set at the high dose of 1000 mg/kg bw.

According to DS's proposal, no classification is justified.

Comments received during public consultation
Two MS agreed on the DS's proposal that classification is not warranted for reproductive toxicity.

Assessment and comparison with the classification criteria
No significant effects were observed on fertility or on development in the multigeneration and developmental studies in rats and rabbits. For developmental studies, no effects on number, growth, survival or development of foetuses *in utero* were observed.

In the rat developmental study, some skeletal major observations were observed on sternum. However, the incidence of affected foetuses was very small (up to 3 foetuses – 1.2%) and not dose related. Also, there was no evidence for a specific effect on other areas of the skeleton. Therefore, the NOAEL can be considered as corresponding to the highest dose tested of (1000 mg/kg bw).

In the developmental study in rabbits, no effect of treatment on skeleton was observed. Only some minor observations or variant were reported, within historical control and without dose-relation. Then, the NOAEL was identified at the highest dose of 1000 mg/kg bw.

The observed effects are not considered adverse and therefore, the RAC agrees with the DS's proposal that classification for reproductive toxicity is not justified according to CLP or DSD.

4.12 Other effects

No other data available.

4.12.1 Non-human information

No other data available.

4.12.1.1 Neurotoxicity

Table 21: Summary table of relevant neurotoxicity studies

Study; Reference	Dose levels	NOAEL	Relevant effects
Acute neurotoxicity Milburn G.; 2005c	0, 200, 600, 2000 mg/kg bw	systemic: 2000 mg/kg bw neurotox.: 2000 mg/kg bw	No adverse effects of treatment and no evidence of neurotoxicity
Subchronic neurotoxicity Pinto P.; 2005c	0, 100, 500 and 2500 ppm/diet (7.4, 37.3, 192.5 mg/kg bw/d ♂ and 8.4, 41, 206.7 mg/kg bw/d ♀)	neurotox.: 2500 ppm (192.5 mg/kg bw/d ♂, 206.7 mg/kg bw/d ♀) systemic tox.: 500 ppm (37.3 mg/kg bw/d ♂, 41 mg/kg bw/d ♀)	no neurotoxic effects -bodyweight ↓ (♂) -bodyweight gain ↓ (♂) -liver weight ↑ (♂♀)

Mandipropamid has been assessed for potential neurotoxicity in an acute and a subchronic neurotoxicity study in the rat and was shown to have no neurotoxic potential in these studies.

In an acute neurotoxicity study, rats received a single oral dose of 0, 200, 600 or 2000 mg/kg bw mandipropamid via gavage. Detailed clinical observations, bodyweights and food consumption and a full range of functional assessments (FOB, including grip strength, tail flick, landing foot splay), brain weight and neuropathology revealed no treatment related effects of mandipropamid.

The NOAEL for systemic and neurotoxic effects in this study was established at 2000 mg/kg bw mandipropamid.

In a subchronic neurotoxicity study, mandipropamid was administered to groups of 12 male and 12 female rats at dose levels of 0, 100, 500 and 2500 ppm (equivalent to 7.4, 37.3 and 192.5 mg/kg bw/d for males and 8.4, 41 and 206.7 mg/kg bw/d for females) in the diet for 90 consecutive days. The highest dose of 2500 ppm resulted in toxicity characterised by reduced bodyweight and bodyweight gain in males and increased liver weight in both sexes.

A comprehensive battery of neurobehavioural tests and neuropathological examination of the central and peripheral nervous system showed no effects of treatment at doses of up to 2500 ppm mandipropamid.

The NOAEL for neurotoxic effects in this study was established at 2500 ppm for male and female rats (192.5 and 206.7 mg /kg bw/d for males and females respectively). The NOAEL for systemic toxicity can be considered at 500 ppm (37.3 and 41 mg/kg bw/d for males and females respectively).

4.12.1.2 Immunotoxicity

No data available.

4.12.1.3 Specific investigations: other studies

No data available.

4.12.1.4 Human information

4.12.2 Summary and discussion

4.12.3 Comparison with criteria

4.12.4 Conclusions on classification and labelling

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 22: Summary of relevant information on degradation

Method	Results	Remarks	Reference

Method	Results				Remarks	Reference
Hydrolysis ECCD 94/37/EC (1994), ECCD 95/36/EC (1995), OECD 111 (1981), US EPA: N: 161-1 (1982), BBA Merkblatt Nr. 55, Teil I und II (1980)	No degradation of mandipropamid occurred, therefore, mandipropamid can be considered hydrolytic stable in a pH range of 4 to 9.					Buckel, T., 2002 NOA 446510 / 0018
Photolysis * ECCD 94/37/EC (1994), ECCD 95/36/EC (1995), US EPA: N: 161-2 (1982), OECD (2000), SETAC (1995) ** ECCD 95/36/EC (1995), US EPA: N: 161-2 (1982), OECD (2000)	Parent: (No metabolites > 10 % AR)					*Hand, L. H., 2004;NOA 44610 / 0041 ** Harrison, C. L., 2004;NOA 446510 / 0197
	*Sterilized buffered solution, pH 7.0: DT_{50} = 1.4 days [^{14}C-methoxy-Ph]-label DT_{50} = 6.7 days [^{14}C-Cl-Ph]-label	*Natural summer light, 40°N: DT_{50} = 1.6 days [^{14}C-methoxy-Ph]-label DT_{50} = 8.0 days [^{14}C-Cl-Ph]-label	**Sterilized natural water, pH 7.4: DT_{50} = 1.0 days [^{14}C-methoxy-Ph]-label DT_{50} = 0.9 days [^{14}C-Cl-Ph]-label	**Natural summer light, 40°N: DT_{50} = 1.9 days [^{14}C-methoxy-Ph]-label DT_{50} = 1.5 days [^{14}C-Cl-Ph]-label		
Readily biodegradable OECD 301F (1992)	**NO** The degradation of mandipropamid technical was < 5 % after 28 days Conclusion: Mandipropamid is not considered readily biodegradable.					Wallace, S. J., 2002

Method	Results	Remarks	Reference
Degradation in water / sediment OECD 308 (2002), SETAC (1995), US-EPA: N (1982)	See table below		*Grosjean, J., Hurt, A. D., 2005 NOA 446510 / 0388 **Hurt, A. D., Bramley, Y. M., Grosjean, J., Davison, K., 2005 NOA 446510 / 0395

Condi-tions	Label	System	Water				Sediment		Total	
			Degradation		Dissipation		Degradation		Degradation	
			$DegT_{50}$	$DegT_{90}$	DT_{50}	DT_{90}	$DegT_{50}$	$DegT_{90}$	$DegT_{50}$	$DegT_{90}$
Aerobic	Me-Ph	Calwich Abbey	Stable	Stable	3.44	19.3	4.41	14.7	10.3	28.7
		Swiss Lake	234	777	4.93	30.4	5.72	19.0	14.1	41.3
	Cl-Ph	Calwich Abbey	Stable	Stable	0.69	2.30	4.86	16.2	5.93	17.2
		Swiss Lake	Stable	Stable	14.1	46.8	7.69	25.6	25.9	61.9
An-aerobic	Me-Ph	Calwich Abbey	Stable	Stable	0.96	3.18	3.04	10.1	4.55	11.7
		Swiss Lake	Stable	Stable	8.33	27.7	4.84	16.1	15.7	37.4
	Cl-Ph	Calwich Abbey	Stable	Stable	6.75	22.4	3.95	13.1	12.76	30.3
		Swiss Lake	34.3	114	20.2	72.5	5.54	18.4	23.7	76.0

Method	Results	Remarks	Reference

<table>
<tr><th>Method</th><th>Results</th><th>Remarks</th><th>Reference</th></tr>
<tr>
<td>Degradation in an outdoor aquatic sediment system

No regulatory guideline existing, following guidelines were taken into consideration: OECD (2002), SETAC (1995), US-EPA: N (1982)</td>
<td>
<table>
<tr><th rowspan="3">Label</th><th colspan="4">Water</th><th colspan="2">Sediment</th><th colspan="2">Total</th></tr>
<tr><th colspan="2">Degradation</th><th colspan="2">Dissipation</th><th colspan="2">Degradation</th><th colspan="2">Degradation</th></tr>
<tr><th>DegT$_{50}$ [days]</th><th>DegT$_{90}$ [days]</th><th>DT$_{50}$ [days]</th><th>DT$_{90}$ [days]</th><th>DegT$_{50}$ [days]</th><th>DegT$_{90}$ [days]</th><th>DegT$_{50}$ [days]</th><th>DegT$_{90}$ [days]</th></tr>
<tr><td>Cl-Ph</td><td>10.6</td><td>35.1</td><td>2.50</td><td>11.8</td><td>3.18</td><td>10.6</td><td>5.86</td><td>16.9</td></tr>
<tr><td>Me-Ph</td><td>14.4</td><td>47.9</td><td>3.19</td><td>12.0</td><td>1.94</td><td>6.45</td><td>5.53</td><td>15.0</td></tr>
</table>
</td>
<td></td>
<td>Oliver, R. G., Webb, J., Edwards, P. A., 2005</td>
</tr>
<tr>
<td>Degradation in soil
Rate of Degradation in soil
Laboratory studies

Field studies
ECCD 94/37/EC (1994), ECCD 95/36/EC (1995)</td>
<td>The laboratory soil degradation rate of mandipropamid was investigated in total 25 experiments using 5 soils with a wide range of soil properties (pH, organic C, texture, origin) under varying test conditions:
Under aerobic conditions, 19 – 25 °C incubation temperature, soil moisture contents close to field capacity and relevant application rates (150 – 675 g ai ha-1), mandipropamid degraded with an overall half-life time in a range of 12.6 – 93.1 days based on SFO kinetics (n = 15, R2 > 0.95). The degradation rate in the lab was strongly depending on the application rate, at higher dose rates degradation significantly slowed down. Based on averaged results for each soil type (n = 5), DT50 values were in a range of 30.6 – 85.7 days with an arithmetic mean of 53.0 days.
Under anaerobic conditions degradation of mandipropamid was significantly slower, DT50 was in a range of 158 – 179 days (based on SFO and DFOP kinetics, n = 2), mean DT50 = 169. Respective DT90 value was 758 days. No degradation rates for anaerobic metabolites could be obtained owing to their low occurrence.

The field dissipation rate of mandipropamid (as one single broadcast application of the formulation to bare soils) was investigated in 10 studies:
Dissipation of mandipropamid followed partly SFO (7 trials) and partly FOMC (3 trials) kinetics. Based on best fit (adjusted R2) DT50 was in a range of 2.0 – 29.2 days (adj. R2 □ 0.84) with an geometric mean of 13.6 days.</td>
<td></td>
<td>Berdat, T., Nicollier, G. 2005 a - b

Evans, P. 2003a
2003b
2005a -g</td>
</tr>
</table>

Method	Results	Remarks	Reference
Soil Photolysis SETAC (1995), OECD (2001), US-EPA: N: 161-3	In photolysis on the soil surface, mandipropamid degraded with an experimental half-life of 14.9 – 25.2 days (n = 4), arithmetic mean = 19.5 days. This DT50 is equivalent to approx. 20 – 40 midsummer days at 40 °N (arithmetic mean 30 days).. No degradation rates for metabolites (all < 10 % of AR) could be obtained.		Kuet, S. F., Dick, J., 2003

5.1.1 Stability

Aquatic hydrolysis
One hydrolysis study in sterile buffer solutions at pH values of 4, 5, 7 and 9 (50 °C over 7 days, 25 °C over 32 days) using ethyl labelled mandipropamid was carried out. No degradation of mandipropamid occurred, therefore, mandipropamid can be considered hydrolytic stable in a pH range of 4 to 9.

Aquatic photolysis
Aquatic photolysis of mandipropamid was investigated in sterile buffer solutions at pH 7 (n = 2) and in sterilized natural water (pH 7, n = 2) using Cl-phenyl and methoxy-phenyl labelled mandipropamid. All test systems were continuously irradiated with a xenon arc lamp (> 290 nm) to simulate natural light. Photo-degradation of mandipropamid was pronounced, the photolytic half-life under experimental conditions varied from 1.4 – 6.7 days in sterile buffer solutions and 0.9 – 1.0 days in sterilized natural water. Experimental half-life times were calculated to correspond to 1.5 – 8.0 environmental midsummer days at a latitude of 40 °N. Under the influence of irradiation, mandipropamid was degraded to a large number of compounds, none of them exceeding 10 % AR individually. No distinct differences in degradation pattern were observed between sterilized buffer and natural water. Formation of CO2 (7.8 % of AR after 7 DAT)using Cl-phenyl mandipropamid was less pronounced indicating a higher stability of the Cl-phenyl moiety against photolysis. In contrast to the Cl-phenyl label, photo-degradation of methoxy-phenyl labelled mandipropamid resulted in extensive formation of multiple polar compounds, which were shown not to exceed 10 % AR individually.

In a separate study the **quantum yield of the direct photochemical degradation** of mandipropamid was investigated. This study was carried out in sterilized buffer solution at pH 7.4 and 25 °C. Mandipropamid was irradiated with a xenon arc lamp at 280, 300 and 330 nm over a test period of 12 hrs. Quantum yield was calculated to be □ = 0.492 (at 280 nm) and □ = 0.370 (at 300 nm). No adsorption owing to mandipropamid was considered at 330 nm (the study was complicated by impurities, which absorbed light at higher wave lengths). Using GC-SOLAR, the notifier calculated expected environmental half-lives of 39 – 71 days in summer and spring at 40 °N. The environmental half-life of mandipropamid, calculated on the basis of the quantum yield (GC-SOLAR), is distinct longer than directly measured in photolysis studies.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

No data available

5.1.2.2 Screening tests

Ready biodegradability of the active substance (OECD Annex IIA 7.7)

Reference:	**NOA446510 technical: Determination of 28 day ready biodegradability**
Author(s), year:	Wallace, S. J., 2002
Report/Doc. number:	NOA 446510 / 0016
Guideline(s):	OECD 301F (1992)
GLP:	Yes
Deviations:	No
Validity:	Yes

Material and Methods:

Test substance:	Mandipropamid technical, purity 97.1 %
Reference substance:	Na-acetate
Inoculum:	Activated sludge from local sewage treatment (30 mg L^{-1} in each treatment)
Treatments:	a) Blank control b) Na-acetate (200 mg L^{-1}) c) Mandipropamid techn. (100 mg L^{-1}) d) Mandipropamid techn. (100 mg L^{-1}) + $HgCl_2$ (64 mg L^{-1}) pH of all treatments approx. 7.5
Analysis:	Chemical oxygen demand (COD)

Findings:

Table 33: Mean biodegradation of techn. mandipropamid and reference substances [% of added].

DAT	Na-acetate	Mandipropamid techn.	Mandipropamid techn. + $HgCl_2$
5	68	< 5	< 5
9	73	< 5	< 5
15	78	< 5	< 5
20	78	< 5	< 5
28	77	< 5	< 5

The degradation of mandipropamid technical was < 5 % after 28 days.

Conclusion:

Mandipropamid is not considered readily biodegradable.

5.1.2.3 Simulation tests

Water/sediment studies

The following 2 studies were combined for discussion:

Reference:	**NOA 446510: Degradation in two aquatic sediment systems (methoxyphenyl ring)**
Author(s), year:	Grosjean, J., Hurt, A. D., 2005
Report/Doc. number:	NOA 446510 / 0388
Guideline(s):	OECD 308 (2002), SETAC (1995), US-EPA: N (1982)
GLP:	Yes
Deviations:	None
Validity:	Yes

Reference:	**NOA 446510: Degradation in two aquatic sediment systems**
Author(s), year:	Hurt, A. D., Bramley, Y. M., Grosjean, J., Davison, K., 2005
Report/Doc. number:	NOA 446510 / 0395
Guideline(s):	OECD 308 (2002), SETAC (1995), US-EPA: N (1982)
GLP:	Yes
Deviations:	None
Validity:	Yes

Dark water/sediment studies (*n* = 8) were conducted under aerobic and anaerobic conditions with two contrasting natural systems, Calwich Abbey and Swiss Lake. Both sites were sampled individually for each label tested, therefore, main properties of water and sediment for Me-Ph and Cl-Ph labelled experiments were slightly different. However, these slight differences are not considered to significantly affect the comparability of the two labels used. The Calwich Abbey represents a loamy sediment rich in organic and microbial C (mean of both samplings: pH of sediment 7.1, silt loam, 5.7 % organic C, 845 µg microbial C g^{-1}), the sandy Swiss Lake sediment is considered as nutrient poor system (pH of sediment 4.8, sand, 0.8 % organic C, 124 µg microbial C g^{-1}). Experiments were conducted at 20 °C in the dark for a period of 120 days (Me-Ph label) and 365 days (Cl-Ph label).

Owing to the high organic C content and high microbial biomass in the Calwich Abbey system, overall degradation of mandipropamid was significantly faster in this system compared to the less active Swiss Lake system.

In general, mineralization of mandipropamid to $^{14}CO_2$ was significantly higher for Me-Ph labelled than for Cl-Ph labelled mandipropamid. One hundred days after onset of the experiment conducted under aerobic conditions, 30.5 - 35.5 % of AR were released as $^{14}CO_2$ from Me-Ph labelled mandipropamid, respective amounts for Cl-Ph labelled mandipropamid were only 3.9 – 4.3 % of AR. Under anaerobic conditions similar amounts of $^{14}CO_2$ were released from Me-Ph labelled mandipropamid (32.0 – 38.6 % of AR after 100 days), from Cl-Ph labelled mandipropamid only negligible amounts of $^{14}CO_2$ (0.4 – 2.5 % of AR) were released. These results clearly indicate that the Cl-Ph moiety of mandipropamid is much more persistent in comparison to the Me-Ph moiety. A distinct amount of radioactivity not trapped in the experimental set-up (indicated by incomplete mass balance), was attributed to the formation of methane (based on results from additional experimental work). The formation of methane (16.5 – 42.2 % of AR by 100 DAT, based on the difference of applied and recovered radioactivity) was much higher under anaerobic conditions and was almost exclusively attributed to the Me-Ph moiety of mandipropamid. Using Cl-Ph labelled mandipropamid the

recovery of applied radioactivity was almost complete, formation of methane considered negligible.
In contrast to the release of $^{14}CO_2$, formation of NER was hardly depending on the label position used, under aerobic conditions maximum levels of 36.5 - 48.1 % of AR (62 to 100 days after onset) were observed, with a decreasing tendency thereafter. Anaerobic incubation led to significantly smaller formation of NER, maximum amounts of 16.2 – 30.9 % of AR (30 to 120 days after onset) were observed irrespective of the label used.

Dissipation of mandipropamid from the water layer was rapid (following SFO kinetics), dissipation half-life varied from 0.7 – 14.1 days (arithmetic mean 5.8 days) under aerobic and 1.0 – 20.2 days (arithmetic mean 9.1 days) under anaerobic conditions. Dissipation of mandipropamid was more pronounced in the Calwich Abbey system reach in organic C, indicating that dissipation from the water layer into the sediment was predominately driven by the high K_{FOC} of mandipropamid. In fact, degradation in the water layer was calculated to be negligible. The high stability of mandipropamid in the water under dark conditions could be expected from the hydrolysis studies (sterile conditions), but was also demonstrated in additional experiments using only the (non-sterilized) water layers of both water/sediment systems without sediment. Concluding, degradation in the water is considered to be negligible for PEC_{SW} and PEC_{SED} calculations using FOCUS surface water STEP 2 and 3.
Subsequent degradation of mandipropamid in the sediment phase was fast, $DegT_{50}$ varied from 4.4 – 7.7 days (arithmetic mean 5.7 days) under aerobic and 3.0 – 5.5 days (arithmetic mean 4.3 days) under anaerobic conditions. Degradation was slightly slower in the nutrient poor Swiss Lake system, different labels used did not differ from each other. Based on the aerobic water/sediment studies, a mean $DegT_{50}$ in the sediment of 5.7 days (n = 4) was considered appropriate for PEC_{SW} and PEC_{SED} using FOCUS surface water STEP 2 and 3 calculations. As mentioned above, mandipropamid significantly dissipated into the sediment at a maximum level of 64.0 % of AR after 1 day of incubation.

