

Alpoxen

MR_xF_f

Teva

Tablett 500 mg

(vita, 18×8 mm, kapselformade med mittskåra, märkta AL på ena sidan, N 500 på den andra sidan)

Antiflogistikum med analgetisk och antipyretisk effekt

Aktiv substans:

Naproxen

ATC-kod:

M01AE02

Läkemedel från Teva omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Miljöinformationen för naproxen är framtagen av företaget AstraZeneca för Vimovo

Miljörisk: Användning av naproxen har bedömts medföra låg risk för miljöpåverkan.

Nedbrytning: Naproxen bryts ned långsamt i miljön.

Bioackumulering: Naproxen har låg potential att bioackumuleras.

Detaljerad miljöinformation

PEC = 3.6 µg/L

PNEC = 15 µg/L

PEC/PNEC = 0.24

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

The PEC is based on the following data:

$$\text{PEC } (\mu\text{g/L}) = (A \cdot 10^9 \cdot (100 - R)) / (365 \cdot P \cdot V \cdot D \cdot 100)$$

$$\text{PEC } (\mu\text{g/L}) = 1.5 \cdot 10^{-6} \cdot A \cdot (100 - R)$$

Where;

A (kg/year) = total sold amount API in Sweden year 2016, data from QuintilesIMS. There were sales of both naproxen (23980.4 kg) and naproxen sodium (0.0132 kg) in Sweden in 2016. Based on molecular weight the naproxen sodium sales are equivalent to 0.012 kg of naproxen, the values for naproxen are summed to calculate the total naproxen sales; A = 23980.412 kg

R (%) = removal rate (due to loss by adsorption to sludge particles, by volatilisation, hydrolysis or biodegradation). R = 0

P = number of inhabitants in Sweden = $9 \cdot 10^6$

V (L/day) = volume of wastewater per capita and day = 200 L/day (ECHA default)

D = factor for dilution of waste water by surface water flow = 10 (ECHA default)

(Note: The factor 10^9 converts the quantity used from kg to μg)

$$\text{PEC} = 1.5 \cdot 10^{-6} \cdot 23980.412 \cdot (100 - R) = 3.6 \mu\text{g/L}$$

Metabolism and excretion

Naproxen is primarily metabolized in humans to form two main metabolites naproxen acyl glucuronide and 6-O-desmethyl-naproxen. 6-O-desmethyl-naproxen is excreted unchanged as well as conjugated with sulphate and glucuronic acid (Ref. 1). After oral administration, nearly all of the dose (>95%) has been reported to be excreted in the urine (Ref. 2). Only about 1% of the dose is excreted as naproxen and 6-O-desmethyl-naproxen, respectively (Ref. 3). 6-O-desmethyl-naproxen sulphate (DM-naproxen-O-sulphate) has been suggested to account for approximately 11% of the dose (Ref. 4), but is less than 1% as active as naproxen in animal models (Ref. 5). As such both 6-O-desmethyl naproxen and its conjugates are considered to be inactive.

Ecotoxicity Data for Naproxen Acid^a and Naproxen Sodium^b

Study Type	Method	Result	Ref
Toxicity to the cyanobacteria, <i>Anabaena flos-aquae</i> , growth inhibition test	OECD 201	72 hour NOEC _(growth rate) = 4.0 mg/L ^a 72 hour LOEC _(growth rate) = 8.7 mg/L ^a 72 hour EC50 _(growth rate) = 27 mg/L ^a 72 hour NOEC _(auc) = 1.1 mg/L ^a 72 hour LOEC _(auc) = 1.7 mg/L ^a 72 hour EC50 _(auc) = 12.3 mg/L ^a	6
	ISO 8692	72 hour EC50 _(growth rate) = 39 mg/L ^b	7
	OECD 201		8

