CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-427

ENVIRONMENTAL ASSESSMENT/FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Duloxetine Hydrochloride, delayed release 20, 30, 40 and 60 mg gelatin capsules

NDA 21-427

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
(HFD-120)

Date Completed: March 11, 2002

FINDING OF NO SIGNIFICANT IMPACT

NDA 21-427

Duloxetine Hydrochloride
Delayed release 20, 30, 40 and 60 mg gelatin capsules

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its new drug application for Duloxetine Hydrochloride, delayed release 20, 30, 40 and 60 mg gelatin capsules, Eli Lilly & Co prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Duloxetine hydrochloride is a chemically synthesized drug that is indicated for the treatment of major depressive disorder and stress urinary incontinence.

Duloxetine hydrochloride may enter the environment from patient use and disposal. It is expected to enter into the aquatic and terrestrial environments. Data indicate that the drug will adsorb to sludge and is susceptible to hydrolysis and photolysis. The toxicity of duloxetine hydrochloride to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at expected environmental concentrations.

Empty or partially empty packages will be disposed by a community's solid waste management system that may include landfills, incineration and recycling. Minimal quantities of the unused drug may be disposed in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

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Attachment: Environmental Assessment
Appended Electronic Signature Page

Environmental Assessment

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IV. Environmental Assessment

IV.A. Description of the Proposed Action

IV.A.1. Requested Approval

Eli Lilly and Company has filed an NDA for duloxetine hydrochloride pursuant to the Federal Food, Drug, and Cosmetic Act. Duloxetine hydrochloride will be marketed as gelatin capsules (20, 30, 40, and 60 mg) packaged in opaque, white HDPE bottles and in 2 mm thick Aclar® blister packs with aluminum foil backing. An Environmental Assessment has been submitted pursuant to 21 CFR part 25.

Duloxetine hydrochloride is not categorically excluded from assessment of environmental impact as dictated in the Federal Register (July 29, 1997, 21 CFR 25.31). The use of duloxetine hydrochloride will result in one major pathway to the environment: sewage treatment facilities receiving influent from the general public. Wastes generated from production facilities are regulated by Federal, State and local environmental protection agencies and are not considered in this environmental assessment.

IV.A.2. Need for Action

Duloxetine hydrochloride, a naphthyl ether amine, inhibits the uptake of serotonin and norepinephrine and lacks affinity for neurotransmitter receptors. Duloxetine hydrochloride is being proposed as a treatment for major depressive disorder and stress urinary incontinence.

IV.A.3. Locations of Use

The location of the use of duloxetine hydrochloride will be primarily in the patient's home and workplace. There is no reason to expect use to be concentrated in a particular geographic region.

IV.A.4. Disposal Sites

Empty or partially empty packages containing duloxetine hydrochloride will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of unused drug could be disposed of in the sewer system.

IV.B. Identification of the Chemical Substance

IV.B.1. Nomenclature

IV.B.1.a. Established Name (USAN):

(+)-N-methyl-γ-(1-naphthalenyloxy)-2-thiophenepropanamine hydrochloride

IV.B.1.b. Brand/Proprietary Name/Tradename

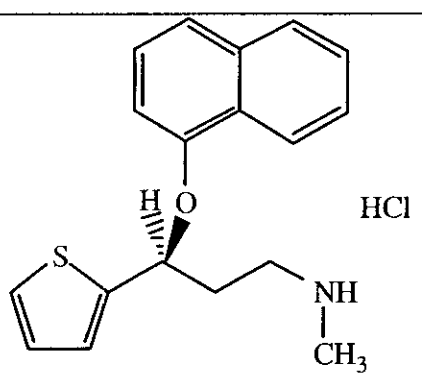
Not yet determined

IV.B.1.c. Chemical Name (Uninverted)

(+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride

IV.B.1.d. Chemical Abstracts Index Name (Inverted)