Table 55: Summary of DT50 and DT90 [days] for the dissipation and degradation of mandipropamid in laboratory water/sediment systems (under aerobic and anaerobic conditions) and in one outdoor pond study (both labels, values shaded in grey were used for PECSW and PECSED calculations).

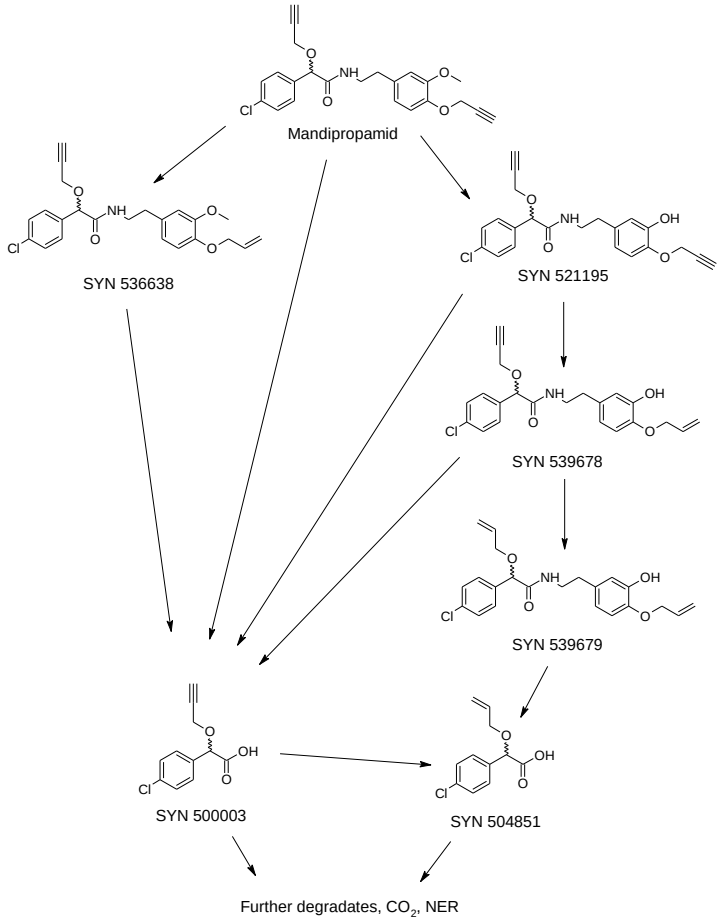
Condi-tions	**Label**	**System[a]**	**Water**				**Sediment**		**Total**	
			Degradation		**Dissipation**		**Degradation**		**Degradation**	
			$DegT_{50}$	**$DegT_{90}$**	**DT_{50}**	**DT_{90}**	**$DegT_{50}$**	**$DegT_{90}$**	**$DegT_{50}$**	**$DegT_{90}$**
Aerobic water/ sediment	**Me-Ph**	Calwich Abbey	Stable	Stable	3.44	19.3	4.41	14.7	10.3	28.7
		Swiss Lake	234	777	4.93	30.4	5.72	19.0	14.1	41.3
	Cl-Ph	Calwich Abbey	Stable	Stable	0.69	2.30	4.86	16.2	5.93	17.2
		Swiss Lake	Stable	Stable	14.1	46.8	7.69	25.6	25.9	61.9
Arithmetic mean			**Stable**	**Stable**	**5.79**	**24.7**	**5.67**	**18.9**	**14.1**	**37.3**
Geometric mean			Stable	Stable	3.58	15.9	5.54	18.4	12.2	33.5
Anaerobic	**Me-Ph**	Calwich Abbey	Stable	Stable	0.96	3.18	3.04	10.1	4.55	11.7

Condi-tions	Label	System[a]	Water				Sediment		Total	
			Degradation		Dissipation		Degradation		Degradation	
			DegT50	DegT90	DT_{50}	DT_{90}	$DegT_{50}$	DegT90	DegT50	DegT90
water/ sediment		Swiss Lake	Stable	Stable	8.33	27.7	4.84	16.1	15.7	37.4
	Cl-Ph	Calwich Abbey	Stable	Stable	6.75	22.4	3.95	13.1	12.76	30.3
		Swiss Lake	34.3	114	20.2	72.5	5.54	18.4	23.7	76.0
Arithmetic mean			**Stable**	**Stable**	**9.06**	**31.4**	**4.34**	**14.4**	**14.2**	**38.9**
Geometric mean			Stable	Stable	5.75	19.4	4.24	14.1	12.1	31.7
Outdoor pond	**Cl-Ph**		10.6	35.1	2.50	11.8	3.18	10.6	5.86	16.9
	Me-Ph		14.4	47.9	3.19	12.0	1.94	6.45	5.53	15.0
Arithmetic mean			**12.5**	**41.5**	**2.85**	**11.9**	**2.56**	**8.53**	**5.70**	**16.0**
Geometric mean			12.4	41.0	2.82	11.9	2.48	8.27	5.69	15.9
Overall arithmetic mean			**-[b]**	**-**	**6.51**	**24.8**	**4.52**	**15.0**	**12.4**	**33.6**
Overall geometric mean			-[b]	-	4.13	16.2	4.24	14.1	10.5	28.2

[a] Properties of the water/sediment systems were not identical for the labels used (considered by RMS not to drastically affect risk assessment).

[b] Considered as stable under dark conditions but not under environmental conditions (irradiation).

Under aerobic conditions, 3 metabolites were observed > 10 % of AR (major) in the total water/sediment system: SYN 504851 (38.5 % of AR after 100 days), SYN 521195 (17.7 % of AR, 14 days) and SYN 539678 (12.6 % of AR, 21 days). One further metabolites, SYN 500003, was close to 10 % of AR (9.4 % of AR) and is more toxic than the parent according to the acute oral toxicity in rats (Pooler, 2006). SYN 500003 was therefore considered relevant for further risk assessment. The minor metabolites SYN 536638 and SYN 539679 did not exceed 8.4 % of AR in sum (metabolites co-eluted in HPLC). In the water phase, only the polar metabolite SYN 504851 exceeded 10 % of AR, the polar metabolite SYN 500003 occurred close to 10 % of AR in the water phase. All other, less polar metabolites were mainly attributed to the sediment phase. Amounts of SYN 504851 steadily increased during incubation, indicating a high stability of this degradate in both, the water and sediment phase. Degradation half-lives of SYN 521195, SYN 539678 and SYN 500003 in the total system were calculated to be 10.0, 29.1 and 43.7 days, respectively. Formation pattern of metabolites were similar between both labels used (SYN 504851 and SYN 500003 can only be observed using Cl-Ph labelled mandipropamid).



Proposed pathway of mandipropamid in water/sediment.

Pattern of metabolites observed under anaerobic conditions were similar to patterns observed under aerobic conditions, however, almost all metabolites occurred at higher levels under anaerobic conditions (all > 10 % of AR). The major metabolite SYN 504851, representing the main sink of radioactivity, steadily increased to maximum levels of 73.5 % of AR 100 days after onset of the experiment. In one experiment, levels of SYN 504851 decreased to 45.5 % of AR after 365 days. The metabolites SYN 539678, SYN 500003, SYN 521195 and the sum of SYN 536638/SYN 539679 reached maximum levels of 29.3 % (30 days), 25.9 % (45 days), 15.4 % (14 days) and 11.7 % (10 days) of AR. None of these metabolites was persistent, $DegT_{50}$ for the total system was 19.2, 28.5, 11.3 and 14.9 days, respectively. Similar to the experiments conducted under aerobic conditions, only the polar metabolites SYN 504851 and SYN 500001 exceeded 10 % of AR in the water phase.

Table 56: Observed maximum occurrence [% of AR] of mandipropamid in the sediment and of metabolites in water/sediment systems (based on individual replicates, data stated in brackets give day of maximum occurrence, values shaded in grey were used for PECSW and PECSED calculations).

Compartment	Water/sediment study	Mandi-propamid	SYN 504851	SYN 521195	SYN 539678	SYN 500003
Total	Aerobic	-	38.5 (100)	17.7 (14)	12.6 (21)	9.4 (45)
	Anaerobic	-	73.5 (100)	15.4 (14)	29.3 (30)	25.9 (45)
	Outdoor pond	-	11.1 (120)	10.8 (15)	6.9 (15)	6.4 (36)
Water	Aerobic	-	22.7 (100)	3.4 (21)	1.9 (42)	9.4 (45)
	Anaerobic	-	56.7 (179)	6.0 (30)	9.2 (30)	20.2 (45)
	Outdoor pond	-	7.2 (120)	nd[a]	nd	5.4 (36)
Sediment	Aerobic	64.0 (1)	28.5 (100)	15.6 (14)	11.2 (30)	3.9 (10)
	Anaerobic	53.6 (1)	45.9 (100)	12.5 (21)	20.1 (30)	11.6 (30)
	Outdoor pond	23.7 (2)	4.5 (71)	10.8 (15)	6.9 (15)	1.7 (71)

[a] nd denotes not detected

Table 57: Summary of degradation half-lives [days] of metabolites in the total system of investigated aquatic systems (values shaded in grey were used for PECSW and PECSED calculations).

Aquatic system		Label	SYN 504851	SYN 521195	SYN 539678	SYN 500003
Aerobic water/sediment	Calwich Abbey	Me-Ph	-[a]	9.7	19.7	-
		Cl-Ph	No decline	4.1	35.1	13.2
	Swiss Lake	Me-Ph	-	10.1	36.9	-
		Cl-Ph	No decline	16.2	25.7	74.1
Arithmetic mean			**No decline**	**10.0**	**29.4**	**43.7**
Geometric mean			No decline	8.98	28.5	31.3
Anaerobic water/sediment	Calwich Abbey	Me-Ph	-	10.6	19.7	-
		Cl-Ph	441	6.3	23.0	34.2
	Swiss Lake	Me-Ph	-	13.2	12.0	-
		Cl-Ph	No decline	15.4	23.0	23.0
Arithmetic mean			**No decline**	**11.4**	**19.4**	**28.6**
Geometric mean			No decline	10.8	18.8	28.1
Outdoor pond		Me-Ph	-	28.4	73.3	-
		Cl-Ph	No decline	21.2	71.0	No decline
Arithmetic mean			**No decline**	**24.8**	**72.2**	**No decline**
Geometric mean			No decline	24.5	72.1	No decline
Overall arithmetic mean			**No decline**	**13.5**	**33.9**	**36.1**
Overall geometric mean			No decline	11.8	29.0	29.6

[a] Not detectable using this label

The degradation behaviour of mandipropamid was additionally elucidated in one **outdoor pond study**, which was designed to account for the impact of natural light and water plants in order to simulate more realistic environmental conditions. As demonstrated in the aquatic photolysis studies, mandipropamid is rather photosensitive, therefore, a higher overall degradation rate of mandipropamid may be expected under outdoor conditions.
The study was carried out in open ponds (1.8 x 1.0 m, approx. 0.3 m of water depth) with two labels (Me-Ph and Cl-Ph, no replicates). Sediment depth was 0.1 m. The pond was partly planted with water plants. Mandipropamid was applied in July (150 g ai ha^{-1}), the duration of the experiment was 120 days. The sediment used was a sandy clay loam, pH 7.2, 1.9 % organic C and 85 µg microbial C g^{-1}.

From total radioactivity recovered, it can be concluded that approx. 45 % (Cl-Ph label) and 70 % (Me-Ph label) of AR were released as CO_2 (and other volatiles, likely methane) after 120 days. However, CO_2 or other volatiles were not trapped in the test system, therefore, these numbers remain indicative. Highest amounts of NER could be found at study end with levels of 27.1 – 29.2 % of AR.
Degradation half-life of mandipropamid in the total outdoor pond system was 5.7 days following SFO kinetics (without normalization, R^2 > 0.95, no difference between labels). In contrast to the dark laboratory water/sediment studies, mandipropamid is also considered to show significant degradation in the water layer (calculated $DegT_{50}$ = 12.5 days), likely owing to the influence of irradiation. In consequence, dissipation from the water phase was fast with an arithmetic mean half-life of 2.9 days. In the sediment layer mandipropamid degraded with a mean half-life of 2.6 days (maximum amounts occurring in the sediment were 23.7 % of AR after 2 days). The comparability of degradation rates between the laboratory water/sediment studies and the outdoor pond studies is clearly restricted due to the non-normalized conditions of the outdoor pond study.
In contrast to the dark water/sediment studies, only the metabolites SYN 504851 and SYN 521195 exceeded 10 % of AR in the total outdoor pond system (11.1 % or AR at study end and 10.5 % of AR after 15 days, respectively). SYN 504851 was almost stable in the system (no decrease during study), $DegT_{50}$ of SYN 521195 was calculated to be 13.5 days.

Route of Degradation in soil

The route and rate of laboratory soil degradation of mandipropamid was extensively investigated in total 25 experiments using 5 soils with a wide range of soil properties (pH, organic C, texture, origin), under varying test conditions (temperature, ai concentration, soil moisture content) and varying incubation conditions (aerobic, anaerobic, sterile). For purposes of an environmental fate assessment only those studies conducted under more realistic conditions (aerobic conditions, 150 – 675 g ai ha^{-1}, moisture conditions close to pF2 and temperatures between 19 – 25 °C) were considered appropriate (which gives a final number of 15 relevant degradation experiments). For each soil type, on which multiple studies were conducted (e.g. dose rate experiments), arithmetic mean DT_{50} and DT_{90} values were used to avoid bias towards any particular soil type.

Degradation of mandipropamid in soil is considered to be mainly driven by soil microbial activity and by photolysis if located close to or on the soil surface. No degradation is observed under sterile conditions. The following degradation processes are considered to mainly attribute to the overall metabolism of mandipropamid in viable soils:

- Hydrolytic cleavage of the 2-propynyl moiety on the chloromandelic acid or methoxyphenyl ring (oxidative dealkylation)
- Hydrolytic methyl-ether cleavage (oxidative dealkylation)
- Reduction of a 2-propynyl moiety to a 2-propenyl moiety (reduction by acetylene hydratase)
- Hydrolytic cleavage of the central amid bridge
- Addition of water to a 2-propynyl group

Under aerobic conditions mineralization of mandipropamid to CO_2 accounts for 9.0 – 44.2 % of AR after 120 days without significant differences between labels used (Cl-phenyl, methoxy-phenyl, ethyl). Formation of NER accounted for maximum 19.4 – 45.4 % of AR by 120 days of incubation. Organic matter fractionation resulted in 5 – 10 % of AR associated with fulvic acids, 5 – 13 % with humic acids and 21 – 28 % of AR bound to insoluble humins. Both ring systems were incorporated into the soil matrix.

Microbial degradation of mandipropamid in soil leads to formation of a large number of minor metabolites, all of them accounting for less than 5 % of AR with the exception of CGA 380778, which reached maximum levels of 6.3 % of AR in one experiment. Further identified minor metabolites (SYN 536638, NOA 458422, CGA 380775, SYN 500003, U7 and U8) were all observed at maximum amounts < 5 % of AR, none of them persistent. Several compounds or metabolite fractions close to 2 % of AR remained unidentified. Most identified minor soil metabolites (among them one unknown fraction observed in one sample at 5.1 % of AR) were included into groundwater risk assessment for reasons of precaution.

Anaerobic experiments were conducted using methoxy-phenyl and Cl-phenyl labels with one soil incubated aerobically for 30 days ('aging period') and waterlogged thereafter. After switching to anaerobic conditions, formation of CO_2 significantly slowed down (almost negligible after 120 days of anaerobic incubation), additional formation of NER during the anaerobic incubation phase accounted for 5.8 – 11.8 % of AR. The degradation pattern of aerobic and anaerobic soil samples were similar, metabolites which were formed owing to reductive processes (e.g. SYN 536638) were also observed in aerobically incubated soils. This is thought to be due to micro-sites of soil aggregates, in which anaerobic conditions might occur. During the anaerobic phase of incubation no metabolite exceeded 5 % of AR.

Soil photolysis of mandipropamid was investigated using methoxy-phenyl and Cl-phenyl labelled mandipropamid applied to dry and moist soil samples. On moist soil surfaces, mandipropamid degraded with a half-life of 27.5 days (Me-Ph label) and 40.2 days (Cl-Ph label) based on midsummer day equivalents at 40 °N. Mineralization of mandipropamid to $^{14}CO_2$ owing to irradiation was more pronounced for methoxy-phenyl labelled than for Cl-phenyl labelled mandipropamid, indicating that the methoxy-phenyl moiety is more sensitive to photo-degradation than the Cl-phenyl moiety. In dark control samples no degradation occurred. The metabolite pattern formed under soil photolysis were similar to the pattern formed in soils owing to microbial degradation. All metabolites observed were < 10 % of AR.

Rate of degradation (laboratory) in soil
(Note: The notifier based their risk assessment exclusively on the usage of arithmetic means (of DT_{50} values) instead of geometric means. This (non-recommended) approach gives more conservative mean DT_{50} values (endpoints) and is therefore accepted by the RMS.)

The laboratory soil degradation rate of mandipropamid could be best described applying first order multi compartment (FOMC) kinetics. This degradation behaviour likely results from weak enantiomer-selective degradation, which leads to a FOMC like degradation behaviour and which was definitively shown in one study investigating both enantiomers (R/S enantiomers) separately. However, enantiomer selectivity of the degradation in soil is weak observed with 1.2 to 1.7fold faster degradation of the R-enantiomer than the S-enantiomer. Therefore, enantiomer-selective degradation has no significant impact on the fate assessment of mandipropamid in soil and was taken into account further.

On the basis of simple first order (SFO) kinetics, mandipropamid degraded with an overall half-life time in a range of 12.6 – 93.1 days (n = 15, R^2 > 0.95), respective DT_{90} was in a range of 41.7 – 309 days. The degradation rate in the lab was strongly depending on the application rate, at higher dose rates degradation significantly slowed down. Based on averaged results for each soil type (n = 5), DT_{50} values were in a range of 30.6 – 85.7 days with an arithmetic mean of 53.0 days (respective DT_{90} values were 102 – 285 days, arithmetic mean 176 days). After transformation to standard conditions (20 °C and pF2), an arithmetic mean DT_{50} of 47.9 days was calculated based on the 5 soil types used.

Based on FOMC kinetics (best fit), arithmetic mean laboratory DT_{50} of the 5 soil types was calculated to be 47.7 days (range of 28.0 – 80.8 days), which is similar to the mean DT_{50} calculated using SFO kinetics (53.0 days). However, arithmetic mean DT_{90} was distinct longer with 346 days (in a range of 131 – 636 days). On the basis of FOMC kinetics it can be concluded, that mandipropamid might have the potential to accumulate in soil under unfavourable conditions. However, in field dissipation studies (n = 10) all DT_{90} values (according to best fit) were less than 365 days, indicating that the risk for accumulation of mandipropamid in soils can be considered low under environmental conditions.

