

Environmental Risk Assessment Data

Tamoxifen

Version 1.1



Tamoxifen is a selective estrogen-receptor modulator (SERM), primarily indicated for the treatment of estrogen receptor positive breast cancer where it acts as an antiestrogen, preventing estrogen binding to the estrogen receptor.

Tamoxifen citrate is an active pharmaceutical ingredient used in the AstraZeneca product Nolvadex.

Tamoxifen is rapidly metabolised by hydroxylation, demethylation and conjugation, giving rise to several metabolites which have a similar pharmacological profile to the parent compound and thus contribute to the therapeutic effect. The metabolites are excreted chiefly as conjugates in the bile, and little or no tamoxifen is eliminated as unchanged drug. Excretion is mainly via the faeces.

Tamoxifen is not readily biodegradable. Once in the aquatic environment tamoxifen may be expected to adsorb to suspended solids and aquatic sediments.

Tamoxifen is an ionisable compound. The octanol water distribution coefficients (Log Dow) values are <4.5 but >3. Predictive models show that within the normal environmental pH range (pH 5 – 9) tamoxifen would not be expected to bioaccumulate. Furthermore, the work of Mills et al (Ref. 1) shows that tamoxifen is likely to be readily metabolised in fish. Overall, the risk of bioaccumulation of tamoxifen in aquatic organisms is considered to be low.

The Predicted Environmental Concentration (PEC) / Predicted No Effect Concentration (PNEC) ratio is 0.073, which means use of tamoxifen is predicted to present an insignificant risk to the environment.

Predicted Environmental Concentration (PEC)

The PEC is based on the following data:

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

A (kg/year) = total patient consumption of tamoxifen citrate in the European country with the highest per capita use in 2016 (Source: IMS Health¹)

R (%) = % removal during wastewater (sewage) treatment (due to loss by adsorption to sludge particles, by volatilisation, hydrolysis or biodegradation). It is assumed that R = 0 as a worst case.

P = number of inhabitants in the country with the highest per capita (Source: IMS Health²).

A/P = 2.6×10^{-5} kg/inhabitant

V (L/day) = volume of wastewater per capita and day = 200 (European Medicines Agency (EMA) default value, Ref. 2)

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

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

$$\text{PEC} = 0.036 \mu\text{g/L}$$

(Note: Whilst tamoxifen is metabolised in the body, little is known about the ecotoxicity of the metabolites. Hence, as a worst case, for the purpose of this calculation, it is assumed that 100% of excreted metabolites have the same ecotoxicity as tamoxifen).

¹ IMS Health, MIDAS International Data for 2016, available for 22 European markets

² The number of persons having their usual residence in a country on 1 January 2016. Available from <http://ec.europa.eu/eurostat/web/population-demography-migration-projections/population-data/main-tables>
Accessed: 20/4/17

Predicted No Effect Concentration (PNEC)

The available aquatic toxicity data include studies undertaken using exposures to both tamoxifen citrate and tamoxifen base. Since the exposure assessment (PEC) is focused on the drug substance, tamoxifen citrate; toxicity values derived from tests performed with tamoxifen base have been adjusted to reflect the equivalent concentration of tamoxifen citrate. This was achieved by multiplying the No Observed Effect Concentration (NOEC) values by 1.517, based on the percentage of tamoxifen by molecular weight.

Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. The primary mode of action of tamoxifen is via estrogen receptor antagonism and therefore tamoxifen has potential to modulate the reproductive endocrine axis. The potential for tamoxifen to effect reproduction in fish has been assessed in a reduced fish full life cycle test with fathead minnows and two further studies, reported in the scientific literature, have also assessed the effects of tamoxifen on reproduction in two other fish species. The PNEC is based on the lowest No Observed Effect Concentration (NOEC) 4.9 µg/L reported for green algae (*Pseudokirchinella subcapitata*) and an assessment factor of 10 is applied, in accordance with EMA guidance (Ref. 2).

$$\text{PNEC} = 4.9 \mu\text{g/L} / 10 = 0.49 \mu\text{g/L}$$

PEC/PNEC

$$\text{PEC} = 0.036 \mu\text{g/L}$$

$$\text{PNEC} = 0.49 \mu\text{g/L}$$

$$\text{PEC/PNEC} = 0.073$$

The PEC/PNEC ratio of 0.073 corresponds to the phrase 'Use of tamoxifen has been considered to result in low environmental risk' in the www.fass.se scheme (Ref. 3).

Environmental Fate Summary

Tamoxifen citrate is not readily biodegradable. However, once in the aquatic environment tamoxifen citrate may be expected to adsorb to suspended solids and sediments.

Tamoxifen is ionisable and expected to be in its unionised (neutral) form at pH 9 and above; therefore, the ionized form is predicted to dominate in the aquatic environment. The octanol/water distribution coefficients suggest that tamoxifen may have potential to bioaccumulate. However, Health Canada (Ref. 4) modelled bioaccumulation potential using several different models and the results suggest that the Bioconcentration Factor (BCF) values for tamoxifen, and its metabolites, are expected to be below the classification threshold for bioaccumulative substances. In addition, the work of Mills et al (Ref. 1) show that tamoxifen is expected to be extensively metabolised and excreted by fish and would not be expected to bioaccumulate. Overall, it is concluded that tamoxifen is unlikely to be bioaccumulative in aquatic organisms.