2-Thiophenepropanamine, N-methyl-γ-(1-naphthalenyloxy)-, hydrochloride, (S)-

Chemical Abstracts Service Number:	136434-34-9
Molecular Formula:	$C_{18}H_{19}NOS \cdot HCl$
Molecular Weight:	333.88
Structural Formula:	

IV.C. Environmental Issues

IV.C.1. Environmental Fate of Released Substances

IV.C.1.a. Physical and Chemical Characterization

Duloxetine is extensively metabolized by humans; less than 10% of the administered dose is excreted as parent compound (Confidential Appendix N). The water solubility of duloxetine hydrochloride was determined to be 21.6, 2.74, and 0.331 g/L at pH 4, 7, and 9, respectively (Appendix B). The dissociation constant (pK_a) of duloxetine hydrochloride was determined to be 9.34 (Appendix C). At pH 4, 7, and 9 the log of the n-octanol/water partition coefficient (log P_{ow}) of duloxetine hydrochloride was determined to be 0.781, 1.54, and 3.35, respectively (Appendix D). The K_d was measured in sewage sludge and ranged between 1166 to 1731 (Appendix E). The K_d can be normalized for the amount of organic carbon in the sludge to calculate a K_{oc} of 2893 to 4296 for duloxetine hydrochloride.

Characteristic	Duloxetine Hydrochloride		
pK_a		9.34	
K_{oc}		2893 to 4296	
K_d		1166 to 1731	
	pH 4	pH 7	pH 9
Solubility g/L	21.6	2.74	0.331
Log P_{ow}	0.781	1.54	3.35

The log P_{ow} at pH 9 is less than 3.5 indicating that the probability for bioaccumulation is low. However, it is greater than 3 suggesting that sorption to biosolids will occur. Indeed, the K_{oc} confirms that duloxetine hydrochloride will sorb to biosolids in wastewater treatment plants.

Vapor pressure of duloxetine hydrochloride was not determined because thermogravimetric analysis of duloxetine hydrochloride showed no weight loss below 160°C. Above this temperature, decomposition and melting occurs. Thus in the environment, release to the atmosphere is not expected.

IV.C.1.b. Environmental Depletion Mechanisms

Duloxetine hydrochloride hydrolyzes slowly at temperatures lower than or equal to 30°C, with a half-life ranging from approximately 1.5 to 3.5 months at 30°C (Appendix F). Based on its ultraviolet-visible absorption spectrum, the theoretical phototransformation of duloxetine hydrochloride is estimated to be 100% within one month (Appendix G). Duloxetine hydrochloride was not significantly biodegraded when incubated with activated sewage sludge for.8 days (Appendix E). However, the presence of a small non-duloxetine radioactive peak indicates that there is potential for transformation of duloxetine. Thus, the primary depletion mechanisms of duloxetine hydrochloride from the aqueous environment are sorption, hydrolysis, and photolysis.

It is not expected that duloxetine will persist in the environment. Its extensive metabolism in humans and the presence of a transformation product in the biodegradation study suggest that duloxetine will be subjected to biodegradation. In addition, duloxetine will slowly hydrolyze in the aqueous environment.

IV.C.1.c. Environmental Concentrations

Expected Introduction Concentration (EIC) in water

Eli Lilly and Company estimates that 5 years post-launch, no more than 100,000 kg of duloxetine (free base) will be sold annually in the United States. From this forecast, the expected introduction concentration (EIC) of duloxetine at the point of entry into the aquatic environment is calculated as follows:

$$EIC_{aquatic}\,(ppb) = \frac{100{,}000kg \times 1{,}000{,}000{,}000\mu g/kg}{1.214x10^{11}\,L/day \times 365days} = 2.3\mu g/L$$

where $1.214x10^{11}$ L/day is the volume of water entering publicly owned treatment works in the United States. This calculation assumes that all duloxetine produced in a year is used and enters the publicly owned treatment works system, drug product usage occurs throughout the United States in proportion to population and the amount of wastewater generated, and there is no human metabolism or microbial degradation.