Degradation half-life of the most pronounced soil metabolite, CGA 380778, maximum occurrence 6.3 % of AR, was obtained from parent studies (n = 15) and from degradation studies with the metabolite (n = 3). Overall DT_{50} was in a range of 5.2 – 37.7 days. Averaged for each soil type (n = 5), an arithmetic mean DT_{50} of 21.7 days (in a range of 8.5 – 36.7 days) was calculated (SFO kinetics). This value is equivalent to a normalized DT_{50} of 20.0 days at 20 °C and pF2. Degradation rates of further minor soil metabolites were partly based on individual observations of these metabolites in parent degradation studies or on separate metabolite degradation studies. All soil metabolites observed degraded faster than the parent.

Under anaerobic conditions degradation of mandipropamid was significantly slower, DT_{50} was in a range of 158 – 179 days (based on SFO and DFOP kinetics, *n* = 2), arithmetic mean DT_{50} was 169 days. Respective DT_{90} was 758 days. No degradation rates for anaerobic metabolites could be obtained owing to their low occurrence.

Under sterile conditions (*n* = 1) no degradation of mandipropamid was observed.

In soil photolysis experiments mandipropamid degraded with an experimental half-life of 14.9 – 25.2 days (*n* = 4), arithmetic mean 19.5 days, equivalent to approx. 20 – 40 midsummer days at 40 °N (arithmetic mean 30 days). No degradation rates for metabolites (all < 10 % of AR) could be obtained. Degradation rates of mandipropamid owing to soil photolysis were in a similar range compared to microbial degradation under aerobic conditions, indicating that soil photolysis does not significantly contribute to the overall dissipation of mandipropamid in soils.

Field dissipation studies

Ten representative bare ground field dissipation studies were conducted with mandipropamid (broadcast spray application) on a representative range of soil types from northern to southern Europe from 2002 - 2004. The trials included eight trials with a single application of 200 g ai ha^{-1} and two trials in Switzerland that were carried out with a single application of 300 and 700 g ai ha^{-1}. The latter trials were conducted to evaluate dissipation under worst case conditions.

The dissipation of mandipropamid in these studies was consistent with degradation, since the decline of residues levels in the 0 – 10 cm increment was not associated with a significant increase in residue levels in the 10 – 20 and 20 – 30 cm depth layer (only trace levels could be found close to the LOQ) and volatilization from soil is considered to be negligible. Dissipation of mandipropamid followed partly SFO (7 trials) and partly FOMC (3 trials) kinetics. Based on best fit, DT_{50} was in a range of 2.0 – 29.2 days (R^2 > 0.87, adj. $R^2 \geq 0.84$) with an arithmetic mean of 17.0 days. Respective DT_{90} values were 42.1 – 240 days, arithmetic mean 92.8 days. The two longest DT_{90} values (199 and 240 days) were observed in field trials which were kept free of any vegetation (both located in Germany), the other field trials were covered by grass. Since DT_{90} of mandipropamid under field conditions is less than 1 year, field accumulation studies are not triggered. Residual amounts of mandipropamid in the ten field studies remaining in soil at trial termination (after 157 – 254 days) were in the range of 1.5 – 6.5 % of nominal applied, indicating a low risk for accumulation. In contrast to the laboratory degradation studies, no dependence of degradation rate on the application rate was observed (one study in Switzerland).

Only low amounts of CGA 380778 were measured in the soil samples and these were within the top 0 – 10 cm soil layer (maximum 3 % of the nominal applied amount). For SYN 536638, residues could not be detected in the 0 – 10 cm layer at or above the LOQ. No residues of CGA 380778 or SYN 536638 could be detected in the 10 – 20 or 20 – 30 cm layer at all.

Field DT_{90} of mandipropamid applied once to the soil is less than 1 year and accumulation studies are not triggered therefore. Nevertheless, an accumulation study (Switzerland, conducted for 6 years) is currently being carried out to investigate the potential for accumulation of mandipropamid, when applied several times a year (up to 6 times as proposed for potatoes). Mandipropamid is applied as foliar spray each year at an application rate of 6 x 150 g ai ha with an interval of 6 – 7 days. The field trial is conducted and maintained according to GAP. Residue data are available for the first 3 years. Regarding to maximum levels observed

no evidence of accumulation of mandipropamid can be deduced in the study, to date. However, residual amounts of mandipropamid detected in soil immediately before the 1st application of the 2nd and 3rd year indicated at least a limited potential for accumulation if applied several times in a year.

Summary: Degradation

Degradation in water: Abiotic degradation: Mandipropamid was hydrolytically rather stable at a pH range of 4 to 9 in the hydrolysis study. Under the influence of irradiation, mandipropamid was rapidly photolytically degraded to a large number of compounds, none of them exceeding 10 % AR individually. Formation of CO2 was 7.8 % of AR after 7 DAT using Cl-phenyl mandipropamid. In contrast to the Cl-phenyl label, photo-degradation of methoxy-phenyl labelled mandipropamid resulted in extensive formation of multiple polar compounds, which were shown not to exceed 10 % AR individually.
Degradation in water: Biotic degradation The results of a **readily biodegradability** study indicate, that mandipropamid is not readily biodegradable. In **water/sediment** degradation of mandipropamid in the total system followed SFO kinetics was fairly rapid irrespective of the label used and of aerobic or anaerobic conditions. Degradation half-life varied from 5.9 – 25.9 days (n = 4, arithmetic mean 14.1 days) under aerobic and 4.6 – 23.7 days (n = 4, arithmetic mean 14.2 days) under anaerobic conditions. The mineralization to CO2 was significantly higher for methoxy-phenyl labelled than for Cl-phenyl labelled mandipropamid. One hundred days after onset of the experiment conducted under aerobic conditions, 30.5 - 35.5 % of AR were released as 14CO2 from methoxy-phenyl labelled mandipropamid, respective amounts for Cl-phenyl labelled mandipropamid were only 3.9 – 4.3 % of AR. **Note:** Aquatic toxicity studies for metabolites SYN 504851, SYN 536638 and SYN 536638 are available but are missing for SYN 521195 and for the major metabolites in the sediment SYN521195 and SYN 539678. Thus a reliable classification regarding the hazardous to aquatic environment for all degradation products is not possible.

Degradation in water:

In an **outdoor pond study** degradation half-life of mandipropamid in the total outdoor pond system was 5.7 days following SFO kinetics (without normalization, R2 > 0.95, no difference between labels). In contrast to the dark laboratory water/sediment studies, mandipropamid is also considered to show significant degradation in the water layer (calculated DegT50 = 12.5 days), likely owing to the influence of irradiation. In consequence, dissipation from the water phase was fast with an arithmetic mean half-life of 2.9 days. In the sediment layer mandipropamid degraded with a mean half-life of 2.6 days. From total radioactivity recovered, it can be concluded that approx. 45 % (Cl-Ph label) and 70 % (Me-Ph label) of AR were released as CO2 (and other volatiles, likely methane) after 120 days.

Note: Aquatic toxicity studies for metabolite SYN 504851 is available but is missing for SYN 521195. Thus a reliable classification regarding the hazardous to aquatic environment for all degradation products is not possible.

Degradation of mandipropamid in soil is considered to be mainly driven by soil microbial activity and by photolysis if located close to or on the soil surface.
Under aerobic conditions DT50 values were in a range of 30.6 – 85.7 days with an arithmetic mean of 53.0 days (n = 5). Mmineralization of mandipropamid to CO2 accounts for 9.0 – 44.2 % of AR after 120 days without significant differences between labels used (Cl-phenyl, methoxy-phenyl, ethyl). Formation of NER accounted for maximum 19.4 – 45.4 % of AR by 120 days of incubation.
Under anaerobic conditions degradation of mandipropamid was significantly slower, DT50 was in a range of 158 – 179 days (based on SFO and DFOP kinetics, n = 2), mean DT50 = 169.

The dissipation of mandipropamid in soil followed partly SFO (7 trials) and partly FOMC (3 trials) kinetics. Based on best fit, DT50 was in a range of 2.0 – 29.2 days (R2 > 0.87, adj. R2 ³ 0.84) with an arithmetic mean of 13.6 days.

Conclusion:

Mandipropamid is not readily biodegradable under test conditions within 28 days. Ultimate degradation could not be shown in discussed abiotic and biotic degradation studies. Available aquatic degradation studies with the exeption of the Hydrolysis study indicate primary degradation, but due to missing data on aquatic toxicity of degradants, it is not possible to show that the metabolites are not classifiable, therefore a non rapid degradation is proposed.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Reasonable adsorption/desorption coefficients (K_{FOC}, 1/n values) were determined for methoxy-phenyl labelled mandipropamid in seven soil batch experiments using four EU and three US soils with a representative spectrum of soil properties. K_{FOC} values were in a range of 405 – 1294 L kg^{-1}, with an arithmetic mean of 847 L kg^{-1}. Respective 1/n values were in a range of 0.80 – 0.92 with an arithmetic mean of 0.85. Adsorption of mandipropamid was strongly correlated with the organic matter content of the soil. No dependency on either pH of soil or other soil characteristics was observed.

Valid batch experiments were also conducted on a large number of soil and water/sediment metabolites of mandipropamid using unlabelled and/or labelled test compounds (CGA 380778, CGA 380775, SYN 536638, SYN 539678, SYN 521195, SYN 500003 and SYN 504851). Arithmetic mean K_{FOC} values of less polar metabolites (all with the exception of SYN 500003 and SYN 504851) were in the range of 448 - 1677 L kg^{-1}, indicating a medium to low mobility of these metabolites in soil. The two polar metabolites SYN 500003 and SYN 504851 exhibited mean K_{FOC} values of 11 and 5 L kg^{-1}, indicating very high mobility in soils. Mean 1/n value (0.76 – 0.92) gave evidence for non-linear adsorption/desorption isotherms for almost all metabolites with the exception of SYN 539678 (1/n = 1.00).

5.2.2 Volatilisation

Mandipropamid has a low vapour pressure of $< 9.4 \times 10^{-7}$ at 25 °C and a Henry's Law constant of
$< 9.2 \times 10^{-5}$ at 25 °C. Therefore volatilisation of mandipropamid would be considered negligible. The low potential for volatilisation from soil and leaf surfaces was also demonstrated in two laboratory studies conducted according to BBA guidelines. Based on a theoretical calculation of the potential for photo-oxidation of mandipropamid in the atmosphere a first order half-life of 1.36 hrs was estimated. Concluding, air is not a likely route of environmental contamination.

5.2.3 Distribution modelling

Not relevant to classification

Summary: Evironmental Distribution (not relevant for classification and labelling)

Evironmental Distribution (not relevant for classification and labelling)				
	Test guideline /	pH	GLP (y/n)	Reliability
Adsorption/Desorption KFOC values were in a range of 405 – 1294 L kg-1, with an arithmetic mean of 847 L kg-1. Respective 1/n values were in a range of 0.80 – 0.92 with an arithmetic mean of 0.85.				
Volatilisation Henry´s constant of < 9.2 × 10-5 Pa m^3/mol (25° C) Vapour pressure of < 9.4 × 10-7 Pa (25° C)				

5.3 Aquatic Bioaccumulation

Table 58: Summary of relevant information on aquatic bioaccumulation

Method	Results	Remarks	Reference
Partition co-efficient ‡ (state temperature, pH and purity)	log $P_{O/W}$ = 3.2 in pure water (990 g/kg) at 25 °C	Effect of pH (4-10): not relevant as the active substance shows no pH dependency	Das R., (2003c) (NOA446510/ 0027) Das R., (2006c) (Doc. 10115098)
Determination of the accumulation and elimination of Mandipropamid OECD 305	Mandipropamid accumulated in whole fish with BCF values of 35 and 48 (the overall mean lipid content was 11 % w/w and was used for normalisation of the BCF)		Roberts, G., Peurou, F., 2003 BL7579/B

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

No estimation available

5.3.1.2 Measured bioaccumulation data

Reference:	**NOA446510: Determination of the accumulation and elimination of [14C]NOA446510 in fathead minnow (*Pimephales promelas*)**
Author(s), year:	Roberts, G., Peurou, F., 2003
Report/Doc. number:	BL7579/B
Guideline(s):	OECD 305
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable

Test substance:	[^{14}C] Mandipropamid (NOA446510), radiochemical purity: 99.5 %, batch: ILA-208.9 and unlabelled Mandipropamid (NOA446510), purity 99 %, batch: AMS 1131/2
Material and methods:	
Test species:	Fathead minnow (*Pimephales promelas*)
Number of organisms:	88 fish per test concentration and solvent control
Weight, length	3.9 (2.0 – 6.6) g, 51.5 (41.3 – 65.2) mm
Type of test, duration:	Flow-through test
Applied concentrations:	
Nominal:	0 (solvent control), 3.2 and 32 µg/L
Measured (mean):	-- (solvent control), 3.2 and 31 µg/L
Solvent	Dimethylformamide (DMF)

Test conditions:	
Water quality:	Dechlorinated tap water, hardness: 43 – 47 mg/L as $CaCO_3$
Temperature:	24.8 – 25 °C
pH:	7.2 – 7.6
O_2 content:	> 60 %, 5.8 – 8.6 mg O_2/L
Light regime:	16 hours light / 8 hours darkness, 20 min transition period
Feeding	Ecostart (proprietary fish food): 2 % of the total fish weight per day
Test parameters:	Concentration of [^{14}C] Mandipropamid equivalents in fish tissues were determined by LSC-method at 3, 6, 12, 24, 48, 119, 167, 190 h (exposure) and 6, 25, 48, 97, 147, 195 h (depuration phase). Four fish for tissue analysis were removed from each test concentration and control at each sampling time. Additionally a lipid analysis (by chloroform/methanol extraction) was carried out on fish sampled at day 0 and day 7 (exposure) and at day 8 (depuration). TLC-analysis of fish tissues were performed at the end of exposure and depuration phase. For chemical analysis (LSC) of NOA446510 in test solutions samples were taken at -48 h (pre-exposure phase), 0, 3, 6, 12, 24, 48, 119, 167, 190 h (exposure) and 6, 25, 48, 97, 147, 195 h (depuration phase)
Calculations/statistics:	BCF was calculated as ratio of [^{14}C] Mandipropamid equivalents concentration in water and [^{14}C] Mandipropamid equivalents concentration of in fish tissues and as ratio of k_d and k_u (rate constant k was determined by KINETICS program)

Findings:

Analytical data – water:

The mean measured concentrations of [^{14}C]-NOA446510 equivalents were 100 % (low concentration) and 97 % (high concentration) of nominal. TLC analysis confirmed that NOA446510 was stable in the high test concentration (32 µg/L), 79 – 89 % was determined as active substance. In the low concentration (3.2 µg/L) some degradation was observed (maybe due to photolysis) and recoveries ranged from 42 to 82 %. It was attempted to minimize the degradation by covering some sensitive parts of the test apparatus with black plastic.

Analytical data – fish tissue (TLC):

Due to very low levels of [^{14}C]-NOA446510 in fish tissues a characterisation and a quantification of active substance or degradation products were not possible.

Lipid content:

No differences between male and female fish were noted.

Mean lipid content on day 0, day 7 and at the end of depuration phase was 10, 11.8 and 9.8 % w/w, respectively. The overall mean lipid content was 11 % w/w and was used for normalisation of the BCF, assuming that the accumulation was wholly contained within the lipid.

Table 59: Uptake, bioconcentration and depuration of [^{14}C]NOA446510 in the fathead minnow

Hour	Mean concentration of [^{14}C]NOA446510 (µg/kg)									
	Viscera		Flesh		Carcass		Whole body			
	3.2 µg/L	32 µg/L	3.2 µg/L	32 µg/L	3.2 µg/L	32 µg/L	3.2 µg/L		32 µg/L	
							µg/kg	BCF	µg/kg	BCF
Uptake phase										
3	100	1090	10	160	20	320	40	12.5	400	12.9
6	160	1850	10	190	20	370	50	15.6	610	19.6
12	330	3060	20	190	20	300	80	25	730	23.5
24	470	4270	40	250	50	640	130	40.6	1080	34.8
48	530	5330	20	260	60	560	100	31.3	1590	51.3
120	490	5750	40	340	50	790	110	34.4	1430	46.1
167	500	7600	20	340	50	650	90	28.1	1570	50.6
190	640	4860	20	300	50	690	130	40.6	1350	43.5
Depuration phase										
6	320	3840	10	140	20	160	60	18.8	880	28.4
25	70	2160	ND	30	10	60	20	6.3	250	8.1
48	70	610	ND	20	10	50	20	6.3	130	4.2
97	20	320	ND	ND	ND	20	ND	< 3	60	1.9
147	20	130	ND	ND	ND	20	10	3	30	1.0
195	20	90	ND	ND	ND	20	ND	< 3	20	0.6

ND = Not detected: < 20 µg/kg for 32 µg/L or < 10 µg/kg for 3.2 µg/L test concentrations.

Table 60: Mean concentrations and measured BCF of Mandipropamid in fish during 190 hours exposure and percentage of elimination after 6 and 165 hours

Parameter	Tissue	3.2 µg/L				32 µg/L			
		Mean (µg/kg)	BCF	% Elimination		Mean (µg/kg)	BCF	% Elimination	
				6 h	165 h			6 h	165 h
Wet weight	Viscera	526 ± 67.3	164	49	96	5885 ± 1200	184	31	98
	Flesh	28 ± 11	9	64	100	310 ± 38.3	10	53	100
	Carcass	52 ± 4.47	16	64	100	673 ± 95.4	21	76	97
	Whole body	112 ± 17.9	35*	46	100	1485 ± 115	48*	46	99
Lipid content	Whole body	1018 ± 163	318	--	--	13500 ± 1043	422	--	--

* The overall mean lipid content was 11 % w/w and was used for normalisation of the BCF

Conclusion:
Mandipropamid accumulated in whole fish with BCF values of 35 and 48. In viscera (non-edible) portions BCF values of 164 and 184 were determined. All BCF values are based on calculations with total ^{14}C-residues. Mandipropamid was stable under test conditions. The plateau concentration was reached after 48 hours. During the depuration period the 14C-residues were completely eliminated (99 – 100 % in whole fish) after 8 days. The depuration half-life (CT50) was < 1 days.

5.3.2 Summary and discussion of aquatic bioaccumulation

Based on determined BCF values (35 and 48) mandipropamid is considered to have a low bioaccumulation potential.

