Pharmaceuticals and Personal Care Products (PPCPs):

Fluoxetine (Prozac)

Yvonne D. Sucich, Matthew Lee, and Antonio Machado
Department of Environmental and Occupational Health
California State University, Northridge

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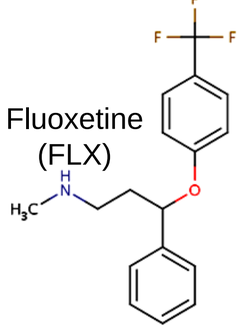
Abstract

Pharmaceutical and Personal Care Products (PPCPs) are a diverse collection of thousands of chemical substances, including prescription drugs.(1) Fluoxetine (FLX) is a commonly prescribed antidepressant (trade name – Prozac). FLX and its metabolites reach the aquatic environment via excretion after human consumption or through improper disposal of unused pharmaceuticals.(2) This project reviewed existing literature of FLX and its primary metabolite, norfluoxetine, to evaluate their possible environmental health effects at low concentrations and chronic exposure. Emphasis was placed on mechanisms that suggest the potential for interactions with other environmental chemicals or hormones.

Introduction

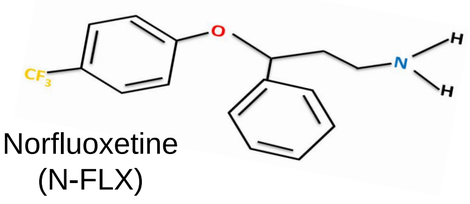
- PPCPs are increasingly identified in aquatic systems in numerous countries.(1) "Increasing populations increases the demand for Earth's limited supply of freshwater. Thus, protecting the integrity of our water resources is one of the most essential environmental issues of the 21st century." (3)
- Fluoxetine (FLX) is an antidepressant in a class of drugs called selective serotonin reuptake inhibitors (SSRIs). FLX affects chemicals in the brain that may become unbalanced causing depression, panic, anxiety, or obsessive-compulsive symptoms.(4)
- FDA approved FLX in December 1987.(2)
- In 2001, Prozac's Patent expired; FLX generics are now common.
- Fluoxetine is one of the most widely used synthetic antidepressants and most prescribed active ingredients of SSRIs. (5)
- In 90 countries and globally prescribed to 40 million people in 2001;(6) U.S. only – prescribed to 30 million people in 2009.(7)
- Fluoxetine, its active metabolite, norfluoxetine (N-FLX), and other metabolites (of unknown activity) are frequently identified in water and soil samples.(4)

Physiochemical and Environmental Fate Parameters of FLX and N-FLX (8, 9)



Physiochemical	Fluoxetine	Norfluoxetine
Empirical formula	$C_{17}H_{18}F_3NO$	$C_{16}H_{16}F_3NO$
Molecular weight	309.33 [g/mol]	295.3 [g/mol]
PK_a (Dissociation constants)	10.06 ± 0.10	9.05 ± 0.13
Vd (volume of distribution, based on 70 kg person)	2450 ± 1470	

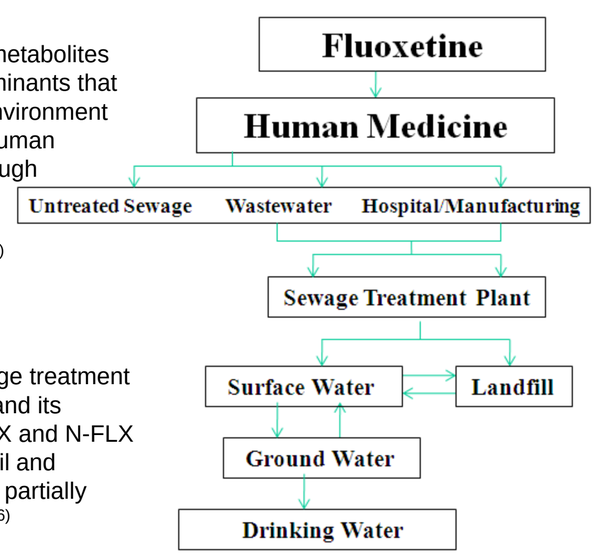
- Lipophilic
- Cross cell membranes
- Accumulate in tissues.