This $EIC_{aquatic}$ can be adjusted for sorption to biosolids. The measured K_d for sorption to biosolids at 2.5 g/L was 1166. K_d is defined as:

$$K_d = \frac{\left(\frac{Duloxetine_{biosolids}}{Mass_{biosolids}}\right)}{\left(\frac{Duloxetine_{water}}{Mass_{water}}\right)}$$

where $Duloxetine_{water}$ and $Duloxetine_{biosolids}$ are the amounts of duloxetine in water and biosolids, respectively. If the total amount of duloxetine in the water and the sludge is $Duloxetine_{total}$, then the above equation can be rearranged to give:

$$Duloxetine_{water} = \frac{Duloxetine_{total} \times Mass_{water}}{Mass_{biosolids} \times \left(K_d + \frac{Mass_{water}}{Mass_{biosolids}}\right)}$$

A typical water treatment facility has a biosolids concentration in the aerator basin of 3 to 6 g/L (Metcalf & Eddy, 1991). Using the more conservative number, in one liter of water, $Duloxetine_{total}$ is 2.3 µg, $Mass_{water}$ is 1000 g (or 1000 mL) and $Mass_{biosolids}$ is 3 g. Solving for $Duloxetine_{water}$, the expected introduction concentration (EIC) in the aqueous phase adjusted for sorption to solids is:

$$EIC_{aquatic} = 0.5\mu g / L$$

Expected Environmental Concentration (EEC) in water

The Expected Environmental Concentration, EEC, can be calculated for the aquatic environment after consideration of dilution of treatment facility effluent by receiving waters. Based on dilution factors for treatment facilities available from the EPA, a dilution factor of 10 is appropriate. This concentration is considered for long-term exposure scenarios.

$$EEC_{aquatic\,(afterdilution)} = 0.05\mu g / L$$

Expected Introduction Concentration (EIC) in solids

It is also possible to determine the amount of duloxetine bound to the biosolids in a wastewater facility. The total duloxetine in one liter is 2.3 µg so in this case, the amount that must be sorbed to 3 g of biosolids is 1.8 µg. Thus:

$$EIC_{biosolids} = 600\mu g / kg$$

The residence time for sludge in wastewater facilities is 5 to 10 days. Appendix E describes a biodegradation study with duloxetine hydrochloride in which it was observed that after 8 days in contact with sludge, at least one degradation product of duloxetine was detected. The lag time to detection of a degradation product may indicate that microorganisms must become adapted in order to use duloxetine as a food source. In a wastewater treatment plant, it is assumed that the duloxetine concentration will be constant and thus the microorganisms will be continually exposed to duloxetine. This could result in greater biodegradation than observed in the study described in

Appendix E. Therefore, it is not unreasonable to assume that, in a wastewater facility, some degradation of duloxetine will occur.

Biosolids from treatment facilities are often applied to land as fertilizer and the majority of the application is to cropland. The rate of application is limited by the quantity of pollutants in the biosolids and by the nitrogen concentration. The total amount of nitrogen in biosolids ranges from 3 to 8% on a dry weight basis (Sullivan, 1998). The total nitrogen includes ammonium-nitrogen and organic nitrogen. Ammonium nitrogen is immediately available for crop use but is also susceptible to loss through volatilization upon application. The organic nitrogen is available following mineralization by soil microbes. For this assessment it is assumed that all of the nitrogen is essentially available to the crops. Therefore, the least amount of nitrogen in biosolids would be 3% on a dry weight basis. Corn silage utilizes a maximum rate of nitrogen at 480 pounds/acre (539 kg/ha, Hammond et al., 1994). Using this application rate of nitrogen, a maximum rate of application of biosolids to agricultural land can be calculated.