5.4 Aquatic toxicity

Table 61: Summary of relevant information on aquatic toxicity

Method	Results							Remarks	Reference
	Test organism	Test condition	Time	Endpoint	Test conc.	NOEC [mg/L]	EC_{50}/LC_{50} [mg/L]		
OECD 203	*Oncorhynchus mykiss* Rainbow trout	static	96 hr	mortality	mm	≥ 2.9	> 2.9 [a)]		Volz 2002
OECD 203	*Pimephales promelas* Fathead minnow	static	96 hr	mortality	mm	≥ 6.04	> 6.04 [a)]		Peter 2002
OECD 203	*Cyprinus carpio* Common carp	flow through [b)]	96 hr	mortality	mm	≥ 2.0	> 2.0		Maynard & Woodyer 2004a
OECD 203	*Cyprinus carpio* Common carp	flow through	96 hr	mortality	mm	5.54	8.63		Matsuura 2005
US EPA OPPTS 850.1075	*Cyprinodon variegatus* Sheephead minnow	flow through	96 hr	mortality	mm	2.8	4.5		Palmer et al 2005a
EPA OPPTS 850.1400	*Pimephales promelas* Fathead minnow	flow-through	32 d	hatchability mortality growth	n	≥ 2.0 0.5 0.5	> 2.0 1.0 1.0		Maynard 2003/ yes
OECD 202	*Daphnia magna* Waterflea	static	48 hr	immobility	nom	5.0	7.1		Maynard & Woodyer 2004b
OECD 202, Part II	*Daphnia magna* Waterflea	semi static	21 d	mortality reproduction length	m	≥ 2.64 0.87 0.28	>2.64 2.64 0.87		Grade 2003/ yes
OECD 201	*Selenastrum capricornutum* Green alga	static	72 hr	biomass growth rate	mm	≥ 27.8	> 27.8 [a)]		Grade 2001a
OECD 201	*Anabaena flos-aquae* Blue alga	static	96 hr	biomass growth rate	mm	≥ 19.8	> 19.8 [a)]		Knauer 2002
OECD 221 (Draft October 2000)	*Lemna gibba* Duckweed	static	7 d	biomass growth rate	mm	3.0	> 4.4		Bätscher 2005
EPA OPPTS 850.1035	*Americamysis bahia* Saltwater mysid	flow through	96 hr	mortality	mm	0.58	1.7		Palmer et al 2005b
EPA OOPTS 850.1025	*Crassostrea virginica* Eastern oyster	flow through	96 hr	shell deposition	mm	0.46	**0.97**		Palmer et al 2005c

Test conc.: test concentration based on mean measured (mm) or nominal (nom) concentration

[a)] highest tested concentration (maximal solubility of test the substance under test conditions)

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Reference:	**Acute Toxicity Test of NOA446510 to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions**
Author(s), year:	Volz, E., 2002
Report/Doc. number:	2023552
Guideline(s):	OECD 203
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable

Test substance:	Mandipropamid (NOA446510), purity: 96.5 %, batch: SEZ2BP007
Material and Methods:	
Test species:	Rainbow trout (*Oncorhynchus mykiss*)
Number of organisms:	7 fish per concentration and control
Weight, length:	1.47 g (1.25 – 1.76 g), 5.6 cm (5.2 – 6.0 cm)
Type of test, duration:	Static test, 96 hours
Applied concentrations:	
Nominal:	0 (control), 0 (solvent control), 0.36, 0.65, 1.2, 2.1, 3.8 mg/L
Measured (mean):	-- (control), -- (solvent control), 0.32, 0.53, 0.96, 1.6, 2.9 mg/L; the highest mean measured concentration represented the maximal solubility of NOA446510 under test conditions
Solvent	0.1 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Filtered and UV sterilized well water, hardness: 177 mg/L as $CaCO_3$
Temperature:	13.5 - 14 °C
pH:	7.9 – 8.0 (0 h), 8.3 (96 h)
O_2 content:	91 – 100 %
Light regime:	16 hours light / 8 hours darkness
Test parameters:	Mortality and sublethal effects were assessed after 2, 24, 48, 72 and 96 hours; for chemical analysis (HPLC method) of NOA446510 in test solutions samples were taken at 0 and 96 hours
Statistics:	None
Findings:	
Analytical data:	The mean measured concentrations at the start and the end of the test were 80 – 83 % and 69 – 78 % of nominal, over study period overall mean measured concentrations were 76 – 87 % of nominal.
Behavioural effects:	None
Mortality:	None in the control and at all treatment group after 2, 24, 48, 72 and 96 hours
Conclusion:	LC_{50} (96 h) > 2.9 mg/L, NOEC ≥ 2.9 mg/L based on mean measured conc.

Reference:	**Acute Toxicity Test of NOA446510 to Fathead Minnow (*Pimephales promelas*) Under Static Conditions**
Author(s), year:	Peter, P., 2002
Report/Doc. number:	2023555
Guideline(s):	OECD 203
GLP:	Yes
Deviations:	Temporarily the oxygen content fell below 60 % saturation after 72 hours and an aeration of test media was required. However this had no adverse influence on the results or quality of the study.
Validity:	Acceptable
Test substance:	Mandipropamid (NOA446510), purity: 96.5 %, batch: SEZ2BP007
Material and Methods:	
Test species:	Fathead Minnow (*Pimephales promelas*)
Number of organisms:	7 fish per concentration and control
Weight, length:	0.23 g (0.18 – 0.32 g), 3.0 cm (2.6 – 3.3 cm)
Type of test, duration:	Static test, 96 hours
Applied concentrations:	
Nominal:	0 (control), 0 (solvent control), 0.65, 1.2, 2.1, 3.8, 6.8 mg/L
Measured (mean):	-- (control), -- (solvent control), 0.67, 1.16, 2.02, 3.53, 6.04 mg/L; the highest mean measured concentration represented the maximal solubility of NOA446510 under test conditions
Solvent	0.1 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Filtered and UV sterilized well water, hardness: 181 mg/L as $CaCO_3$, from 72 hours on gently aerated
Temperature:	24.6 – 25.1 °C
pH:	7.7 – 7.4 (0 h), 7.5 – 7.6 (96 h)
O_2 content:	69 – 101%, except at 72 hours when it dropped temporarily below 60 % for the three highest test concentrations
Light regime:	16 hours light / 8 hours darkness
Test parameters:	Mortality and sublethal effects were assessed after 2, 24, 48, 72 and 96 hours; for chemical analysis (HPLC method) of NOA446510 in test solutions samples were taken at 0 and 96 hours
Statistics:	None
Findings:	
Analytical data:	Mean measured concentrations were 90 – 101 % (start) and 88 – 114 % (end) of nominal, overall mean measured concentrations over the study period were 89 – 107 % of nominal
Behavioural effects:	None
Mortality:	None in the control and at all treatment groups after 2, 24, 48, 72 and 96 hours
Conclusion:	LC50 (96 h) > 6.04 mg/L, NOEC ≥ 6.04 mg/L based on mean

	measured conc.

Reference:	**NOA446510: Acute toxicity to common carp (*Cyprinus carpio*) in a flow-through test system**
Author(s), year:	Maynard, S. & Woodyer, J., 2004a
Report/Doc. number:	BL7872/B
Guideline(s):	OECD 203
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable
Test substance:	Mandipropamid (NOA446510), purity: 96.5 %, batch: SEZ2BP007
Material and Methods:	
Test species:	Common carp (*Cyprinus carpio*)
Number of organisms:	10 fish per concentration and control
Weight, length:	0.9 g (0.68 – 1.17 g), 3.3 cm (3.0 – 3.5 cm)
Type of test, duration:	Flow through Limit-test, 96 hours
Applied concentrations:	
Nominal:	0 (control), 0 (solvent control), 2.0 mg/L
Measured (mean):	-- (control), -- (solvent control), 2.0 mg/L
Solvent	0.1 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Dechlorinated tap water, hardness: 49.3 mg/L as $CaCO_3$
Temperature:	21.7 °C
pH:	7.49 – 7.61 (0 h), 7.34 – 7.62 (96 h)
O_2 content:	74 – 101 %
Light regime:	16 hours light / 8 hours darkness
Test parameters:	Mortality and sublethal effects were assessed after 0, 24, 48, 72 and 96 hours; for chemical analysis (HPLC method) of NOA446510 in the test solution samples were taken at 0, 48 and 96 hours
Statistics:	None
Findings:	
Analytical data:	Mean measured concentration at 0, 48 and 96 hours was 100 % of nominal at each sample time
Behavioural effects	None
Mortality:	None in the control and in all treatment levels after 0, 24, 48, 72 and 96 hours
Conclusion:	LC50 (96 h) > 2.0 mg/L, NOEC ≥ 2.0 mg/L based on mean measured conc.

Reference:	**A 96-hour Acute Toxicity Test of NOA 446510 (Mandipropamid) with Common Carp**
Author(s), year:	Matsuura, T., 2005
Report/Doc. number:	93451
Guideline(s):	OECD 203
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable

Test substance:	Mandipropamid (NOA446510), purity: 96.5 %, batch: SEZ2BP007
Material and Methods:	
Test species:	Common carp (*Cyprinus carpio*)
Number of organisms:	10 fish per concentration and control
Weight, length:	1.4 ± 0.16 g, 5.1 ± 0.18 cm
Type of test, duration:	Flow through test, 96 hours
Applied concentrations:	
Nominal:	0 (control), 0 (solvent control), 4.55, 5.92, 7.67, 10, 13 mg/L
Measured (mean):	-- (control), -- (solvent control), 4.92, 5.54, 7.16, 9.3, 12 mg/L
Solvent	0.1 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Dechlorinated tap water, hardness: 49.3 mg/L as $CaCO_3$
Temperature:	22.5 – 22.8 °C
pH:	7.8 – 8.7
O_2 content:	> 60 %
Light regime:	16 hours light / 8 hours darkness
Test parameters:	Mortality and sublethal effects were assessed after 3, 24, 48, 72 and 96 hours; for chemical analysis (HPLC method) of NOA446510 in test solutions samples were taken at 0, 48 and 96 hours
Statistics:	LC50: Probit analysis, NOEC: directly from the raw data
Findings:	
Analytical data:	Mean measured concentrations were 90.8 – 97.4 % (0 h) and 89.1 – 94.9 % (96 h)
Behavioural effects	At 7.16 mg/L and higher concentrations loss of equilibrium, reduced activity, surface swimming and lethargy were observed.
Mortality:	See table below

Table 62: Cumulative mortality of carps (C. carpio) exposed to Mandipropamid

Mean measured concentration (mg/L)	**Cumulative mortality (%)**				
	3 hours	**24 hours**	**48 hours**	**72 hours**	**96 hours**
Blank control	0	0	0	0	0
Solvent control	0	0	0	0	0

Mean measured concentration (mg/L)	Cumulative mortality (%)				
	3 hours	24 hours	48 hours	72 hours	96 hours
4.92	0	0	0	0	0
5.54	0	0	0	0	0
7.16	0	0	20	20	40
9.30	0	0	30	50	50
12.0	10	70	70	80	90
NOEC = 5.54 mg/L					
LC50 = 8.63 mg/L (95% CL 7.5 – 10.1 mg/L)					

Conclusion: LC50 (96 h): 8.63 mg/L, NOEC: 5.54 mg/L based on mean measured conc.

Reference:	**NOA446510: A 96-Hour Flow-Through Acute Toxicity Test with the Sheephead Minnow (*Cyprinodon variegatus*)**
Author(s), year:	Palmer. S.J:, Kendall, T.Z. & Krueger, H.O., 2005a
Report/Doc. number:	528A-138
Guideline(s):	US EPA OPPTS 850.1075
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable.

Test substance:	Mandipropamid (NOA446510), purity: 96.1 %, batch: SEZ3BP004
Material and Methods:	
Test species:	Sheephead minnow (*Cyprinodon variegatus*)
Number of organisms:	7 fish per concentration and control
Weight, length:	0.23 g (0.11 – 0.45 g), 2.5 cm (2.1 – 3.0 cm)
Type of test, duration:	Flow-through test, 96 hours
Applied concentrations:	
Nominal:	0 (control), 0 (solvent control), 1.3, 2.2, 3.6, 6.0, 10 mg/L
Measured (mean):	-- (control),-- (solvent control), 1.1, 1,8, 2.8, 4.3, 6.1 mg/L
solvent	0.1 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Filtered natural seawater diluted with well water, salinity: 20 ‰
Temperature:	21.8 – 21.9 °C
pH:	8.2 – 8.3 (0 h), 8.3 (96 h)
O_2 content:	> 60 %, 7.2 – 8.0 mg O_2/L
Light regime:	16 hours light / 8 hours darkness
Test parameters:	Mortality and sublethal effects were assessed after 3, 24, 48, 72 and 96 hours; for chemical analysis (HPLC method) of NOA446510 in test solutions

	samples were taken at 0, 24 and 96 hours
Statistics:	LC_{50}: Probit analysis, NOEC: directly from raw data
Findings:	
Analytical data:	Overall mean measured concentrations were in the range of 61 – 85 % of nominal concentrations.
Behavioural effects	At 4.3 mg/L and next higher concentration sublethal effects like erratic swimming, surfacing and lying on the bottom of the aquarium were observed. Thus the NOEC is 2.8 mg/L
Mortality:	See table below

Table 63: Cumulative mortality of sheephead minnow exposed to Mandipropamid

Measured concentration (mg/L)	**Cumulative mortality (%)**				
	3 hours	**24 hours**	**48 hours**	**72 hours**	**96 hours**
Blank control	0	0	0	0	0
Solvent control	0	0	0	0	0
1.1	0	0	0	0	0
1.8	0	0	0	0	0
2.8	0	0	0	0	0
4.3	0	0	40	40	40
6.1	10	30	100	100	100
NOLC = 2.8 mg/L					
LC_{50} = 4.5 mg/L (95%CL 2.8 – 6.1 mg/L)					

Conclusion: LC_{50} (96 h) 4.5 mg/L, NOEC 2.8mg/L based on mean measured conc.

5.4.1.2 Long-term toxicity to fish

Reference:	**NOA446510 tech: Early-life stage toxicity test to the fathead minnow (*Pimephales promelas*)**
Author(s), year:	Maynard, S., 2003
Report/Doc. number:	BL7577/B
Guideline(s):	EPA OPPTS 850.1400
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable

Test substance:	Mandipropamid (NOA446510), purity: 96.5 %, batch: SEZ2BP007
Material and Methods:	
Test species:	Fathead minnow (*Pimephales promelas*)
Number of organisms:	4 replicates x 20 eggs per test concentration and control
Age:	Eggs < 24 hours
Type of test, duration:	Flow-through test, 28 days post hatch
Applied concentrations:	
Nominal:	0 (control), 0 (solvent control), 0.13, 0.25, 0.5, 1.0, 2.0 mg/L

Measured (mean):	-- (control), -- (solvent control), 0.13, 0.23, 0.48, 0.87, 1.8 mg/L
Solvent	Dimethylformamide (DMF)
Test conditions:	
Water quality:	Dechlorinated tap water, hardness: 38 – 58 mg/L as $CaCO_3$
Temperature:	24 – 25.5 °C
pH:	7.5 – 7.9
O_2 content:	> 60 %, 5.6 – 8.4 mg O_2/L
Light regime:	16 hours light / 8 hours darkness
Feeding	Larvae were fed with rotifers from hatch until day 7 of post hatch, on day 7 (post hatch) additionally brine shrimp eggs were offered and from day 8 (post hatch) on only brine shrimp were fed, feeding was performed 3 x daily from Monday – Friday and 2 x daily on weekend. From day 16 (post hatch) on high protein pelleted fish food was fed *ad libidum*.
Test parameters:	Mortality and abnormal appearance or behaviour were assessed daily, the length and the weight were determined at test termination (endpoints: hatchability, survival and growth of larvae). For chemical analysis (HPLC method) of NOA446510 in test solutions samples were taken at 0, 4, 10, 18, 24 and 32 days
Statistics:	Hatchability and survival data: Steel's Many-One Rank Test (non-parametric method), larval length and weight: ANOVA followed by Dunnett's test or Wilcoxon Rank Sum Test (in the case of heterogeneous variance data)
Findings:	
Analytical data:	Overall mean measured concentrations were 87 – 100 % of nominal.
Biological observation:	Time to hatch: Hatching was completed at day 4. During hatching and until 8 day post hatch hatched fry were observed to be smaller, less active and took longer to "swim up" at 1.0 and 2.0 mg/L. At days 14, 21 and 27 (post hatch) fry at the highest test concentration (2 mg/L) were slightly smaller and less active. At 0.13, 0.25 and 0.5 mg/L concentration levels and at controls all surviving fish appeared normal and healthy during the test.
Effects:	See table 64 and table 65

Table 64: Hatchability and survival

NOA446510 nominal in mg/L	Mean number of eggs at start	Mean number of larvae hatched	Hatch in %	Mean number of larvae surviving at 28 d post hatch	Survival in %
control	21.25	19.5	92	18.75	96
solvent control	19.75	19.25	97	19.25	100
0.13	21	20.25	96	20	99
0.25	17.5	16.75	96	16.5	99
0.5	20.25	19	94	18.	95
1.0	20.5	19	93	16.5	87*
2.0	20.5	18.5	90	12.25	66*

* significant difference when compared to pooled control (p=0.05)

Table 65: Length and Weight

NOA446510 nominal in mg/L	Number of fish	Mean length (± SD) in mm	Relative SD in %	Mean weight (± SD) in mg	Relative SD in %
control	75	20.0 ± 1.92	10	138.0 ± 37.6	27
solvent control	77	19.4 ± 2.02	10	129.5 ± 39.0	30
0.13	80	19.7 ± 1.46	7	129.8 ± 30.0	23
0.25	66	20.2 ± 1.51	7	140.4 ± 34.3	24
0.5	72	19.3 ± 1.69	9	125.2 ± 34.0	27
1.0	66	19.0 ± 2.03*	11	119.8 ± 40.1*	33
2.0	49	18.2 ± 2.15*	12	106.8 ± 39.1*	37

* significant difference when compared to pooled control (p=0.05)

Conclusion: Mortality: NOEC: 0.5 mg/L, LOEC: 1.0 mg/L;
Hatchability: NOEC ≥ 2 mg/L, LOEC > 2 mg/l;
Growth (weight and length): NOEC: 0.5 mg/L, LOEC: 1.0 mg/L;
based on nominal concentrations

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

Reference:	**NOA446510: Acute toxicity to *Daphnia magna***
Author(s), year:	Maynard, S. & Woodyer, J., 2004b
Report/Doc. number:	BL7871/B
Guideline(s):	OECD 202
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable

Test substance:	NOA446510, purity: 96.5 %, batch: SEZ2BP007
Material and Methods:	
Test species:	Waterflea (*Daphnia magna*)
Number of organisms:	4 replicates each with 5 daphnids per treatment
Age:	First instar < 24 hours old
Type of test, duration:	Static test, 48 h
Applied	

concentrations:	
Nominal:	0 (control), 0 (solvent control), 0.63, 1.3, 2.5, 5.0, 10 mg/L
Measured (mean):	-- (control), -- (solvent control), 0.65, 1.3, 2.5, 4.9, 11 mg/L
Solvent	0.01 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Elendt's M4 medium, hardness: 226 mg/L as $CaCO_3$
Temperature	20.0 – 20.2 °C
pH	7.93 – 8.07 (0 h), 7.98 – 8.01 (48 h)
O_2 content:	99 %, 9.0 mg O_2/L
Light regime:	16 hours light / 8 hours darkness
Test parameters:	Immobility was assessed after 24 and 48 hours. For chemical analysis (HPLC method) of NOA446510 in the test media samples were taken at test initiation (0 h) and termination (48 h).
Statistics:	EC50: Binominal method, NOEC: directly from the raw data
Findings:	
Analytical data:	The mean measured concentrations at the start and end of the test were in the range of 96 – 110 %, overall mean measured concentration ranged from 98 – 110 % of nominal.
Effects:	After 48 hours no immobility was observed in the control, solvent control and in test concentrations up to 5 mg/L, at 10 mg/L all daphnids (100 %) were immobile. Thus the NOEC was determined to be 5 mg/L and the EC50 was calculated to be 7.1 mg/L (95% CL: 5 – 10 mg/L).
Conclusion:	EC50 (48 h): 7.1 mg/L, NOEC: 5.0 mg/L based on nominal conc.