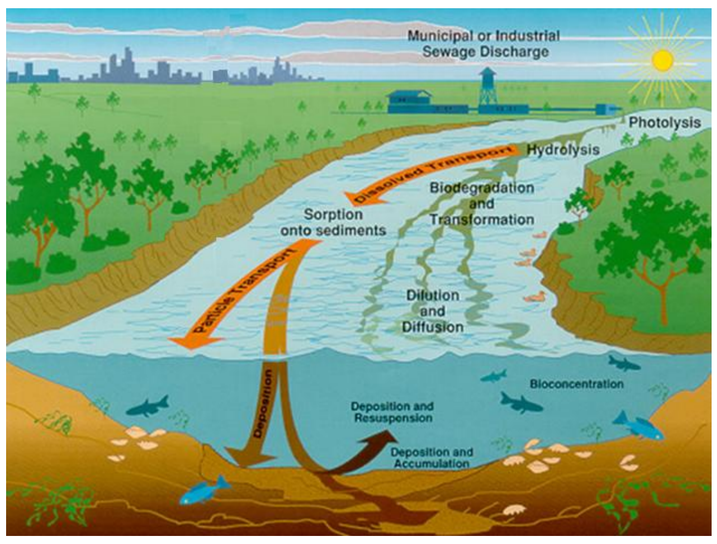
Norfluoxetine
(N-FLX)

Fate & Transport

- Fluoxetine and its metabolites are chemical contaminants that reach the aquatic environment via excretion after human consumption or through improper disposal of unused pharmaceuticals.(2, 3)



- Effluents from sewage treatment plants contain FLX and its metabolites. (15) FLX and N-FLX readily sorbs into soil and sediment. FLX only partially absorbs to sludge.(16)



- Reports of removal in sewage treatment plants compared to the influents has been as low as 23% to as high as 91% for FLX and 79%-89% for N-FLX.(17, 18)
- FLX and N-FLX are subject only to limited degradation by photolytic, hydrolytic, and microbial means, which contributes to its persistence in the environment. (19, 20, 21)
- Removal processes for FLX and its metabolites can vary in sewage treatment plants, depending on the characteristics of the sewage, weather conditions, the design and operation of the treatment processes. (6)
- Glucuronidated FLX can be reactivated in wastewater treatment plants by cleavage of the glucoronide. (22)

Bioactivity and Potential Effects

- FLX is a SSRI and works by preventing the reuptake of one neurotransmitter, serotonin, by nerve cells after it has been released. Since re-uptake is an important mechanism for removing released neurotransmitters and terminating their actions on adjacent nerves, the reduced uptake from the pre-synaptic nerve cleft caused by fluoxetine increases free serotonin that stimulates nerve cells in the brain. (26)
- Serotonin participates in regulatory and endocrine functions. Thus, altered levels of serotonin may cause changes in appetite, immune system, reproduction, and other functions. [2, 24]
- FLX is also known to inhibit hepatic P450s (including CYP2D6, 2C19, 2C9, 2C10, 3A3, 3A4) (4, 10)
- FLX and N-FLX acts additively for a wide range of endpoints.(5)
- For these reasons, the presence of SSRIs in the environment can potentially cause adverse effects on aquatic and terrestrial organisms. (2)

Ecotoxicological Effects of FLX and N-FLX.

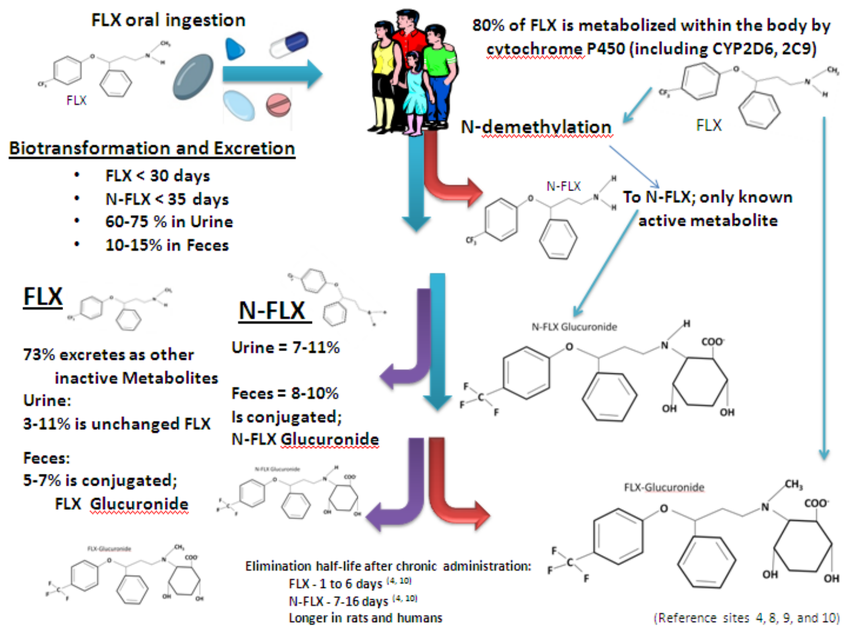
Drug	Taxon	Species	LOEC (µg/L)	Toxicological Endpoint
FLX	Freshwater Snail	*P. antipodarum*	0.81	Embryos without shell(2)
FLX	Midge	*C. riparius*	1120	reduce emergence (2, 27)
FLX	Fish	*D. rerio*	0.32	reduce egg production(28)
FLX	Crustacean	*C. dubia*	56	increase fecundity(2)
N-FLX	Bivalves	*D. polymorpha*	1	increased reproduction(28)
N-FLX	Bivalves	*M. leucophaeata*	0.5	increased reproduction(28)
N-FLX	Bivalves	*S. striatinum*	10	increased reproduction(28)
FLX	Crustacean	*D. magna*	31	length inhibited (2, 30)
FLX	Algae	*P. subcapitata*	13.6	growth inhibition(2)
FLX	Amphipod	*H. azteca*	100	growth inhibition(2)
FLX	Midge	*C. tentans*	1300	growth inhibition(2)
FLX	Fish	*D. rerio*	0.32	decreased 17β-estradiol(28)
FLX	Fish	*O. latipes*	0.1	increased 17β-estradiol(31)