$$\frac{539\text{kg}_{\text{Nitrogen}}}{\text{ha}} \times \frac{100\text{kg}_{\text{biosolids}}}{3\text{kg}_{\text{Nitrogen}}} = 17{,}967\text{kg}_{\text{biosolids}} / \text{ha} = 18\text{metrictons}_{\text{biosolids}} / \text{ha}$$

An incorporation depth of 15 cm into the top layer is typical in land application of biosolids (EPA, 1993). Assuming that the mass of soil is 1500 kg/m^3, the concentration of duloxetine in the soil after application of biosolids with 600 µg duloxetine/kg concentration is estimated to be:

$$\frac{18{,}000\text{kg}_{\text{biosolids}} \times 600\mu\text{g}_{\text{duloxetine}} / \text{kg}_{\text{biosolids}}}{10{,}000\text{m}^2 \times 0.15\text{m} \times 1500\text{kg}_{\text{soil}} / \text{m}^3} = 4.8\mu\text{g}_{\text{duloxetine}} / \text{kg}_{\text{soil}}$$

IV.C.1.d. Summary

Duloxetine hydrochloride will enter the environment through its use by the general population. While human metabolism of duloxetine is extensive, estimations of concentrations of duloxetine in the environment were calculated based on total elimination as the parent compound. The Expected Introduction Concentration in the aqueous environment ($EIC_{aquatic}$) could be as high as 2.3 µg/L. The primary depletion mechanism of duloxetine from the aqueous environment is sorption to biosolids at water treatment facilities. Consideration of this depletion mechanism is used to calculate an adjusted $EIC_{aquatic}$ of 0.5 µg/L. The concentration in biosolids could be as high as 600 µg/kg. If biosolids are applied to land, then duloxetine may enter the terrestrial environment at a concentration in the soil ($EIC_{terrestrial}$) of 4.8 µg/kg. Duloxetine is not expected to volatilize and therefore will not enter the atmospheric environment. Duloxetine is not expected to be persistent in the environment due to its potential for degradation.

IV.C.2. Environmental Effects of Released Substances

The environmental effects of duloxetine hydrochloride in aquatic organisms were investigated in a battery of toxicity studies conducted according to OECD guidelines. The results of these studies are summarized below.

Microbial Inhibition (Tier One)

The effect of duloxetine hydrochloride on sewage microorganisms was tested by incubating activated sludge with duloxetine for 3 hours (Appendix H). The endpoint measured was respiration rate. The no-observed-effect concentration (NOEC) was 2 mg/L and the EC50 was determined to be 36.5 mg/L (expressed as duloxetine free base).

Fish Acute Toxicity (Tier Two)

The acute toxicity of duloxetine hydrochloride to rainbow trout was determined in juvenile fish following exposure to the compound for 96 hours (Appendix I). The endpoint measured was mortality. The NOEC was 0.45 mg/L and the 96-hour LC50 was estimated to be 1.3 mg/L (expressed as duloxetine free base).

Invertebrate Acute Toxicity (Tier Two)

The acute toxicity of duloxetine hydrochloride to *Daphnia magna* was determined following exposure to the compound for 48 hours (Appendix J). The endpoint measured was immobilization. The NOEC was determined to be 1.1 mg/L and the 48-hour EC50 was estimated to be 2.4 mg/L (expressed as duloxetine free base).

Algal Toxicity (Tier Two)

The most sensitive aquatic species to duloxetine is algae. The acute toxicity of duloxetine hydrochloride to green algae was determined using the species *Psuedokirchneriella subcapitata* (Appendix K). The algal cells were exposed for 72 hours and the endpoints measured were inhibition of biomass and average growth rate. Biomass, the area under the growth curve, was most sensitive to duloxetine with a 72-hour EC50 of 0.064 mg/L and a NOEC of 0.011 mg/L (expressed as duloxetine free base).