5.4.2.2 Long-term toxicity to aquatic invertebrates

Reference:	***Daphnia magna* Reproduction Test: Effects of NOA 446510 on the Reproduction of the Cladoceran *Daphnia magna* STRAUS in a Semi-Static Laboratory Test**
Author(s), year:	Grade, R. 2003
Report/Doc. number:	2013604
Guideline(s):	OECD 202, Part II
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable

Test substance:	NOA446510, purity: 99 ± 2 %, batch: KI-6380/1
Material and Methods:	
Test species:	Waterflea (*Daphnia magna*)
Number of organisms:	12 replicates each with one daphnid per treatment and control
Age:	First instar < 24 hours old
Type of test, duration:	Semi static test, 21 d, renewals of test solutions: 0, 2, 5, 7, 9, 12, 14, 16, 19 days
Applied concentrations:	

Nominal:	0 (control), 0 (solvent control), 0.033, 0.10, 0.30, 0.90, 2.7 mg/L
Measured (mean):	-- (control), -- (solvent control), 0.023, 0.085, 0.28, 0.87, 2.64 mg/L
Solvent	0.1 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Elendt's M4 medium, hardness: 264 mg/L as $CaCO_3$
Temperature	20.1 – 22 °C
pH	7.8 – 8.3 (fresh solution), 8.2 – 8.6 (old solution)
O_2 content:	90 – 99 % saturation
Light regime:	16 hours light / 8 hours darkness, 30 min transition period
Feeding	Daily (except Sunday) with *Scenedesmus obliquus* suspension (1 x 10^8 cells/L)
Test parameters:	Survival, time to first brood, production of young and other sublethal effects were controlled and recorded daily, the length of daphnids was measured at the end of the exposure; for chemical analysis (HPLC method) of NOA446510 in the test solution samples were taken from fresh (on days 7, 14, 19) and old solutions (on days 2, 9, 16, 21) from each test concentration.
Statistics:	EC_{50} (mortality): Probit model, NOEC: Dunnett's Test (mortality), Bartlett's Test (reproduction)
Findings:	
Analytical data:	The mean measured concentrations ranged from 69.7 – 97.8 %
Effects:	See table 66

Table 66: Summary of effects of long-term exposure of NOA446510 on Daphnia magna

Treatment (mean measured concentrations in mg a.s./L)	**Adult mortality at day 21 (%)**	**Mean time to first brood (days)**	**Mean number of live offspring per female over 21 days**	**Mean length of parent (μm)**
Blank control	0	8.5	113	4086
Solvent control	0	8.4	100	4001
0.023	0	8.1	100	3952
0.085	0	8.3	107	3981
0.28	0	8.3	96	3945
0.87	0	8.3	91	3862*
2.64	0	11.0*	16*	3302*
NOEC	≥ 2.64 mg/L	0.87 mg/L	0.87 mg/L	0.28 mg/L
EC_{50}	--	--	1.64 mg/l	--

* Statistically significantly different from control ($p < 0.05$)

Conclusion: Mortality adult: NOEC ≥ 2.64 mg/L, LOEC > 2.64 mg/L
Reproduction: NOEC: 0.87 mg/L, LOEC: 2.64,
Length: NOEC 0.28 mg/L, LOEC 0.87 mg/L
EC_{50} (number of live offspring): 1.64 mg/L
based on mean measured concentrations

5.4.3 Algae and aquatic plants

Reference:	**Growth inhibition test of NOA 446510 to green algae (*Selenastrum capricornutum*) under static conditions**
Author(s), year:	Grade, R., 2001a
Report/Doc. number:	2013586
Guideline(s):	OECD 201
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable

Test substance:	Mandipropamid (NOA446510), purity: 99 ± 2 %, batch: KI-6380/1
Material and Methods:	
Test species:	Green alga (*Selenastrum capricornutum*)
Number of organisms:	1.03×10^4 cells/mL; 3 replicates of each concentration, 6 replicates of the medium control
Type of test, duration:	Static test, 72 h
Applied concentrations:	
Nominal:	0 (medium control), 0 (solvent control), 1.25, 2.5, 5.0, 10, 20, 40 mg/L
Measured (mean):	-- (medium control), -- (solvent control),1.15, 2.1, 4.2, 8.45, 17.9, 27.8 mg/L

Solvent	0.01 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Alga culture medium (according to OECD guideline), hardness 28 mg/L as $CaCO_3$
Temperature	22 ± 1 °C
pH	Treatments: 7.9 – 8.1 (0 h), 8.5 – 9.0 (72 h); control: 7.9 (0 h), 9.0 (72 h)
Incubation:	Continuous illumination with cool white fluorescent light (approx. 8000 lux), orbital shaking at 150 rpm
Test parameters:	Cell densities were measured using CytoFluor II (Fluorescence Multi-Well Plate Reader), growth rate and biomass were determined after 24, 48 and 72 hours; for chemical analysis (HPLC with UV-detection) of test the substance, samples of test solution were taken from freshly prepared test solution (0 h) and at the end of the exposure (72 h)
Statistics:	EC50 Logit analysis, NOEC: Dunnett's test (α = 0.05)
Findings:	
Analytical data:	Mean measured concentrations test ranged from 60.5 – 98 % (start) and from 78.5 to 89.5 % (end) of nominal concentrations.
Effects:	
Morphological effects:	None
Biomass & growth rate:	See table 67

Table 67: Effects of Mandipropamid (NOA446510) on the green alga S. capricornutum

NOA446510 [mg/L] nominal	**NOA446510 [mg/L] mean measured**	**Biomass (AUC) % inhibition in 72 h**	**Growth rate % inhibition in 72 h**
1.25	1.15	2	1
2.5	2.1	4	0
5.0	4.2	14	1
10	8.45	39	7
20	17.9	25	4
40	27.8	18	2
EC_{50} (0-72 h)		> 27.8 mg/L	> 27.8 mg/L
NOEC (0-72 h)		≥ 27.8 mg/L	≥ 27.8 mg/L

Conclusion: E_bC_{50} (0-72 h): > 27.8 mg/L, NOEC (0-72 h): ≥ 27.8 mg/L, E_rC_{50} (0-72 h): > 27.8 mg/L, NOEC (0-72 h): ≥ 27.8 mg/L based on mean measured concentrations

Reference:	**Growth inhibition test of NOA446510 tech. to Blue Algae (*Anabaena flos-aquae*) under static conditions**
Author(s), year:	Knauer, K., 2002
Report/Doc. number:	2023553
Guideline(s):	OECD 201
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable

Test substance:	Mandipropamid (NOA446510), purity: 96.5 %, batch: SEZ2BP007
Material and Methods:	
Test species:	Blue alga (*Anabaena flos-aquae*)
Number of organisms:	2.04×10^4 cells/mL; 3 replicates per each concentration, 6 replicates for the medium control
Type of test, duration:	Static test, 96 h

Applied concentrations:	
Nominal:	0 (medium control), 0 (solvent control), 1.25, 2.5, 5.0, 10, 20 mg/L
Measured (mean):	-- (medium control), -- (solvent control), 1.43, 2.8, 6.03, 13.7, 19.8 mg/L
Solvent	0.01 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Alga culture medium (according to OECD guideline), hardness 20 mg/L as $CaCO_3$
Temperature	23 ± 2 °C
pH	7.6 – 7.8 (0 h), 7.4 – 8.1 (72 h); control: 7.6 (0 h), 8.2 (96 h)
Incubation:	Continuous illumination with cool white fluorescent light (approx. 2000 lux), shaking rate at 100 rpm
Test parameters:	Cell densities were measured using CytoFluor II (Fluorescence Multi-Well Plate Reader), growth rate and biomass were determined after 24, 48, 72 and 96 hours; for chemical analysis (HPLC with UV-detection) of the test substance, samples of test solution were taken from freshly prepared test solution (0 h) and at the end of exposure (96 h)
Statistics:	EC_{50} Logit analysis, NOEC: Dunnett's test (α = 0.05)
Findings:	
Analytical data:	Mean measured concentrations ranged from 101 to157 % (start) and from 97 to 122 % (end) of nominal concentrations.
Effects:	
Morphological effects:	None
Biomass & growth rate:	See table below

Table 68: Effects of Mandipropamid (NOA446510) on the blue alga A. flos-aquae

NOA446510 [mg/L] nominal	**NOA446510 [mg/L] mean measured**	**Biomass (AUC) % inhibition in 96 h**	**Growth rate % inhibition in 96 h**
1.25	1.43	0.97	0
2.5	2.8	0	0
5.0	6.03	33	5.3
10	13.7	35	9.2
20	19.8	29	1.9
EC_{50} (0-96 h)		> 19.8 mg/L	> 19.8 mg/L
NOEC (0-96 h)		≥ 19.8 mg/L	≥ 19.8 mg/L

Conclusion: E_bC_{50} (0-96 h): > 19.8 mg/L, NOEC (0-96 h): ≥ 19.8 mg/L, E_rC_{50} (0-96 h): > 19.8 mg/L, NOEC (0-96 h): ≥ 19.8 mg/L based on mean measured concentrations

Reference:	**NOA-446510 - Toxicity to the Aquatic Higher Plant *Lemna gibba* in a 7-Day Static Growth Inhibition Test**
Author(s), year:	Bätscher, R., 2005
Report/Doc. number:	857050
Guideline(s):	OECD 221 (Draft October 2000)
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable

Test substance:	Mandipropamid (NOA446510), purity: 96.5 %, batch: SEZ2BP007
Material and Methods:	
Test species:	Duckweed (*Lemna gibba*)
Number of organisms:	12 fronds (3 colonies with 4 fronds) per vessel; 3 replicates for each concentration, control and solvent control
Type of test, duration:	Static test, 7 d
Applied concentrations:	
Nominal:	0 (medium control), 0 (solvent control), 0.1, 0.26, 0.64, 1.6, 4.0, 10 mg/L
Measured (mean):	-- (medium control), -- (solvent control), 0.1, 0.25, 0.62, 1.6, 3.0, 4.2 mg/L
Solvent	0.01 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	20XAP growth medium (according to OECD guideline), hardness 300 mg/L as $CaCO_3$
Temperature	23 ± 2 °C
pH	7.6 – 7.8 (0 h), 7.4 – 8.1 (72 h); control: 7.6 (0 h), 8.2 (96 h)
Incubation:	Continuous illumination with cool white fluorescent light (mean 7540 Lux) in a temperature controlled water bath
Test parameters:	Frond numbers were counted at 0, 3, 5 and 7 days to determine growth rate and biomass (AUC), final biomass was determined on the basis of dry weight; for chemical analysis (HPLC analysis with UV/VIS) of test the substance, samples of test solution were taken from freshly prepared test solutions (0 h) and at the end of exposure (7 d)
Statistics:	NOEC: Dunnett's test, one tailed (α = 0.05)
Findings:	
Analytical data:	Overall mean measured concentrations ranged from 42 % (10 mg/L) to 100 % (0.1 mg/L) of nominal.
Effects:	
Morphological effects:	None

Biomass & growth rate:	Doubling time T_d of the control = 2.0 d (fulfilled the validity criterion), see also table below

Table 69: Effects of Mandipropamid (NOA446510) on duckweed Lemna gibba

NOA446510 [mg/L] nominal	**NOA446510 [mg/L] mean measured**	**Biomass (AUC) % inhibition in 7 d**	**Growth rate % inhibition in 7 d**
solvent control	--	0.0	0.0
control	--	-1.1	-0.6
0.1	0.1	1.0	0.7
0.26	0.25	-2.6	-0.9
0.64	0.62	4.6	3.2
1.6	1.6	1.4	2.2
4.0	3.0	1.0	0.1
10	4.2	9.3*	6.8*
EC_{50} (0-7 d)		> 4.2 mg/L	> 4.2 mg/L
NOEC (0-7 d)		3.0 mg/L	3.0 mg/L

* Significant difference (α=0.05) from the control

Conclusion:	E_bC_{50} (7 d): > 4.2 mg/L, NOEC (7d): 3.0 mg/L, E_rC_{50} (7 d): > 4.2 mg/L, NOEC (7d): 3.0 mg/L, based on mean measured concentrations
Comment:	Mandipropamid is a fungicide and therefore a study on higher aquatic plants is not required according to directive 91/414/EEC. However, in general an exposition of *Lemna gibba* is possible and therefore the study is considered in the aquatic risk assessment.

5.4.4 Other aquatic organisms (including sediment)

Reference:	**NOA-446510 - A 96-Hour Flow-Through Acute Toxicity Test with the Saltwater Mysid (*Americamysis bahia*)**
Author(s), year:	Palmer, S., Kendall, T. & Krueger, H., 2005b
Report/Doc. number:	WIL 528A-137
Guideline(s):	EPA OPPTS 850.1035
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable.

Test substance:	Mandipropamid (NOA446510), purity: 96.1 %, batch: SEZ3BP007
Material and Methods:	
Test species:	Saltwater mysid (*Americamysis bahia*)
Number of organisms:	2 replicates each with 10 mysids per treatment and control
Age:	Juveniles < 24 hours old
Type of test, duration:	Flow-through test, 96 h

Applied concentrations:	
Nominal:	0 (control), 0 (solvent control) 0.65, 1.1, 1.8, 3.0, 5.0 mg/L
Measured (mean):	-- (control),-- (solvent control), 0.58, 0.94, 1.5, 2.3, 3.9 mg/L
solvent	0.1 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Filtered natural seawater diluted with well water, salinity: 20 ‰
Temperature	23.9 – 24.8 °C
pH	8.1 – 8.3 (0 h), 7.98 – 8.01 (48 h)
O_2 content:	> 60 %, 6.3 – 7.4 mg O_2/L
Light regime:	16 hours light / 8 hours darkness
Test parameters:	Mortality and sublethal effects were assessed after 7, 24, 48, 72 and 96 hours. For chemical analysis (HPLC method) of NOA446510 in the test solution samples were taken at 0, 24 and 96 hours.
Statistics:	EC_{50}: Probit analysis, NOEC: directly from the raw data
Findings:	
Analytical data:	Overall mean measured concentrations were in the range of 77 – 89 % of nominal concentrations.
Behavioural effects	At 1.5 mg/L and higher concentrations sublethal effects like erratic swimming, lethargy and loss of equilibrium were observed.
Mortality:	
Analytical data:	Overall mean measured concentration ranged from 77 – 89 % of nominal.
Effects:	See table below

Table 70: Cumulative mortality of saltwater mysids exposed to Mandipropamid

Mean measured concentration (mg/L)	**Cumulative mortality (%)**				
	7 hours	**24 hours**	**48 hours**	**72 hours**	**96 hours**
Control	0	0	0	0	0
Solvent control	0	0	0	0	0
0.58	0	0	0	0	0
0.94	0	5	10	10	10
1.5	0	5	15	20	30
2.3	0	40	45	55	85
3.9	0	20	95	100	100
NOEC = 0.58 mg/L					
LC_{50} (96 h) = 1.7 mg/L (95%CL 1.5 – 2.0 mg/L)					

Conclusion:	EC_{50} (48 h): 1.7 mg/L, NOEC: 0.58 mg/L based on mean measured conc.

Reference:	**NOA-446510 - A 96-Hour Flow-Through Shell Deposition Test with the Eastern Oyster (*Crassostrea virginica*)**
Author(s), year:	Palmer, S., Kendall, T. & Krueger, H., 2005c
Report/Doc. number:	WIL 528A-139
Guideline(s):	EPA OOPTS 850.1025
GLP:	Yes
Deviations:	None of relevance
Validity:	Acceptable

Test substance:	Mandipropamid (NOA446510), purity: 96.5 %, batch: SEZ2BP007
Material and Methods:	
Test species:	Eastern Oyster (*Crassostrea virginica*)
Number of organisms:	20 oysters per treatment and control
Length:	41.7 ± 2.6 mm
Type of test, duration:	Flow-through test, 96 h
Applied concentrations:	
Nominal:	0 (control), 0 (solvent control), 0.13, 0.25, 0.50, 1.0, 2.0 mg/L
Measured (mean):	-- (control),-- (solvent control), 0.13, 0.25, 0.46, 0.8, 1.6 mg/L
solvent	0.1 mL/L Dimethylformamide (DMF)
Test conditions:	
Water quality:	Filtered natural seawater diluted with well water, salinity: 20 ‰
Temperature	19.1 – 19.7 °C
pH	8.3 (0 h), 8.01 (96 h)
O_2 content:	> 60 %, 6.4 – 7.7 mg O_2/L
Light regime:	16 hours light / 8 hours darkness
Test parameters:	Observations of mortalities were made at 1, 24, 48, 72 and 96 hours, the shell growth was determined at test termination. For chemical analysis (HPLC method) of NOA446510 in the test solution samples were taken at 0, 48 and 96 hours.
Statistics:	EC_{50}, NOEC: Kruskal-Wallis (ANOVA) and Dunn's multiple comparison
Findings:	
Analytical data:	Overall mean measured concentrations were in the range of 80 – 100 % of nominal concentrations.
Mortality:	None
Shell Deposition:	See table below

Table 71: Mean shell deposition of eastern oysters (C. virginica) exposed to Mandipropamid

Mean measured concentration (mg/L)	Mean shell deposition (mm ± SD)	Inhibition of shell growth (%)
Pooled control [a)]	4.5 ± 1.1	--
0.13	4.0 ± 0.73	11
0.25	4.1 ± 1.2	8.9
0.46	4.3 ± 0.97	4.4

Mean measured concentration (mg/L)	Mean shell deposition (mm ± SD)	Inhibition of shell growth (%)
0.80	2.9 ± 1.3*	36
1.6	0.08 ± 0.36	68
NOEC = 0.46 mg/L		
EC_{50} (96 h) = 0.97 mg/L (95%CL 0.78 – 1.1 mg/L)		

[a)] no statistically significant difference between dilution control and solvent control

* statistically significant difference from the pooled control ($p \leq 0.05$)

Conclusion: EC_{50} (48 h): 0.97 mg/L, NOEC: 0.46 mg/L based on mean measured conc.

Summary and discussion: Acute (short-term) aquatic toxicity:

Data element: Acute (short-term) aquatic toxicity of the active substance Mandipropamid Generally expressed in terms of LC50 or EC50 (mg/L)				
	L(E)C50 [mg/L]	Test guideline / design	GLP (y/n)	Reliability
Fish (96 hr LC50):				
Oncorhynchus mykiss Rainbow trout	> 2.9[a)]	OECD 203	y	y
Pimephales promelas Fathead minnow	> 6.04 [a)]	OECD 203	y	y
Cyprinus carpio Common carp	> 2.0	OECD 203	y	y
Cyprinus carpio Common carp	8.63	OECD 203	y	y
Cyprinodon variegatus Sheephead minnow	4.5	US EPA OPPTS 850.1075	y	y
Crustacea (48 hr EC50):				
Daphnia magna	7.1	OECD 202	y	y
Algae and water plants: (ErC50)				
Selenastrum capricornutum Green alga	> 27.8 [a)] growth rate	OECD 201	y	y
Anabaena flos-aquae Blue alga	> 19.8 [a)] growth rate	OECD 201	y	y
Lemna gibba	> 4.4 (14d) growth rate	OECD 221 (Draft October 2000)	y	y
Other aquatic organisms (96 hr LC50):				
Americamysis bahia Saltwater mysid	1.7	EPA OPPTS 850.1035	y	y
Crassostrea virginica Eastern oyster	**0.97**	EPA OOPTS 850.1025	y	y
Conclusion: Based on the results from the acute aquatic tests, mandipropamid is very toxic to the most sensitive species the saltwater oyster *Crassostrea virginica* with an EC50 of 0.97 mg/L.				

[a)] highest tested concentration (maximal solubility of test the substance under test conditions)

Summary and discussion: Chronic (long-term) aquatic toxicity

Data element: Chronic (long-term) aquatic toxicity of the active substance Mandipropamid Generally expressed in terms of NOEC (mg/L)				
	NOEC [mg/L]	Test guideline / design	GLP (y/n)	Reliability
Fish (NOEC):				
Pimephales promelas	0.5 mortality growth	EPA OPPTS 850.1400	y	y
Crustacea (21 d NOEC,):				
Daphnia magna	**0.28** length	OECD 202, Part II 4	y	y
Algae and water plants: (NOEC)				
Selenastrum capricornutum Green alga	≥ 27.8	OECD 201	y	y
Anabaena flos-aquae Blue alga	≥ 19.8	OECD 201	y	y
Lemna gibba Duckweed	3.0	OECD 221 (Draft October 2000)	y	y
Conclusion: Mandipropamid is chronic toxic to fish and daphnids (*Daphnia magna*). The most sensitive species is *Daphnia magna* with a NOEC= 0.28 mg/L.				