Study Type	Method	Result	Ref
Toxicity to green algae, <i>Ps eudokirchinella subcapitata</i> , growth inhibition test		72 hour NOEC (growth rate) = 6.2 mg/L ^a 72 hour LOEC (growth rate) = 12 mg/L ^a 72 hour EC50 (growth rate) > 35 mg/L ^a 72 hour NOEC (yield) = 2.8 mg/L ^a 72 hour LOEC (yield) = 6.2 mg/L ^a 72 hour EC50 (yield) = 14.5 mg/L ^a	
Toxicity to green algae, <i>D esmodesmus subspicatus</i> , growth inhibition test	OECD 201	72 hour EC50 (growth rate) = 39 mg/L ^a 72 hour EC50 (yield) = 21 mg/L ^a	9
	92/69/EEC C.3	72 hour EC50 (growth rate) = 656 mg/L ^b	10
		72 hour EC50 (growth rate) > 320 mg/L ^b	11
Toxicity to the duck weed, <i>Lemna minor</i>	ISO 20079	7 day EC50 (growth rate) = 24 mg/L ^b	11
Acute toxicity to the oligochaete, <i>Lumbriculus variegatus</i>	Non-standard method	96 hour NOEC (symptoms of toxicity) = 3.2 mg/L ^a 96 hour LC50 (mortality) = 68 mg/L ^a	12
Acute toxicity to the freshwater shrimp, <i>Gamm arus pulex</i>	Non-standard method	96 hour NOEC (mortality and symptoms of toxicity) = 12 mg/L ^a 96 hour LC50 (mortality) = 110 mg/L ^a	13
Acute toxicity to the freshwater shrimp, <i>Hyalell a azteca</i>	Non-standard method	96 hour LC50 (mortality) = 383 mg/L ^b	9
Acute toxicity to the sediment dwelling midge, <i>Chironomus riparius</i>	Non-standard method	48 hour NOEC (mortality) = 9.7 mg/L ^a 48 hour LC50 (mortality) = 110 mg/L ^a	14
	ASTM E1440/91		7

Study Type	Method	Result	Ref
Acute toxicity to the rotifer, <i>Brachionus calyciflorus</i>		24 hour LC50 (mortality) = 62 mg/L ^a	
		24 hour LC50 (mortality) = 55 mg/L ^b	
Acute toxicity to the Beavertail fairy shrimp, <i>Thamnocephalus platyurus</i>	Thamno-toxkit	24 hour LC50 (mortality) = 84 mg/L ^a	
		24 hour LC50 (mortality) = 44 mg/L ^b	
Acute toxicity to the giant water flea, <i>Daphnia magna</i>	OECD 202	48 hour EC50 (immobilisation) = 37 mg/L ^a	9
	EPS1/RM/11	48 hour EC50 (immobilisation) > 0.032 mg/L ^a	15
	92/69/EEC C.2	48 hour EC50 (immobilisation) = 174 mg/L ^b	11
		48 hour EC50 (immobilisation) = 166 mg/L ^b	10
Acute toxicity to the water flea, <i>Ceriodaphnia dubia</i>	EPA600/4-90/027	48 hour EC50 (immobilisation) = 66 mg/L ^a	7
		48 hour EC50 (immobilisation) = 45 mg/L ^a	
Acute toxicity to the fresh-water polyp, <i>Hydra attenuata</i>	Non-standard method	96 hour LC50 (mortality) = 22 mg/L ^a	16
Acute toxicity to rainbow trout, <i>Oncorhynchus mykiss</i>	OECD 203	96 hour LC50 (mortality) = 52 mg/L ^a	17
	Not specified	96 hour LC50 (mortality) = 690 mg/L ^b	9
Acute toxicity to bluegill sunfish, <i>Lepomis macrochirus</i>	Not specified	96 hour LC50 (mortality) = 560 mg/L ^b	
Chronic toxicity to the rotifer, <i>Brachionus calyciflorus</i>	ISO 20666	48 hour EC50 (population growth) = 0.56 mg/L ^a	7
Chronic toxicity to the water flea, <i>Ceriodaphnia dubia</i>	EPS1/RM/12	7 day NOEC (survival, reproduction) = 0.68 mg/L ^b	15
		7 day NOEC (survival, reproduction) > 0.032 mg/L ^a	