- FLX and N-FLX most commonly caused reproduction and growth effects with LOECs as low as 0.32 µg/L. (28)
- 17β-estradiol levels were altered in fish treated with FLX. (28, 31) This effect may have repercussions on reproduction and growth in aquatic organisms.

Effects of FLX and Clofibric Acid on D. Magna(32)

FLX(µg/L)	Clofibric acid (µg/L)	Effect
36	0	Increases fecundity
0	10	Increases sex-ratio
36	10	Significant deformities
36	100	Mortality

Distribution and Biotransformation



- FLX has a high *V*d, and accumulates in the brain with a 3:1 brain to plasma ratio. (4)
- Rats and mice show FLX readily crosses the placental barrier.(11,12)
- Not all fish produce norfluoxetine as a metabolite. (13)
- Mammals have faster hepatic metabolisms compared to some fish. (13)
- FLX concentrations in fish tissue reveal bioaccumulation. (14)

Degree of Contamination: Measurements in Aquatic Systems

- FLX and its metabolites are continually introduced into aquatic environments and are present at detectable concentrations .(23)
- Recent improvements in analytical methods permit the detection of FLX and N-FLX at environmentally relevant concentrations in aqueous systems.(3, 9)

Detection of FLX and N-FLX in Water Sources Globally

Drug	Sample (ng/L)	Source	Country
FLX	1.1-18.7	STP influent	Norway(17)
FLX	3.1-3.5	STP influent	Canada(2)
FLX	2.0-3.7	STP effluent	Canada(2)
FLX	0.6-8.4	STP effluent	Norway (24)
FLX	1.7	STP effluent	South Korea (2)
FLX	12	STP effluent	USA/Canada(25)
FLX	<1.0	Surface water	South Korea(2)
FLX	0.42-1.3	Surface water	Canada(2)
FLX	21.4	Surface water	Spain[16]
FLX	12	Surface water	USA(2)
FLX	56	Ground water	USA(25)
FLX	0.64	Drinking water	USA(2)
N-FLX	1.8-4.2	STP influent	Canada(2)
N-FLX	0.7-9.3	STP influent	Norway(24)
N-FLX	<0.54-2.4	STP effluent	Norway(24)
N-FLX	1.7-1.8	STP effluent	Canada(2)
N-FLX	1.2-1.3	Surface water	Canada(2)
N-FLX	0.77	Drinking water	USA(2)

Potential Health Interactions

- FLX has been identified in the environment at concentrations about 2 orders of magnitude smaller than the toxic concentration in algae. (5)
- FLX and N-FLX are additive in their physiologic effects. Thus, FLX metabolites must be considered in any risk assessment of environmental FLX. (5)
- Since FLX and N-FLX act as endocrine disruptors, they may potentially synergize with other endocrine disruptors; further studies are needed to assess these potential effects.
- Potential toxicological endpoints arising from the environmental presence of FLX and N-FLX include reproductive impairment, cancer, and increased toxicity of chemical mixtures.(5)

Conclusions

- **The excessive production, use, and disposal of human antidepressants, especially SSRIs, raise concerns for potential adverse human and ecological health effects.**
- **Research shows that FLX and N-FLX can enter the environment, disperse and persist to a greater extent than initially anticipated.(2)**
- **More studies are needed to understand the mechanisms by which environmentally relevant levels of FLX and N-FLX impact biological systems.**
- **Environmental levels of FLX and N-FLX can be dramatically lowered by proper disposal. The key to accomplishing this is public awareness and education.**

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For more information;

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