Chronic Toxicity (Tier Three)

The chronic toxicity of duloxetine hydrochloride was determined using *Daphnia magna* in a full life-cycle test with endpoints of size, survival, and reproduction (Appendix L). Along with body length, the most sensitive endpoint in the study was reproduction. The EC50 and NOEC values of 0.28 mg/L and 0.011 mg/L (expressed as duloxetine free base), respectively, were determined.

Risk Assessment

To assess the environmental risk of duloxetine in the environment, the median effect concentration was compared to the Maximum Expected Environmental Concentration, or MEEC. To protect all species, the quotient of the two numbers (the Assessment Factor) must be above 1000 for Tier One screening, above 100 for Tier Two, and above 10 for Tier Three screening as suggested by guidance from the FDA.

Effects Concentrations compared to expected environmental concentrations.

Species	NOEC (µg/L free base)	LC50 or EC50 (µg/L free base)	MEEC (µg/L free base)	LC50 or EC50/ MEEC	Required Assessment Factor
Sewage microorganisms (3 hours)	2000	36,500	0.5	73,000	≥1000
Rainbow trout (96 hours)	450	1300	0.5	2600	≥100
Daphnia magna (48 hours)	1100	2400	0.5	4800	≥100
Pseudokirchneriella subcapitata (72 hours)	11	64	0.5	128	≥100
Daphnia magna (21 days)	11	280	0.05*	5600	≥10

*Note: for chronic exposure a dilution factor of 10 was utilized.

The calculated assessment factors in all cases are greater than the required factors and in no case were sublethal effects observed at concentrations equal to the MEEC. These results indicate that duloxetine release to sewage treatment plants and the environment does not pose an environmental risk.

IV.C.3. Other Issues

Effects of Serotonin Reuptake Inhibitors on Aquatic Organisms

There is evidence in the literature that serotonin reuptake inhibitors have sublethal effects on aquatic organisms that are related to reproduction. These effects are presumed to occur by disrupting the normal physiological events regulated by serotonin. In fact, many studies have used selective serotonin reuptake inhibitors (SSRIs) as tools to probe the normal physiological role of serotonin in aquatic organisms. For example, Khan and Thomas (1992) demonstrated that fluoxetine (a potent SSRI) itself had no effect on the release of gonadotropin or on gonadotropin releasing hormone's stimulation of gonadotropin in Atlantic croaker (10 mg/kg by injection). With co-administration of serotonin by injection, 10 mg/kg fluoxetine did potentiate serotonin's increase of gonadotropin releasing hormone's stimulation of gonadotropin. In goldfish, as well, injected fluoxetine had no effect on gonadotropin levels itself, but did potentiate the effect of serotonin (Somoza et al., 1988).

Invertebrates appear to be sensitive to direct exposure of fluoxetine and other SSRIs. Fluoxetine has been shown to increase gonadal development in crustaceans with injections of 15 mg/kg in crayfish (Kulkarni et al., 1992) and about 18 mg/kg in crabs (Sarojini, 1993). Bivalves appear to be very sensitive to the effects of fluoxetine and other SSRIs on physiological endpoints. Ram et al. (1993) showed that serotonin (in water or by injection) induces zebra mussels to spawn within hours. Fong (1998) demonstrated that 5 μM (15.50 mg/L) of fluoxetine caused 100% spawning in male mussels while 0.05 μM (0.015 mg/L) was the lowest effective concentration of fluoxetine and induced 20% of males to spawn. Females were not as sensitive. Duloxetine also has serotonin reuptake inhibitory activity. In a chronic toxicity study with *Daphnia magna*, both body length and reproduction were sensitive endpoints to duloxetine exposure. The NOEC for both body length and reproduction was 0.011 mg/L (0.03 μM). This concentration is more than 20 times greater than the maximum concentration of duloxetine expected to be discharged into surface water.