Study Type	Method	Result	Ref
	ISO20665	7 day NOEC _(survival, reproduction) = 0.33 mg/L ^a	7
Chronic toxicity to the giant water flea, <i>Daphnia magna</i>	OECD 211	21 day LOEC _(survival, reproduction, growth) = 0.47 mg/L ^a 21 day NOEC _(survival, reproduction, growth) = 0.15 mg/L ^a	18
Fish Early-Life Stage Toxicity with fathead minnow, <i>Pimephales promelas</i>	OECD 210	32 day LOEC _(hatch, survival, growth) > 1.0 mg/L ^a 32 day NOEC _(hatch, survival, growth) = 1.0 mg/L ^a	19
Activated sludge, respiration inhibition test	OECD 209	3 hour NOEC = 32 mg/L ^a 3 hour EC50 > 100 mg/L ^a	20
Toxicity to the sediment dwelling midge, <i>Chironomus riparius</i>	OECD 218	28 day NOEC _(total emergence, development rate, sex ratio) = 25 mg/kg ^a dry weight 28 day LOEC _(total emergence, development rate, sex ratio) = 50 mg/kg ^a dry weight	21

^a Exposure conducted with Naproxen Acid

^b Exposure conducted with Naproxen Sodium

NOEC No Observed Effect Concentration

LOEC Lowest Observed Effect Concentration

EC50 the concentration of the test substance that results in a 50% effect

ECx the concentration of the test substance that results in a x% (e.g. EC50 = 50%) effect

LC50 the concentration of the test substance that results in a 50% mortality

Auc Area under curve

Predicted No Effect Concentration (PNEC)

Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. Therefore, the PNEC is based on the lowest No Observed Effect Concentration (NOEC). The lowest NOEC from a long-term test is 0.15 mg/L (equivalent to 150 µg/L) which was reported for *Daphnia magna* from an exposure to Naproxen acid. An assessment factor of 10 is applied, in accordance with ECHA guidance (Ref 22).

$$\text{PNEC} = 150 \mu\text{g/L} / 10 = 15 \mu\text{g/L}$$

Environmental Risk Classification (PEC/PNEC ratio)

$$\text{PEC} = 3.6 \mu\text{g/L}$$

$$\text{PNEC} = 15 \mu\text{g/L}$$

$$\text{PEC/PNEC} = 0.24$$

In accordance with the fass.se guidance (Ref 23), the PEC/PNEC ratio decides the wording of the aquatic environmental risk phrase, and the risk phrase for PEC/PNEC = 0.24 reads as follows; "Use of naproxen has been considered to result in low environmental risk" has been assigned.

In Swedish: Användning av naproxen har bedömts medföra låg risk för miljöpåverkan.

Environmental Fate Data for Naproxen Acid^a and Naproxen Sodium^b

Study Type	Method	Result	Ref
Hydrolysis	OECD 111	<10% hydrolysis after 5 days at pH 3, 7 & 9 Estimated half-life \geq 1 year ^a	24
Ready biodegradation	OECD 301B - CO ₂ Evolution (Modified Sturm Test)	Low test concentration (0.10 mg/L) Half-life = 10 days ^a 65% mineralisation (¹⁴ CO ₂) after 28 days ^a High test concentration (0.50 mg/L) Half-life = 9.8 days ^a 69% mineralisation (¹⁴ CO ₂) after 28 days ^a Naproxen is biodegradable, but cannot be classified as "readily biodegradable" ^a	25
	OECD 301F - Manometric Respirometry	>91 % removal based on removal of parent compound within 7 days ^a	26
Inherent biodegradation	OECD 302C	Inherently biodegradable (mineralization rates as BOD/ThOD) long lag phase ^a :	9