Aquatic Toxicity Data for Tamoxifen^a and Tamoxifen citrate^b

Study Type	Method	Result	Ref
Activated sludge, respiration inhibition test ^b	Internal Laboratory SOP	3 hour EC ₅₀ >100 mg/L respiration inhibition 3 hour EC ₅₀ >100 mg/L nitrification	5
Toxicity to green algae, <i>Pseudokirchinella subcapitata</i> , growth inhibition test ^b	FDA Technical Assistance Document 4.01	14 day NOEC = 4.9 µg/L based on maximum specific growth rate	6
Toxicity to blue-green algae, <i>Microcystis aeruginosa</i> ^b	FDA Technical Assistance Document 4.01	21 day NOEC = 98 µg/L based on maximum specific growth rate	7
Acute toxicity to Bluegill Sunfish, <i>Lepomis macrochirus</i>	FDA Technical Assistance Document 4.11	96 hour LC50 = 0.23 mg/L based on mortality	8
Acute toxicity to Rainbow Trout, <i>Oncorhynchus mykiss</i>	OECD 203	96 hour LC50 = 0.32mg/L based on mortality	9
	FDA Technical Assistance Document 4.11	96 hour LC50 = 0.41 mg/L based on mortality	10
Population growth inhibition of the rotifer, <i>Brachionus calyciflorus</i> ^a	Non-standard	48 hour EC ₅₀ = 250 µg/L (equivalent to 379 µg/L tamoxifen citrate) endpoints based on reproduction	11
Chronic toxicity to <i>Daphnia magna</i> ^b	FDA Technical Assistance Document 4.09	21 day NOEC = 43 µg/L C endpoints based on reproduction and survival	12
Chronic toxicity to <i>Daphnia magna</i> ^a	Based on the principles of OECD 211)	21 day NOEC = 60 µg/L (equivalent to 91 µg/L tamoxifen citrate) endpoints based on reproduction and survival	13
Chronic toxicity to <i>Daphnia pulex</i> ^a	Multigeneration , Non-standard method.	56 day NOEC = 0.67 µg/L (equivalent to 1.02 µg/L tamoxifen citrate) endpoints based on reproduction, body length and intrinsic rate of reproduction.	14
Chronic toxicity to <i>Ceriodaphnia dubia</i> ^a	based on the principles of ISO/CD 20665 test guideline	7 day EC ₅₀ 0.81 µg/L (equivalent to 1.23 µg/L tamoxifen citrate) endpoints based on reproduction	11
Pair breeding study with Japanese medaka, <i>Oryzias latipes</i> ^b	Non-standard method	21 day NOEC = 5.0 µg/L based on genetic sex ratio	15

Study Type	Method	Result	Ref
Pair breeding study with the fathead minnow, <i>Pimephales promelas</i> ^b	based on USA EPA, Fish Life-Cycle Toxicity Tests; EPA 540/9-86-137	42 day NOEC = 5.6 µg/L based on reproduction (fecundity) 42 day NOEC = 0.18 µg/L based on vitellogenin	16
Fish full life cycle test with the fathead minnow, <i>P. promelas</i> ^b	based on USA EPA, Fish Life-Cycle Toxicity Tests; EPA 540/9-86-137	284 day NOEC = 5.12 µg/L based on growth and reproduction 284 day NOEC = 0.08 µg/L based on vitellogenin	17

^a Exposure conducted using tamoxifen free base

^b Exposure conducted using tamoxifen citrate

NOEC No Observed Effect Concentration

LOEC Lowest Observed Effect Concentration

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

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

Environmental Fate Data for Tamoxifen citrate

Study Type	Method	Result	Ref
Aerobic biodegradation	OECD 301F Modified (innoculum 30 mg/L activated sludge)	10% biodegradation after 28 days based on biological oxygen demand and confirmed by test substance analysis. Not readily biodegradable	18
Aerobic biodegradation	OECD 301C Modified (acclimatised activated sludge)	0% biodegradation (28 days) based on biological oxygen demand and confirmed by test substance analysis. No toxicity at test concentration (20 mg/L). Not readily biodegradable	19
Anaerobic biodegradation	ISO 11734 Modified based on UK DoE method	Not readily biodegradable based on gas production, carbon or parent analysis (40 days)	20
Adsorption/desorption to soils	FDA Technical Assistance Document 3.08	Silty clay loam (pH 4.9, OC 1.6%) Koc $>1.3 \times 10^6$ Sandy loam (pH 5.8, OC 2.2%) Koc 1.6×10^5 Sandy loam (pH 7.7, OC 3.1%) Koc not determinable	21
Bioaccumulation potential	Estimated - EPIWIN	Ionised form, estimated BCF = 61 – 538 Unionised form, estimated BCF = 1695	4

OC Organic Carbon

Koc Organic carbon normalized adsorption coefficient

Physical Chemistry Data for Tamoxifen citrate

Study Type	Method	Result	Ref
Hydrolysis	FDA Technical Assistance Document 3.09	pH 5 = 6% hydrolysis after 5 days at 50°C pH 7 = 90% hydrolysis after 8 days at 25°C pH 9 = 90% hydrolysis after 8 days at 25°C	22
Vapour pressure	FDA Technical Assistance Document 3.03	2.0×10^{-6} pa at 25°C	23
Disassociation constant	Not stated	pKa = 5.67 and 7.73	24
Water solubility at 25°C	FDA Technical Assistance Document 3.01	4.9 mg/L at pH 5 6.6 mg/L at pH 7 0.87 mg/L at pH 9	25
Octanol/water partition coefficient	FDA Technical Assistance Document 3.02	Log D _{ow} = 4.24 at pH 5 Log D _{ow} = 3.68 at pH 7 Log D _{ow} = 4.49 at pH 9	26

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