Note: Aquatic toxicity studies for metabolites SYN 504851 and SYN 536638 are available but are missing for SYN 521195 and for the major metabolites in the sediment SYN521195 and SYN 539678. Thus a reliable classification regarding the hazardous to aquatic environment for all degradation products is not possible.

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

Endpoint	Classifcation Criteria (criteria in bold)		Evidence for Mandipropamid
	CLP (2nd ATP)	**DSD**	
Degradation			
Mandipropamid	Mandipropamid is not readily biodegradable under test conditions within 28 days. Ultimate degradation could not be shown in abiotic and biotic aquatic degradation studies. Available degradation studies with the exception of the hydrolysis studies indicate primary degradation, but due to missing data on aquatic toxicity of some degradants it is not possible to show that the metabolites are not classified as hazardous to the aquatic environment. Therefore a non rapid degradation is proposed.		The classification as **R53** according to Directive 67/548/EEC is based on the fact that the active substance is not considered as ready biodegradable/rapid degradable.
Bioaccumulation			
Criteria LogKow	**Log K_{ow} is < 4** Mandipropamid Log K_{ow} = 3.2	**Log K_{ow} is < 3** Mandipropamid Log K_{ow} = 3.2	The measured BCF after normalization to 11 % lipid content is in the range of 35 and 48 and is below the two classification criteria of 100 (DSD) and 500 (CLP), therefore Mandipropamid is considered to have **a low bioaccumulation potential.**
Criteria BCF	**BCF < 500** Mandipropamid BCF is in the range of 35 and 48	**BCF < 100** Mandipropamid BCF is in the range of 35 and 48	
Acute aquatic toxicity			
Criteria	**LC/EC_{50} ≤ 1 mg/L**		Mandipropamid is of high acute toxicity to saltwater oyster Crassostrea virginica with an EC50 of 0.97 mg/L and fulfills the criteria for the proposed classification as **R50** according to Directive 67/548/EEC and the criteria for the proposed classification as **H400** according to Regulation EC 1272/2008. **A M-factor of 1** is applicable based on 0.1 <$L(E)C_{50}$ ≤1 mg/l.
	Crassostrea virginica EC50 = 0.97 mg/L		

Endpoint	**Classifcation Criteria (criteria in bold)**			**Evidence for Mandipropamid**
	CLP (2nd ATP)		**DSD**	
Chronic aquatic toxicity				
Criteria	**For non rapidly degradable substances: 0.1 <NOEC ≤1 mg/l**			Mandipropamid is chronic toxic to daphnids (*Daphnia magna*) with a NOEC= 0.28 mg/L. Therefore Mandipropamid fulfills the criteria for the proposed classification as **H411** according to Regulation EC 1272/2008.
	Daphnia magna	NOEC(21d) = 0.28mg/L		

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

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

Mandipropamid 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

Conclusion of environmental classification according to Regulation EC 286/2011 (2nd ATP to EC 1272/2008)

Based on the CLP Regulation, mandipropamid should be classified as:

Classification categories	aquatic environmental hazard **acute category 1** aquatic environmental hazard **chronic category 2**	
GHS Pictogram		
Signal Word	Warning	
Hazard Statement	H400 H411	'Very toxic to aquatic life', 'Toxic to aquatic life with long lasting effects'
M-factor (acute)	1	

6 OTHER INFORMATION

Environmental fate properties and environmental hazard assessments of this CLH report are based on studies and summaries of the Draft Assessment Report and its addenda

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

The DS proposes to classify mandipropamid for aquatic environment hazards in acute category 1 with M = 1, and in chronic category 2. The proposal is mainly based on the information presented in the draft assessment report (DAR) of mandipropamid under Directive 91/414/EEC.

Mandipropamid shows limited solubility in water with a measured value of 4.2 mg/L in pure water (substance purity = 990 g/kg, 25°C, OECD TG 105), while some reported maximum test concentrations in ecotoxicity studies were lower (2.0 mg/L) or higher (up to 28 mg/L). The purity of mandipropamid batches in ecotoxicity tests ranged from 96.1 to 99 %.

Degradation

Mandipropamid was hydrolytically stable in a study conducted in sterile buffer solutions at pH values of 4, 5, 7, and 9 (50°C over 7 days, 25°C over 32 days).

Biodegradation was studied in a ready biodegradability test. After 28 days less than 5% was degraded (measured as chemical oxygen demand, COD).

Several water/sediment degradation studies indicated primary degradation with mean half-lives of ca 14 days, but mineralisation after 100 days under aerobic conditions was limited to around 4% or 30-35%, depending on the radio-labelled moiety. Due to missing data on aquatic toxicity of several degradants, it was not possible to show that the metabolites are not classifiable. In conclusion the DS proposes to consider mandipropamid as not rapidly degradable.

Bioaccumulation

The measured log Kow of mandipropamid was 3.2 at 25°C and showed no pH-dependency. A fish bioaccumulation study (OECD TG 305, *Pimephales promelas*) was performed with test concentrations of 32 µg/L and 3.2 µg/L, using dimethylformamide as a dispersing agent. The flow-through test was conducted with 190 hrs exposure and 195 hrs depuration phases. Plateau concentrations were reached after 48 hrs, and the test resulted in BCF values of 35 (low conc.) and 48 (high conc.) for the whole body (overall mean lipid content of 11% used for normalisation). In conclusion the DS suggested that mandipropamid shows low potential for bioaccumulation.

Acute aquatic toxicity

Several acute and chronic aquatic toxicity data were available. The toxicity studies followed guideline standards and were throughout marked as GLP studies and reliable by the dossier submitter.

In relation to short-term aquatic hazards, while no effects were observed in three tests with algae and aquatic plants (duckweed), mortalities in two out of five short-term fish tests (with carp and sheephead minnow) were observed at concentrations starting from ca. 7 and 4 mg/l, with calculated LC_{50} values of 8.6 and 4.5 mg/l, respectively.

Three short-term tests with invertebrates were reported: a 48hrs water flea test according to OECD TG 202 resulted in a calculated LC_{50} of 7.1 mg/l (nominal, mean measured concentrations were 96 to 110%). In a 96hrs flow-through test with saltwater mysid the calculated LC50 based on measured concentrations was 1.7 mg/l (NOEC 0.58 mg/l). Another acute toxicity test was available for the Eastern oyster, following the US EPA test guideline

OPPTS 850.1025, with 96 hrs test duration resulting in an EC_{50} (shell deposition) of 0.97 mg/l.

In conclusion, the DS proposed to classify mandipropamid for short-term aquatic hazards as Aquatic Acute with M = 1.

Chronic aquatic toxicity
One 28d early life stage test with fathead minnow was reported, with a NOEC of 0.5 mg/l and a LOEC of 1.0 mg/l (nominal, mean measured concentrations were 87 to 100%) for growth (weight and length) as well as for mortality of hatched fish larvae. Moreover, the DS reported one semi-static 21d reproduction test with water fleas according to OECD TG 202, Part II (now TG 211), with NOECs of 0.28 (growth, length), 0.87 (reproduction), and ≥ 2.64 mg/l (mortality), reported as mean measured concentrations.

In conclusion, considering the long-term data and the the lack of rapid degradation, the DS proposed to classify mandipropamid for long-term aquatic hazards as Aquatic Chronic 2.

Comments received during public consultation
Five comments were received from four MSs and one manufacturing company. All MSs supported the classification proposed by the DS, either in general or by specifying agreement with no classification for human health hazard classes or with specific reference to the justification for the proposed environmental classification. Industry informed about another Daphnia reproduction study (Minderhout et al. 2009, report no. 528A-181B) which had not been considered in the submitted dossier. In contrast to the MS comments, industry disagrees with the proposed classification based on the acute toxicity study with Eastern oyster, arguing that shell deposition in oyster cannot be considered as an endpoint equivalent to the crustacean 48 hour EC_{50}.
The company suggests the acute fish (*Oncorhynchus mykiss*) test result of LC_{50} > 2.9 mg/l (without further specification for this selection from the five available fish tests) as "the most sensitive and appropriate" value resulting in a R51 (DSD) classification.

After public consultation the DS agreed that the provided additional chronic study on daphnids justifies classification as Aquatic Chronic 1.

Additional key elements
The RAC Rapporteurs assessed the full study report of the additional *Daphnia magna* reproduction study (Minderhout et al. 2009) and noted that the 21d semi-static test was conducted in compliance with the OECD TG 211 and GLP. Therefore they considered this study as reliable and acceptable. Technical mandipropamid with 96.1% active ingredient was used as test substance with mean measured (nominal) concentrations of 0.039 (0.038), 0.076 (0.075), 0.150 (0.150), 0.292 (0.300), and 0.551 (0.600) mg/l. The NOEC for growth reduction (length, dry weight) and reproduction (reduced numbers of neonates) was 0.076 mg/l (LOEC = 0.15 mg/l, EC50 for reproduction = 0.226 mg/ll).

A robust study summary of this additional test is given below:

21-day reproductive and growth test on *Daphnia magna* exposed to mandipropamid[1]

A 21-days test was performed by Minderhout et al. (2009) to study the effects of mandipropamid on growth and reproduction of the water flea (*Daphnia magna*). The used study protocol was based on US EPA TG 850.1300, OECD TG 211 and ASTM E1193-97. Static-renewal conditions were applied and the exposure waters were renewed every 48 hrs except over the weekends every 72 hrs. Ten replicate test chambers per test concentration (20 chambers for the control group) were used each having one individual at the beginning of the

experiment. Only neonates (<24 hrs old) were selected for the study and were exposed to five mandipropamid (purity 96.1%) concentrations. The measured mandipropamid concentrations varied less than 20% between water renewals at all exposure concentrations; at some concentrations the variation between any newly prepared and "the used" exposure waters was less than 10%. Mandipropamid concentrations in the negative controls were below the detection limit (<0.02 mg/l).

During the course of the study the first generation daphnids were observed daily for mortality, onset of reproduction and clinical signs of toxicity. Following the onset of reproduction, the numbers of the 2nd generation was followed three times a week. At the end of the study body weight and dry weight of the survived first generation were measured.

Survival rate of the first generation adults varied from 70% to 90% and was not statistically significant in any mandipropamid concentration when compared to the negative control (Exact test p≥0.05). Mean number of neonates per surviving adult was highest in the control group and the neonate production in the two lowest mandipropamid concentrations did not differ significantly from the control. However, the number of neonates per adult at the three highest concentrations were significantly lower (p<0.05, Dunnett's test) than in the control group. Similarly, the mean length and weight of the surviving adults were significantly lower in the three highest concentrations (p<0.05) than in the control group. Since statistically significant effect on reproduction and growth was not observed at or below 0.076 mg/l of mandipropamid, it can be used as the NOEC value of this study.

Summary of survival, reproduction and growth of Daphnia magna exposed to mandipropamid for 21 days.

Mean measured concentration (µg a.i./L)	Percent Adult Survival	Mean number of Neonate per Surviving Adult	Mean length ± Std. Dev. (mm)	Mean Dry Weight ± Std Dev. (mg)
Negative control	85	220±23	5.2±0.18	0.82±0.11
0.039	80	218±23	5.3±0.23	0.80±0.12
0.076	80	214±20	5.3±0.15	0.84±0.077
0.150	70	138±43	4.7±0.38	0.59±0.20
0.292	80	85±19	4.2±0.29	0.74±0.069
0.551	90	41±21	3.7±0.33	0.37±0.16

Assessment and comparison with the classification criteria

Degradation
The RAC agrees with the DS's proposal to consider mandipropamid as not rapidly degradable. The substance is hydrolytically stable at all pH from 4 to 9. In a ready biodegradability test the measured biodegradation was < 5%. Moreover, several water/sediment studies showed primary degradation but mineralisation was well below 70% within 28d (4 or 30-35% after 100d). In addition, insufficient information is available regarding classification of several relevant degradation products.

Bioaccumulation
A log Kow of 3.2 at 25°C without pH-dependency was measured, i.e. below the CLP cut-off criterion of 4 Likewise, measured BCFs of 35 for the low and 48 for the high concentration)

were also well below the CLP cut-off criterion of 500. The RAC therefore agrees with the DS's conclusion that mandipropamid shows no potential for bioaccumulation according to the classification criteria.

Aquatic Toxicity
Studies are available for both acute and chronic aquatic toxicity.

Acute toxicity
Most of the reported acute toxicity test results, i.e. for fish and crustaceans, are above the 1 mg/l cut-off value for CLP Category Acute 1. Some values, e.g. 8.7 mg/l even exceed the limit of water solubility determined with a test conducted according to the OECD TG 105 in pure water (4.2 mg/l).

However, another test, i.e. an oyster acute toxicity test (shell deposition), resulted in an EC_{50} consistently lining up at the lower end of the other acute test results, with a value of 0.97 mg/l just under the 1 mg/l cut-off value. While this 96hrs acute test with Eastern Oyster is rather rarely available in Europe for regulatory decisions on classification, the RAC notes that it has been conducted according to the US-EPA Ecological Effects Test Guideline OPPTS 850.1025, which is validated as a standardised test method and designed for measuring acute toxicity using the shell deposition endpoint. In principle, classification is based on the principle of using results from adequately designed and conducted standard tests with organisms from only a few taxonomic groups and with selected measurements (endpoints), provided that they can be considered as relevant surrogates for all aquatic organisms. The RAC considers that this prerequisite is fulfilled for the acute oyster test.

The corresponding acute M-factor for $0.1 < 0.97 \leq 1.0$ mg/l is 1.

Chronic toxicity
Three conclusive results from chronic toxicity tests are available, two of them meeting the NOEC ≤ 1 mg/l criterion for CLP Category Chronic 2 (non-rapidly degradable substances), i.e. the NOEC of 0.5 mg/l in a fish early life stage test, and the NOECs of 0.87 and 0.27 mg/l for reproduction and growth (length), respectively, in a water flea reproduction test.

Conclusive results from the additional *Daphnia* reproduction test, i.e. the NOEC of 0.076 mg/l for growth (length) and reproduction, do however meet the NOEC ≤ 0.1 mg/l criterion for CLP Aquatic Chronic 1 (non-rapidly degradable substances). The corresponding chronic M-factor for $0.01 < 0.076 \leq 0.1$ mg/l is 1.

Conclusion on classification
Mandipropamid is considered as **non-rapidly degradable**. Its bioaccumulation potential is low and does not meet the criteria for classification.

Overall, the available acute and chronic toxicity test data allow a complete evaluation for short- and long-term environmental hazards.

For both acute and chronic data, the relevant toxicity range is within just one order of magnitude. The lowest values, however, meet the respective cut-off criteria for acute and chronic categories 1.

Acute toxicity to fish and crustaceans were in the same range as the acute mollusc test that had the lowest acute toxicity value and was used as the decisive study for short-term hazard classification. Algae and other aquatic plants were not affected at the applied test concentrations of mandipropamid.

The *Daphnia* reproduction test provided during the PC, the RAC concludes that the DS's original proposal for chronic toxicity is not justified. However, the RAC agrees with the DS's response to

the public consultation comment that Aquatic Chronic 1 is justified based on the new chronic toxicity data.

In summary, the RAC concludes that the environmental hazard classification of mandipropamid is Aquatic **Acute 1 (H400) with M = 1** and Aquatic **Chronic 1 (H410) with M = 1** according to CLP.

The RAC agrees with the dossier submitter's proposal that mandipropamid should be classified as N; R50-53 according to DSD since its acute aquatic toxicity is below 1 mg/l (oyster) and it is not readily degradable. The corresponding specific concentration limits are:

N; R50-53: C ≥ 25%
N; R51-53: 2.5% ≤ C <25%
R52-53: 0.25% ≤ C < 2.5%

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
Das, R.	2002a	Melting point / melting range of NOA 446510 Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 109673 GLP Not Published Syngenta File N° NOA446510/0024	Y	SYN
Das, R.	2003a	Boiling point / boiling range of NOA 446510 Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 109674 GLP Not Published Syngenta File N° NOA446510/0038	Y	SYN
Vehling, H.	2005	Thermal stability / stability in air Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Process Hazards Section, Huddersfield, United Kingdom, Report No HT05/284 GLP Not Published Syngenta File N° NOA446510/0401	Y	SYN
Füldner, H.	2003	Density of solids of NOA 446510 Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L02-009577 GLP Not Published Syngenta File N° NOA446510/0031	Y	SYN
Geoffroy, A.	2003	Vapour pressure curve of NOA 446510 Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L03-002392 GLP Not Published Syngenta File N° NOA446510/0064	Y	SYN
Das, R.	2006d	NOA 446510 - Statement on Method used for	Y	SYN

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
		vapour pressure Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 10115200 not GLP Not Published		
Baker, S.D.	2005	Henry's law constant Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection, Guildford, United Kingdom Syngenta File N° NOA446510/0445	Y	SYN
Das, R.	2002b	General physico-chemical properties of NOA 446510 Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 109670 GLP Not Published Syngenta File N° NOA446510/0025	Y	SYN
Das, R.	2005a	NOA 446510 tech. - Color, physical state and odor Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 114667 GLP Not Published Syngenta File N° NOA446510/0376	Y	SYN
Oggenfuss, P.	2004	NOA 446510 - Spectra Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 111640 GLP Not Published Syngenta File N° NOA446510/0082	Y	SYN
Das, R.	2003b	Water solubility of NOA 446510 Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 109671 GLP Not Published	Y	SYN

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
		Syngenta File N° NOA446510/0026		
Das, R.	2006a	NOA 446510 - Statement on Method used for water solubility Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 10115199 not GLP Not Published	Y	SYN
Das, R.	2004a	CGA 380775 - Water solubility Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113111 GLP Not Published Syngenta File N° CGA380775/0001	Y	SYN
Das, R.	2004b	CGA 380778 - Water solubility Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 112389 GLP Not Published Syngenta File N° CGA380778/0001	Y	SYN
Das, R.	2004c	SYN 500003 - Water solubility Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113440 GLP Not Published Syngenta File N° SYN500003/0001	Y	SYN
Das, R.	2005b	SYN 504851 - Water solubility Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113684 GLP Not Published Syngenta File N° SYN504851/0005	Y	SYN
Das, R.	2004d	SYN 535839 - Water solubility Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113301	Y	SYN

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		GLP Not Published Syngenta File N° SYN535839/0001		
Das, R.	2005c	SYN 536638 - Water solubillity Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113638 GLP Not Published Syngenta File N° SYN536638/0001	Y	SYN
Das, R.	2005d	NOA 458422 - Water solubility Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113718 GLP Not Published Syngenta File N° CA4011/0005	Y	SYN
Das, R.	2005e	NOA 446510 tech. - Solubility in organic solvents Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 114668 GLP Not Published Syngenta File N° NOA446510/0375	Y	SYN
Das, R.	2006b	NOA 446510 - Statement on Method used for solubility in organic solvents Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 10115182 not GLP Not Published	Y	SYN
Das, R.	2003c	Octanol / water partition coefficient of NOA 446510 Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 109672 GLP Not Published Syngenta File N° NOA446510/0027	Y	SYN
Das, R.	2006c	NOA 446510 - Statement on Method used for	Y	SYN