Study Type	Method	Result	Ref
		0 - 13 days = ≤ 4 % Day 14 = 24 % Day 16 = 59 % Day 18 = 73 % Day 28 = 98 %	
Aerobic Mineralisation in Surface Water - Simulation Biodegradation Test	OECD 309 - suspended sediment test (1 g/L)	High organic matter sediment: Half-life = 794 days at 0.010 mg/L ^a Half-life = 836 days at 0.10 mg/L ^a Low organic matter sediment: Half-life = 120 days at 0.010 mg/L ^a Half-life = 709 days at 0.10 mg/L ^a	27
Preliminary Screening Test for Aerobic Transformation in Aquatic Sediment Systems	OECD 308	High organic matter sediment: 40% mineralisation (¹⁴ CO ₂) after 14 days ^a Low organic matter sediment: 3% mineralisation (¹⁴ CO ₂) after 14 days ^a	28
Degradation Half-life	Field study, Lake Greifensee, Switzerland	Estimated half-life = 14 days ^a	29
Soil Adsorption Coefficient	Batch Equilibrium Method	Loamy sand soil pH 7.54, Log Koc = 2.45 ^a Sandy loam soil pH 7.06, Log Koc = 2.48 ^a Silty clay soil pH 7.48, Log Koc = 2.69 ^a Silt loam soil pH 7.14, Log Koc = 2.72 ^a	30
Sludge Adsorption Coefficient	OPPTS 835.1110	K _d < 10 at 0.11 mg/L in activated sludge ^a	31
Bioconcentration Factor (Blood Plasma) in Rainbow Trout, <i>Oncorhynchus mykiss</i>	Non-standard method	BCF = 22 - 28 L/Kg after 14 days uptake ^a	32

^a Exposure conducted with Naproxen Acid

^b Exposure conducted with Naproxen Sodium

BCF Bioconcentration Factor

BOD Biological oxygen demand

ThOD Theoretical oxygen demand

Kd Distribution coefficient for adsorption

Koc Organic carbon normalized adsorption coefficient

Biodegradation

Naproxen is classified as not readily biodegradable; however, results show that after a lag phase in an OECD 301B and OECD 301F (Refs. 32, 35) naproxen undergoes almost complete primary biodegradation in the presence of sewage sludge. Naproxen was also rapidly degraded in aquatic sediments in an OECD 308 preliminary test (up to 40% mineralisation after 14 days, Ref. 33) but in comparison was relatively stable in water in an OECD 309 test (Ref. 31). Overall the weight of evidence suggests that the presence of sludge and sediment plays an important role in the biotransformation of naproxen in the environment, and the phrase 'Naproxen is slowly degraded in the environment' reasonably reflects the available data.

In Swedish: Naproxen bryts ned långsamt i miljön.

Bioaccumulation Data

The octanol-water partition coefficient for naproxen, measured across the environmentally relevant pH range, are low (< 4) therefore, naproxen has low potential for bioaccumulation.

In Swedish: Naproxen *har låg potential att bioackumuleras*.

Physical Chemistry Data for Naproxen Acid^a and Naproxen Sodium^b

Study Type	Method	Result	Ref
Water solubility	Not specified	250 g/L ^b	33
	Not specified	15.9 mg/L at 25°C ^a	34
	Potentiometric Titration	14 mg/L at 25°C ^a	35
Dissociation Constant	Not specified	pK _a = 4.15 ^a	36
Distribution Coefficient Octanol Water	OECD 107	pH 3, Log D = >1.34 ^a pH 7, Log D = 0.639 ^a pH 9, Log D = -1.16 ^a	37
	Not specified	pH < 2.18, Log P = 3.18 ^a	38
	Not specified	Log P = 3.24 ^a	35

^a Exposure conducted with Naproxen Acid

^b Exposure conducted with Naproxen Sodium

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