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		Octanol/Water Partition Coefficient Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 10115098 not GLP Not Published		
Das, R.	2005f	CGA 380775 - Octanol / water partition coefficient Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113112 GLP Not Published Syngenta File N° CGA380775/0003	Y	SYN
Das, R.	2004e	Octanol / water partition coefficient Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 112390 GLP Not Published Syngenta File N° CGA380778/0002	Y	SYN
Das, R.	2005g	SYN 500003 - Octanol / water partition coefficient Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113441 GLP Not Published Syngenta File N° SYN500003/0006	Y	SYN
Das, R.	2005h	Octanol/water parition coefficient Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113685 GLP Not Published Syngenta File N° SYN504851/0008	Y	SYN
Das, R.	2004f	Octanol/water partition coefficient Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113302 GLP	Y	SYN

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Das, R.	2005i	SYN 536638 - Octanol / water partition coefficient Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113639 GLP Not Published Syngenta File N° SYN536638/0002	Y	SYN
Das, R.	2005j	NOA 458422 - Octanol/water partition coefficient Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection Münchwilen AG, Münchwilen, Switzerland, Report No 113720 GLP Not Published Syngenta File N° CA4011/0007	Y	SYN
Buckel, T	2002	Hydrolysis of [Ethyl-1- 14C]-labelled NOA446510 under Laboratory Conditions Syngenta Crop Protection AG, Basel, Switzerland, Report No 02TB01 GLP Not Published Syngenta File N° NOA446510/0018	Y	SYN
Hand, L H	2003	Aqueous Photolysis of 14C-Methoxyphenyl-NOA446510 under Laboratory Conditions Syngenta - Jealott's Hill International, Bracknell, Berkshire, United Kingdom, Report No RJ3395B GLP Not Published Syngenta File N° NOA446510/0041	Y	SYN
Schmidt, E.	2004	Quantum yield of the direct photochemical degradation of NOA 446510 in aqueous solution Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L02-009816 GLP Not Published Syngenta File N° NOA446510/0118	Y	SYN

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Martin, N.	2003	Dissociation constant of NOA 446510 in water Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L02-009578 GLP Not Published Syngenta File N° NOA446510/0029	Y	SYN
Martin, N.	2004a	Dissociation constant of CGA 380775 in water Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L04-006774 GLP Not Published Syngenta File N° CGA380775/0002	Y	SYN
Martin, N.	2004b	Dissociation constant of CGA 380778 in water Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L04-006773 GLP Not Published Syngenta File N° CGA380778/0004	Y	SYN
Martin, N.	2004c	Dissociation constant of SYN 500003 in water Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L04-007084 GLP Not Published Syngenta File N° SYN500003/0002	Y	SYN
Richner, D.	2005a	Dissociation constant of SYN 504851 in water Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L04-008071 GLP Not Published Syngenta File N° SYN504851/0004	Y	SYN
Martin, N.	2004d	Dissociation constant of SYN 535839 in water Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L04-	Y	SYN

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		006772 GLP Not Published Syngenta File N° SYN535839/0003		
Martin, N.	2005	Dissociation constant of SYN 536638 in water Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L04-007792 GLP Not Published Syngenta File N° SYN536638/0003	Y	SYN
Richner, D.	2005b	Dissociation constant of NOA 458422 in water Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L05-000123 GLP Not Published Syngenta File N° CA4011/0006	Y	SYN
Widmer, H	2003	Atmospheric Oxidation of NOA446510 by Hydroxyl Radicals; Rate Estimation Syngenta Crop Protection AG, Basel, Switzerland, Report No 95A2003006WI Not GLP Not Published Syngenta File N° NOA446510/0035	Y	SYN
Jackson, W.	2005a	Flammability (solids) Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Process Hazards Section, Huddersfield, United Kingdom, Report No HT05/280 GLP Not Published Syngenta File N° NOA446510/0405	Y	SYN
Jackson, W.	2005b	Relative self-ignition temperature for solids Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Process Hazards Section, Huddersfield, United Kingdom, Report No HT05/282 GLP Not Published Syngenta File N° NOA446510/0403	Y	SYN

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Jackson, W.	2005c	Explosive properties Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Process Hazards Section, Huddersfield, United Kingdom, Report No HT05/281 GLP Not Published Syngenta File N° NOA446510/0404	Y	SYN
Richner, D.	2005c	Surface tension of NOA 446510 tech. Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L05-002772 GLP Not Published Syngenta File N° NOA446510/0426	Y	SYN
Jackson, W.	2005d	Oxidising properties Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Process Hazards Section, Huddersfield, United Kingdom, Report No HT05/283 GLP Not Published Syngenta File N° NOA446510/0402	Y	SYN

7.2 Human health hazard assessment

Author(s)	Annex point/ reference number	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
Annex II Data and Information					
Barlow, S.	KIIA 5.8.1	2005	Threshold of Toxicological Concern (TTC) A tool for assessing substances of unknown toxicity present at low levels in the diet	N	
Brammer, A.	KIIA 5.3.4/01	2005 b	NOA 446510: 1 Year Oral Toxicity Study in Dogs Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No PD1273-REG GLP Not Published Syngenta File N° NOA446510/0521	Y	SYN
Callander, R.	KIIA 5.4.1/01	2005	NOA446510: Bacterial Mutation Assay In S Typhimurium And E.Coli Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No YV6190/REV-001 GLP Not Published Syngenta File N° NOA446510/0487	Y	SYN
Callander, R. D.	KIIA 5.8.1/02	2006	SYN 500003: Bacterial Mutation Assay in S. Typhimurium and E. Coli Syngenta Central Toxicology Laboratory, Alderley Park, Cheshire Report No YV7195-REG GLP Not Published Syngenta File N° T003954-05	Y	SYN
Callander, R. D.	KIIA 5.8.2/01	2006	SYN 545038: Bacterial Mutation Assay in S. Typhimurium and E. Coli Syngenta Central Toxicology Laboratory, Alderley Park, Cheshire Report No YV7241-REG GLP Not Published Syngenta File N° T013670-05	Y	SYN

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Clay, P.	KIIA 5.4.3/01	2002	NOA446510: L5178Y TK+/- mouse lymphoma mutation assay Syngenta Limited, Cheshire, United Kingdom Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No CTL/VV0286/REG/REPT/REV-001 GLP Not Published Syngenta File N° NOA446510/0014	Y	SYN
Clay, P.	KIIA 5.4.5/01	2005	NOA446510: In Vivo Rat Liver Unscheduled DNA Synthesis Assay Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No SR1193 GLP Not Published Syngenta File N° NOA446510/0438	Y	SYN
Fox, V.	KIIA 5.4.2/01	2002	NOA446510: In vitro cytogenetic assay in human lymphocytes Syngenta Limited, Cheshire, United Kingdom Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No CTL/SV1144/REG/REPT GLP Not Published Syngenta File N° NOA446510/0015	Y	SYN
Fox, V.	KIIA 5.4.4/01	2005	NOA446510: Mouse Bone Marrow Micronucleus Test Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No SR1176 GLP Not Published Syngenta File N° NOA446510/0486	Y	SYN

Author(s)	**Annex point/ reference number**	**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, I.	KIIA 5.2.4/01	2004a	MANDIPROPAMID: Skin Irritation Study in the Rabbit Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Alderley Park, Macclesfield, Cheshire, United Kingdom Report No CTL/EB4953 GLP Not Published Syngenta File N° NOA446510/0106	Y	SYN
Johnson, I.	KIIA 5.2.5/01	2004b	MANDIPROPAMID: Eye Irritation Study in the Rabbit Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Alderley Park, Macclesfield, Cheshire, United Kingdom Report No CTL/FB5931 GLP Not Published Syngenta File N° NOA446510/0113	Y	SYN
Johnson, I.	KIIA 5.2.6/01	2004c	NOA446510: Local Lymph Node Assay Syngenta Limited, Cheshire, United Kingdom Central Toxicology Laboratory (CTL), Alderley Park, Macclesfield, Cheshire, United Kingdom Report No CTL/GM7664 GLP Not Published Syngenta File N° NOA446510/0096	Y	SYN
Kilgour J., Lister N.	KIIA 5.8.1	2006	Case for non-relevance using a Threshold of Toxicological Concern (TTC) approach	N	
Kilgour, J.	KIIA 5.2.3/01	2003	MANDIPROPAMID: 4-Hour acute inhalation toxicity study in rats (EPA and OECD) Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Alderley Park, Macclesfield, Cheshire, United Kingdom Report No CTL/HR2410/REG/REPT GLP Not Published Syngenta File N° NOA446510/0030	Y	SYN

Author(s)	**Annex point/ reference number**	**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**
Kilgour, J. D. et al	KIIA 5.8.2/02	2006	Statement: Mandipropamid (NOA446510) Impurities: Relevance of Potentially Significant Impurities in Relation to the Technical Specification	Y	SYN
Kroes, R.	KIIA 5.8.1	2003	Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet	N	
Kuhn, J.	KIIA 5.2.2/01	2005	NOA-446510 Technical (Batch SEZ2BP007) - Acute Dermal Toxicity Study in Rats Syngenta Crop Protection AG, Basel, Switzerland Stillmeadow Inc., Houston, United States Report No 9169-05 T003767-05 GLP Not Published Syngenta File N° NOA446510/0504	Y	SYN
Lees, D.	KIIA 5.3.7/01	2005	NOA 446510: 21/28 Day Dermal Toxicity Study In Rats Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No LR0596-REG GLP Not Published Syngenta File N° NOA446510/0568	Y	SYN
Milburn, G.	KIIA 5.5.3/01	2005 a	NOA 446510: 80 Week Carcinogenicity Study In Mice Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No PM1275/REG GLP Not Published Syngenta File N° NOA446510/0562	Y	SYN
Milburn, G.	KIIA 5.6.1/01	2005 b	NOA 446510:Two Generation Reproduction Toxicity Study In Rats Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No RR0990/REG GLP Not Published Syngenta File N° NOA446510/0565	Y	SYN

Author(s)	**Annex point/ reference number**	**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**
Milburn, G.	KIIA 5.7.1/01	2005c	NOA 446510: Acute Neurotoxicity Study in Rats Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No AR7352-REG GLP Not Published Syngenta File N° NOA446510/0513	Y	SYN
Moore, G.	KIIA 5.2.1/01	2004	Acute Oral Toxicity Up and Down Procedure in Rats Syngenta Crop Protection AG, Basel, Switzerland Product Safety Labs, East Brunswick, United States Report No 14702 GLP Not Published Syngenta File N° NOA446510/0092	Y	SYN
Moxon, M.	KIIA 5.6.10/01	2005a	NOA 446510:Prenatal Developmental Toxicity Study in Rats Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No RR0963-REG GLP Not Published Syngenta File N° NOA446510/0531	Y	SYN
Moxon, M.	KIIA 5.6.11/01	2005b	NOA 446510:Prenatal Developmental Toxicity Study In The Rabbit Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No RB0962/REG GLP Not Published Syngenta File N° NOA446510/0543	Y	SYN

Author(s)	**Annex point/ reference number**	**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**
Pinto, P.	KIIA 5.3.2/01	2005 a	MANDIPROPAMID:90 Day Dietary Toxicity Study In Rats Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Alderley Park, Macclesfield, Cheshire, United Kingdom Report No CTL/PR1263/REG/RE GLP Not Published Syngenta File N° NOA446510/0535	Y	SYN
Pinto, P.	KIIA 5.5.2/01	2005 b	NOA 446510:Two Year Chronic Toxicity And Carcinogenicity Study In Rats Syngenta Crop Protection AG, Basel, Switzerland Syngenta Limited, Cheshire, United Kingdom, Report No PR1274-Reg GLP Not Published Syngenta File N° NOA446510/0560	Y	SYN
Pinto, P.	KIIA 5.7.4/01	2005 c	NOA 446510: Subchronic Neurotoxicity Study In Rats Syngenta Crop Protection AG, Basel, Switzerland Central Toxicology Laboratory (CTL), Cheshire, United Kingdom, Report No PR1294/REG GLP Not Published Syngenta File N° NOA446510/0508	Y	SYN
Pooles, A.	KIIA 5.8.1/01	2006	SYN 500003: Acute Oral Toxicity in the Rat – Up and Down Procedure Syngenta Central Toxicology Laboratory, Alderley Park, Cheshire Safepharm Laboratories Limited, Shardlow Business Park, Derbyshire, SPL Project No 0006/0737 GLP Not Published	Y	SYN
Renwick A.G.	KIIA 5.8.1	2005	Structure-based thresholds of toxicological concern: guidance for application to substances present at low levels in the diet	N	

Author(s)	**Annex point/ reference number**	**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**
Roberts, K.	KIIA 5.1/02	2005 a	NOA 446510: Tissue depletion following a single oral dose (3 mg/kg and 300 mg/kg) in the rat Central Toxicology Laboratory (CTL), Alderley Park, Macclesfield, Cheshire, United Kingdom Report No CTL/UR0761/REG/REPT GLP Not published Syngenta File N° NOA446510/0533	Y	SYN
Roberts, K.	KIIA 5.1/03	2005 b	NOA 446510: Tissue accumulation and depletion following multiple oral dosing (3 mg/kg) in the rat Central Toxicology Laboratory (CTL), Alderley Park, Macclesfield, Cheshire, United Kingdom Report No CTL/UR0786/REG/REPT GLP Not published Syngenta File N° NOA446510/0527	Y	SYN
Silcock, R. and Duerden, A.	KIIA 5.1/01	2005	NOA 446510: Absorption, distribution and excretion in the rat Central Toxicology Laboratory (CTL), Alderley Park, Macclesfield, Cheshire, United Kingdom Report No CTL/UR0719/REG/REPT GLP Not published Syngenta File N° NOA446510/0563	Y	SYN
Wake, A.	KIIA 5.1/04	2005	NOA 446510: Biotransformation in the rat Central Toxicology Laboratory (CTL), Alderley Park, Macclesfield, Cheshire, United Kingdom Report No CTL/UR0758/REG/REPT GLP Not published Syngenta File N° NOA446510/0561	Y	SYN

7.3 Environmental hazard assessment

7.3.1 Fate and Behaviour in the environment

Author(s)	Annex point/ reference number	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
Adam, D.	KIIA 7.4.2/01	2004	Adsorption/desorption of 14C-CGA 380778 on Various Soils Syngenta Crop Protection AG, Basel, Switzerland RCC Ltd., Itingen, Switzerland, Report No 855381 GLP Not Published Syngenta File N° CGA380778/0005	Y	SYN
Adam, D.	KIIA 7.4.2/08	2005	Adsorption / Desorption of SYN539679 on Soils Syngenta Crop Protection AG, Basel, Switzerland RCC Ltd., Itingen, Switzerland, Report No A04037 GLP Not Published Syngenta File N° SYN539679/0001	Y	SYN
Berdat, T., Nicollier, G.	KIIA 7.2.3/01	2005a	Rate of Degradation of [14C]CGA 380778 (Metabolite of NOA 446510) in Various Soils under Aerobic Laboratory Conditions at 20oC Syngenta Crop Protection AG, Basel, Switzerland, Report No T004943-04 GLP Not Published Syngenta File N° CGA380778/0010	Y	SYN
Berdat, T., Nicollier, G.	KIIA 7.2.3/05	2005b	Rate of Degradation of [Chlorophenyl-U-14C]-labelled SYN 521195 (Metabolite of NOA446510) in Various Soils under Aerobic Laboratory Conditions at 20°C Syngenta Crop Protection AG, Basel, Switzerland, Report No T013941-04 GLP Not Published Syngenta File N° SYN521195/0003	Y	SYN
Berdat, T., Nicollier, G.	KIIA 7.4.2/06	2004	Adsorption / Desorption of NOA 458422 in Various Soils Syngenta Crop Protection AG, Basel, Switzerland, Report No T013298-04	Y	SYN

Author(s)	Annex point/ reference number	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
			GLP Not Published Syngenta File N° CA4011/0004		
Bramley, Y., Oliver, S.	KIIA 7.1.3/02	2005	Soil Photolysis of 14C-Chlorophenyl Ring Labelled NOA446510 under Laboratory Conditions Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3535B GLP Not Published Syngenta File N° NOA446510/0236	Y	SYN
Buckel, T	KIIA 7.5/01	2002	Hydrolysis of [Ethyl-1- 14C]-labelled NOA446510 under Laboratory Conditions Syngenta Crop Protection AG, Basel, Switzerland, Report No 02TB01 GLP Not Published Syngenta File N° NOA446510/0018	Y	SYN
Clark, A.	KIIA 7.1.1/03 KIIA 7.2.1/03	2004	Metabolism of [^{14}C-Chlorophenyl]-NOA-446510 in Viable Soil under Aerobic Conditions Syngenta Crop Protection AG, Basel, Switzerland Syngenta Crop Protection, Inc., Greensboro, United States, Report No 680-02 GLP Not Published Syngenta File N° NOA446510/0152	Y	SYN
Dorn, R.	KIIA 7.2.3/06	2005a	Re-evaluation of times degradation times of NOA446510 and some selected metabolites in various soil under laboratory conditions Syngenta Crop Protection AG, Basel, Switzerland, Report No Ass05RD03 Syngenta File N° NOA446510/0416	Y	SYN
Dorn, R.	KIIA 7.3/01	2005b	Summary of half-lives of NOA446510 in soil in various field trials across Europe Syngenta Crop Protection AG, Basel, Switzerland, Report No Ass05RD05 Syngenta File N° NOA446510/0418	Y	SYN

Author(s)	Annex point/ reference number	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.	KIIA 7.8.3/03	2005c	Evaluation of half-lives of selected metabolites of NOA446510 in aquatic systems Syngenta Crop Protection AG, Basel, Switzerland, Report No Ass05RD04 Syngenta File N° NOA446510/0417	Y	SYN
Evans, P.	KIIA 7.3.1/01	2003a	Dissipation Study with NOA446510 in or on Soil in Switzerland Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Jealott's Hill International, Bracknell, Berkshire, United Kingdom, Report No RJ3451B GLP Not Published Syngenta File N° NOA446510/0055	Y	SYN
Evans, P.	KIIA 7.3.1/02	2003b	Dissipation Study with NOA446510 in or on Soil in Switzerland Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Jealott's Hill International, Bracknell, Berkshire, United Kingdom, Report No RJ3450B GLP Not Published Syngenta File N° NOA446510/0054	Y	SYN
Evans, P.	KIIA 7.3.1/03	2005a	Mandipropamid 250 g/L SC formulation (A12946C): Dissipation in or on Soil in Spain (2003) Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3662B GLP Not Published Syngenta File N° NOA446510/0372	Y	SYN
Evans, P.	KIIA 7.3.1/04	2005b	Mandipropamid 250 g/L SC formulation (A12946C): Dissipation in or on Soil in France (North) 2003 Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3663B GLP Not Published Syngenta File N° NOA446510/0392	Y	SYN

Author(s)	Annex point/ reference number	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
Evans, P.	KIIA 7.3.1/05	2005c	Mandipropamid 250 g/L SC formulation (A12946C): Dissipation in or on Soil in France (South) 2003 Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3664B GLP Not Published Syngenta File N° NOA446510/0391	Y	SYN
Evans, P.	KIIA 7.3.1/07	2005d	Mandipropamid 250 g/L SC formulation (A12946B): Dissipation in or on Soil in France (South) 2004 Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3667B GLP Not Published Syngenta File N° NOA446510/0394	Y	SYN
Evans, P.	KIIA 7.3.1/08	2005e	Mandipropamid 250 g/L SC formulation (A12946B): Dissipation in or on Soil in France (North) 2004 Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3666B GLP Not Published Syngenta File N° NOA446510/0393	Y	SYN
Evans, P.	KIIA 7.3.1/09	2005f	Mandipropamid 250 g/L SC formulation (A12946B): Dissipation in or on Soil in Spain (2004) Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3665B GLP Not Published Syngenta File N° NOA446510/0373	Y	SYN
Evans, P.	KIIA 7.3.3/01 KIIIA 9.2.3/01	2005g	Mandipropamid 250 g/L SC formulation: 6-Years Long Term Residue Study in or on Soil in Switzerland – Interim Report Syngenta Crop Protection AG, Basel,		

Author(s)	Annex point/ reference number	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
			Switzerland, Report No RJ3708B GLP Not Published Syngenta File N° NOA446510/0511		
Gibbings, E., Ricketts, D.	KIIA 7.2.3/02	2005	Rate of Degradation of Water Sediment Metabolite SYN504851 in Three Soils under Laboratory Conditions Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Jealott's Hill International, Bracknell, Berkshire, United Kingdom, Report No RJ3652B GLP Not Published Syngenta File N° NOA446510/0396	Y	SYN
Grosjean, J., Hurt, A.	KIIA 7.8.3/01	2005	NOA446510: Degradation in Two Aquatic Sediment Systems (Methoxyphenyl Ring) Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3580B GLP Not Published Syngenta File N° NOA446510/0388	Y	SYN
Hand, L H	KIIA 7.6/01	2003	Aqueous Photolysis of 14C-Methoxyphenyl-NOA446510 under Laboratory Conditions Syngenta - Jealott's Hill International, Bracknell, Berkshire, United Kingdom, Report No RJ3395B GLP Not Published Syngenta File N° NOA446510/0041	Y	SYN
Hand, L., Fleming, E.	KIIA 7.4.2/07	2005	Adsorption/Desorption Properties of a Metabolite (SYN539678) in Three Soils Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3674B GLP Not Published Syngenta File N° SYN539678/0001	Y	SYN
Hand, L., Fleming, E.	KIIA 7.4.9/01	2004a	Volatilisation from Soil Surfaces Syngenta Crop Protection AG, Basel,	Y	SYN

Author(s)	Annex point/ reference number	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
			Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3464B GLP Not Published Syngenta File N° NOA446510/0079		
Hand, L., Fleming, E.	KIIA 7.4.9/02	2004b	Volatilisation from Leaf Surfaces Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3468B GLP Not Published Syngenta File N° NOA446510/0081	Y	SYN
Hand, L., Howdle, M.	KIIA 7.2.1/04	2004	NOA 446510: Rate of Degradation in One Soil Under Various Laboratory Conditions Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3487B GLP Not Published Syngenta File N° NOA446510/0117	Y	SYN
Harrison, C.	KIIA 7.4.2/13	2005	NOA446510: Adsorption/Desorption Properties of a Water Sediment Metabolite SYN504851 in Three Soils Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3633B GLP Not Published Syngenta File N° SYN504851/0011	Y	SYN
Harrison, C.	KIIA 7.6/03	2004	Methoxyphenyl Labelled Photolysis in Sterile Natural Water under Laboratory Conditions Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3481B GLP Not Published Syngenta File N° NOA446510/0197	Y	SYN
Hurt, A., Bramley, Y., Grosjean, J.,	KIIA 7.8.3/02	2005	NOA446510: Degradation in Two Aquatic Sediment Systems Syngenta Crop Protection AG, Basel,	Y	SYN

Author(s)	Annex point/ reference number	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
et., al.			Switzerland Syngenta - Jealott's Hill International, Bracknell, Berkshire, United Kingdom, Report No RJ3669B GLP Not Published Syngenta File N° NOA446510/0395		
Indergand, P, Nicollier, G.	KIIA 7.4.2/11	2005c	Adsorption / Desorption of [Phenyl-U-14C] SYN 500003 in Various Soils Syngenta Crop Protection AG, Basel, Switzerland, Report No T006595-04 GLP Not Published Syngenta File N° SYN500003/0017	Y	SYN
Indergand, P., Nicollier, G.	KIIA 7.2.3/04	2005a	Rate of Degradation of [Phenyl-U-14C]-labelled SYN500003 (Metabolite of NOA446510) in Various Soils under Aerobic Laboratory Conditions at 20°C Syngenta Crop Protection AG, Basel, Switzerland, Report No T006596-04 GLP Not Published Syngenta File N° SYN500003/0018	Y	SYN
Indergand, P., Nicollier, G.	KIIA 7.4.2/05	2005b	Adsorption / Desorption of [Chlorophenyl-U-14C]-labelled SYN 521195 in Various Soils Syngenta Crop Protection AG, Basel, Switzerland, Report No T013384-04 GLP Not Published Syngenta File N° SYN521195/0004	Y	SYN
Kuet, S., Dick, J.	KIIA 7.1.3/01	2003	Soil Photolysis of 14C-Methoxyphenyl Ring labelled NOA446510 under Laboratory Conditions Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Jealott's Hill International, Bracknell, Berkshire, United Kingdom, Report No RJ3400B GLP Not Published Syngenta File N° NOA446510/0056	Y	SYN
Kuet, S., Dick, J., Stapleton,	KIIA 7.1.1/01 KIIA	2004	Metabolism and Rate of Degradation of ^{14}C-Chlorophenyl Ring Labelled NOA446510 under Aerobic Laboratory	Y	SYN

Author(s)	Annex point/ reference number	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
C.	7.2.1/06		Conditions, in Three Soils at 20°C Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3469B GLP Not Published Syngenta File N° NOA446510/0119		
Kuet, S., Stapleton, C.	KIIA 7.6/04	2004	Photolysis of 14C-Chlorophenyl Ring Labelled NOA446510 in Sterile Natural Water under Laboratory Conditions Syngenta Crop Protection AG, Basel, Switzerland Syngenta, Jealott's Hill, United Kingdom, Report No RJ3510B GLP Not Published Syngenta File N° NOA446510/0166	Y	SYN
Mamouni, A.	KIIA 7.2.3/03	2005a	SYN536638: Degradation in three soils incubated under aerobic conditions Syngenta Crop Protection AG, Basel, Switzerland RCC Ltd., Itingen, Switzerland, Report No 859080 GLP Not Published Syngenta File N° SYN536638/0009	Y	SYN
Mamouni, A.	KIIA 7.4.2/02	2005b	Adsorption / Desorption of SYN 536638 on Soils Syngenta Crop Protection AG, Basel, Switzerland RCC Ltd., Itingen, Switzerland, Report No RCC 856844 GLP Not Published Syngenta File N° SYN536638/0005	Y	SYN
Mamouni, A.	KIIA 7.4.2/03	2005c	Adsorption of SYN 535839 on Soils Syngenta Crop Protection AG, Basel, Switzerland RCC Ltd., Itingen, Switzerland, Report No 855163 GLP Not Published Syngenta File N° SYN535839/0004	Y	SYN

Author(s)	Annex point/ reference number	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
Mamouni, A.	KIIA 7.4.2/10	2005d	Adsorption of SYN500003 on Soils Syngenta Crop Protection AG, Basel, Switzerland RCC Ltd., Itingen, Switzerland, Report No 855434 GLP Not Published Syngenta File N° SYN500003/0016	Y	SYN
Mamouni, A.	KIIA 7.4.2/12	2005e	Adsorption of SYN504851 on Soils Syngenta Crop Protection AG, Basel, Switzerland RCC Ltd., Itingen, Switzerland, Report No 855435 GLP Not Published Syngenta File N° SYN504851/0009	Y	SYN
Nicollier, G	KIIA 7.4.1/01	2003c	Adsorption/Desorption of [Methoxyphenyl-U-14C]-labelled NOA446510 in Various Soils Syngenta Crop Protection AG, Basel, Switzerland, Report No 02TB04 GLP Not Published Syngenta File N° NOA446510/0048	Y	SYN
Nicollier, G, Glänzel, A	KIIA 7.2.1/05	2002	Rate of Degradation of [Ethyl 1-14C] labelled NOA446510 in 'Gartenacker' and 'Borstel' Soil at Different Dose Levels under Aerobic Laboratory Conditions at 20 °C Syngenta Crop Protection AG, Basel, Switzerland, Report No 02GN01 GLP Not Published Syngenta File N° NOA446510/0017	Y	SYN
Nicollier, G.	KIIA 7.1.1/02 KIIA 7.1.2/01 KIIA 7.2.1/01 KIIA 7.2.4/01	2003a	Metabolism of [Chlorophenyl-U-^{14}C]-labelled NOA446510 under Aerobic and Aerobic/Anaerobic Laboratory Conditions in one Soil at 20 °C Syngenta Crop Protection AG, Basel, Switzerland, Report No 02TB03 GLP Not Published Syngenta File N° NOA446510/0050	Y	SYN
Nicollier, G.	KIIA	200	Metabolism of [Methoxyphenyl-U-14C] Labelled NOA446510 under	Y	SYN

Author(s)	Annex point/ reference number	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
	7.1.1/04 KIIA 7.1.2/02 KIIA 7.2.1/02 KIIA 7.2.4/02	3b	Aerobic, Aerobic / Anaerobic and Sterile Aerobic Laboratory conditions in One Soil at 20 °C Syngenta Crop Protection AG, Basel, Switzerland, Report No 02RF02 GLP Not Published Syngenta File N° NOA446510/0065		
Nicollier, G.	KIIA 7.6/02	2003d	Aqueous Photolysis of [Chlorophenyl-U-14C]-labelled NOA446510 under Laboratory Conditions Syngenta Crop Protection AG, Basel, Switzerland, Report No 02GN07 GLP Not Published Syngenta File N° NOA446510/0051	Y	SYN
Nicollier, G., Berdat, T.	KIIA 7.4.1/02	2004	NOA 446510: Adsorption / Desorption of [Methoxyphenyl-U-14C]-labelled NOA 446510 in Various US Field Soils Syngenta Crop Protection AG, Basel, Switzerland, Report No 04TB01 GLP Not Published Syngenta File N° NOA446510/0214	Y	SYN
Oliver, R., Webb, J., Edwards, P.	KIIA 7.8.1/01	2005	NOA446510: Degradation in an Outdoor Aquatic Sediment System Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Jealott's Hill International, Bracknell, Berkshire, United Kingdom, Report No RJ3569B GLP Not Published Syngenta File N° NOA446510/0400	Y	SYN
Schmidt, E.	KIIA 7.6/05	2004	Quantum yield of the direct photochemical degradation of NOA 446510 in aqueous solution Syngenta Crop Protection AG, Basel, Switzerland Solvias AG, Basel, Switzerland, Report No L02-009816 GLP Not Published Syngenta File N° NOA446510/0118	Y	SYN
Simon, P.	KIIA 7.3.1/06	2005a	Mandipropamid 250 g/L SC: Residues in/on soil, Germany 2003	Y	SYN

Author(s)	Annex point/ reference number	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
			Syngenta Crop Protection AG, Basel, Switzerland Syngenta Agro GmbH, Maintal, Germany, Report No gbg714003 GLP Not Published Syngenta File N° NOA446510/0364		
Simon, P.	KIIA 7.3.1/10	2005b	Mandipropamid 250 g/L SC: Residues in/on soil, Germany 2004 Syngenta Crop Protection AG, Basel, Switzerland Syngenta Agro GmbH, Maintal, Germany, Report No gbg711004 GLP Not Published Syngenta File N° NOA446510/0358	Y	SYN
Tummon, O.	KIIA 7.3.1/12	2005	Mandipropamid: Residue Stability Study for Mandipropamid (NOA466510) and CGA380778 in Soil under Freezer Storage Conditions Syngenta Crop Protection AG, Basel, Switzerland Syngenta - Jealott's Hill International, Bracknell, Berkshire, United Kingdom, Report No RJ3728B GLP Not Published Syngenta File N° NOA446510/0545	Y	SYN
Volkel, W.	KIIA 7.4.2/04	2005a	Adsorption / Desorption of SYN 521195 on Soils Syngenta Crop Protection AG, Basel, Switzerland RCC Ltd., Itingen, Switzerland, Report No 855433 GLP Not Published Syngenta File N° SYN521195/0001	Y	SYN
Volkel, W.	KIIA 7.4.2/09	2005b	Adsorption/Desorption of CGA380775 on Soils Syngenta Crop Protection AG, Basel, Switzerland RCC Ltd., Itingen, Switzerland, Report No 855162 GLP Not Published Syngenta File N° CGA380775/0004	Y	SYN

Author(s)	Annex point/ reference number	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
Völlmin, S	KIIA 7.1.1/05 KIIA 7.3.1/11	2002	Field Dissipation of NOA446510 after Bareground Application of [1-^{14}C] NOA446510 Syngenta Crop Protection AG, Basel, Switzerland, Report No 01SV09 GLP Not Published Syngenta File N° NOA446510/0013	Y	SYN
Wallace, S.	KIIA 7.7/01	2002	NOA446510 technical: Determination of 28 day ready biodegradability Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory, Brixham, United Kingdom, Report No BL7358/B GLP Not Published Syngenta File N° NOA446510/0016	Y	SYN
Widmer, H	KIIA 7.10/01	2003	Atmospheric Oxidation of NOA446510 by Hydroxyl Radicals; Rate Estimation Syngenta Crop Protection AG, Basel, Switzerland, Report No 95A2003006WI Not GLP Not Published Syngenta File N° NOA446510/0035	Y	SYN

7.3.2 Aquatic Toxicity

Author(s)	Annex point/ reference number	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
Grade, R.	IIA 8.2.5	2003	*Daphnia magna* Reproduction Test: Effects of NOA 446510 on the Reproduction of the Cladoceran *Daphnia magna* STRAUS in a Semi-Static Laboratory Test.	Y	SYN

Author(s)	Annex point/ reference number	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
			Syngenta Crop Protection AG, Basel, Switzerland Report No 2013604 GLP Not Published Syngenta File N° NOA446510/0033		
Grade, R.	IIA 8.2.6	2001a	Growth inhibition test of NOA 446510 to green algae (*Selenastrum capricornutum*) under static conditions Syngenta Crop Protection AG, Basel, Switzerland Report No 2013586 GLP Not Published Syngenta File N° NOA446510/0002	Y	SYN
Knauer, K.	IIA 8.2.6	2002	Growth inhibition test of NOA446510 tech. to Blue Algae (*Anabaena flos-aquae*) under static conditions Syngenta Crop Protection AG, Basel, Switzerland Syngenta AG, Basel, Switzerland Report No 2023553 GLP Not Published Syngenta File N° NOA446510/0023	Y	SYN
Matsuura, T.	IIA 8.2.1	2005	A 96-hour Acute Toxicity Test of NOA 446510 (Mandipropamid) with Common Carp Syngenta Crop Protection AG, Basel, Switzerland Kurume Laboratory, Chemical Biotesting Centre, Fukuoka Prefecture, Japan Report No 93451 GLP Not Published Syngenta File N° NOA446510/0254	Y	SYN
Maynard, S.	IIA 8.2.1	2005b	NOA446510 metabolite (SYN504851): Acute toxicity to rainbow trout (*Oncorhynchus mykiss*) Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory, Brixham, United Kingdom Report No BL7967/B GLP Not Published Syngenta File N° SYN504851/0001	Y	SYN
Maynard, S.	IIA	200	NOA446510 tech: Early-life stage	Y	SYN

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	8.2.2.2	3	toxicity test to the fathead minnow (*Pimephales promelas*) Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory, Brixham, United Kingdom Report No BL7577/B GLP Not Published Syngenta File N° NOA446510/0063		
Maynard, S.	IIA 8.2.4	2005c	NOA446510 metabolite (SYN504851): Acute toxicity to Daphnia magna in a 48-hour immobilization test Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory, Brixham, United Kingdom Report No BL7968/B GLP Not Published Syngenta File N° SYN504851/0002	Y	SYN
Maynard, S.	IIA 8.2.6	2005d	NOA446510 metabolite (SYN504851): Acute toxicity to the green alga *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory, Brixham, United Kingdom Report No BL7969/B GLP Not Published Syngenta File N° SYN504851/0003	Y	SYN
Maynard, S., Woodyer, J.	IIA 8.2.1	2004a	NOA446510: Acute toxicity to common carp (*Cyprinus carpio*) in a flow-through test system Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory, Brixham, United Kingdom Report No BL7872/B GLP Not Published Syngenta File N° NOA446510/0111	Y	SYN
Maynard, S., Woodyer, J.	IIA 8.2.4	2004b	NOA446510: Acute toxicity to *Daphnia magna* Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory,	Y	SYN

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			Brixham, United Kingdom Report No BL7871/B GLP Not Published Syngenta File N° NOA446510/0112		
Maynard, S., Young, B.	IIA 8.2.1	2005a	NOA446510 metabolite (SYN500003): Acute toxicity to rainbow trout (*Oncorhynchus mykiss*) Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory, Brixham, United Kingdom Report No BL7964/B GLP Not Published Syngenta File N° SYN500003/0003	Y	SYN
Maynard, S., Young, B.	IIA 8.2.4	2005b	NOA446510 metabolite (SYN500003): Acute toxicity to *Daphnia magna* in a 48-hour immobilization test Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory, Brixham, United Kingdom Report No BL7965/B GLP Not Published Syngenta File N° SYN500003/0004	Y	SYN
Maynard, S., Young, B.	IIA 8.2.6	2005c	NOA446510 metabolite (SYN500003): Acute toxicity to the green alga *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum)* Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory, Brixham, United Kingdom Report No BL7966/B GLP Not Published Syngenta File N° SYN500003/0005	Y	SYN
Palmer, S., Kendall, T., Krueger, H.	IIA 8.2.1	2005a	NOA-446510 - A 96-Hour Flow-Through Acute Toxicity Test with the Sheepshead Minnow (*Cyprinodon variegatus*) Syngenta Crop Protection AG, Basel, Switzerland Wildlife International Ltd., Easton, MD, United States Report No WIL 528A-138 GLP	Y	SYN

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			Not Published Syngenta File N° NOA446510/0287		
Palmer, S., Kendall, T., Krueger, H.	IIA 8.2.4	2005b	NOA-446510 - A 96-Hour Flow-Through Acute Toxicity Test with the Saltwater Mysid (*Americamysis bahia*) Syngenta Crop Protection AG, Basel, Switzerland Wildlife International Ltd., Easton, MD, United States Report No WIL 528A-137 GLP Not Published Syngenta File N° NOA446510/0290	Y	SYN
Palmer, S., Kendall, T., Krueger, H.	IIA 8.2.4	2005c	NOA-446510 - A 96-Hour Flow-Through Shell Deposition Test with the Eastern Oyster (*Crassostrea virginica*) Syngenta Crop Protection AG, Basel, Switzerland Wildlife International Ltd., Easton, MD, United States Report No WIL 528A-139 GLP Not Published Syngenta File N° NOA446510/0288	Y	SYN
Peter, P.	IIA 8.2.1	2002	Acute Toxicity Test of NOA446510 to Fathead Minnow (*Pimephales promelas*) Under Static Conditions Syngenta Crop Protection AG, Basel, Switzerland Report No 2023555 GLP Not Published Syngenta File N° NOA446510/0011	Y	SYN
Roberts, G., Peurou, F.	IIA 8.2.3	2003	NOA446510: Determination of the accumulation and elimination of [14C]NOA446510 in fathead minnow (*Pimephales promelas*) Syngenta Crop Protection AG, Basel, Switzerland Brixham Environmental Laboratory, Brixham, United Kingdom Report No BL7579/B GLP Not Published Syngenta File N° NOA446510/0062	Y	SYN
Volz, E.	IIA 8.2.1	2002	Acute Toxicity Test of NOA446510 to Rainbow Trout (*Oncorhynchus mykiss*) Under Static Conditions Syngenta Crop Protection AG, Basel,	Y	SYN

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			Switzerland Report No 2023552 GLP Not Published Syngenta File N° NOA446510/0012		

8 ANNEXES