Potential Effects on Terrestrial Organisms

Because duloxetine strongly associates with biosolids at sewage treatment facilities, it may be applied with biosolids to soil at levels up to 4.8 μg/kg (in soil). This concentration is substantially lower than the predicted environmental concentration in soil that is used to trigger terrestrial ecotoxicity tests for veterinary medicinal products according to the 2000 VICH guidelines (100 μg/kg). This level is also lower than the no-observed-effect level from a chronic study with *Daphnia magna*.

Potential Effects on Humans

If a human were to drink two liters of surface water at the maximum EEC of 0.05 μg/L duloxetine, the dose would be 0.1 μg. This dose would be at least 100,000 times less than the therapeutic dose of duloxetine. Thus, it is not expected that humans will be adversely affected by environmental concentrations of duloxetine.

IV.C.4. Summary

Duloxetine and related metabolites in the environment originate from wastewater facilities. In wastewater facilities, duloxetine is expected to partition to the solids resulting in a reduction of the aqueous concentration. The expected duloxetine environmental concentration in water is not expected to affect aquatic organisms based on the toxicity of duloxetine to fish, invertebrates and algae. Duloxetine is not expected to persist in the aquatic environment because it is subject to degradation, hydrolysis, and photolysis. The maximum concentration of duloxetine in soil resulting from agricultural land application of biosolids is less than the trigger for terrestrial ecotoxicity tests in the VICH guidelines. The amount of duloxetine that humans could be exposed to by drinking surface water with the maximum expected environmental concentration of duloxetine would be substantially less than the therapeutic dose range. In summary, no adverse environmental effects have been identified from the use of duloxetine in the treatment of human populations.

IV.D. Mitigation Measures

As no adverse environmental effects have been identified in this environmental assessment from the use of duloxetine in the treatment of major depressive disorder and stress urinary incontinence, no mitigation measures are needed. This action has no known effects on endangered or threatened species or historic properties.

IV.E. Alternatives to the Proposed Action

As no adverse environmental effects have been identified from the use of duloxetine in the treatment of major depressive disorder and stress urinary incontinence, there is no need for alternatives to the proposed action.

IV.F. List of Preparers

Authors

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See Appendix M for curriculum vitae

Consulting Agencies

See Confidential Appendix O for contract testing laboratories

IV.G. References

[EPA] Environmental Protection Agency. 1993. Rules and regulations: standards for the use or disposal of sewage sludge. Fed Regist, February 58(32):9285.

[EPA] Environmental Protection Agency. 1996. Draft - Ecological effects test guidelines: OPPTS 850.1300 Daphnid chronic toxicity test, EPA 712-C-96-120. Washington: US EPA.

Fong PP. 1998. Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitors. Biol Bull 194(2):143-149.

Hammond C, Segars B, Gould C. 1994. Land application of livestock and poultry manure. In: University of Georgia College of Agricultural & Environmental Sciences Cooperative Extension Service. circular 826. Athens: University of Georgia. p 1-9.

Khan IA, Thomas P. 1992. Stimulatory effects of serotonin on maturational gonadotropin release in the Atlantic croaker, *Micropogonias undulatus*. Gen Comp Endocrinol 88(3):388-396.

Kulkarni GK, Nagabhushanam R, Amaldoss G, Jaiswal RG, Fingerman M. 1992. In vivo stimulation of ovarian development in the red swamp crayfish, *Procambarus clarkii* (Girard), by 5-hydroxytryptamine. Invertebr Reprod Dev 21(3):231-239.

Metcalf & Eddy Inc, Tchobanoglous G, Burton FL. 1991. In: Clark BJ, Morriss JM. Wastewater engineering: treatment, disposal, and reuse. 3rd ed. Boston: Irwin/McGraw-Hill 1334 p.

[OECD] Organisation for Economic Cooperation and Development. 1984. Activated sludge, respiration inhibition test, No. 209. In: OECD guidelines for testing of chemicals. Paris: OECD.

[OECD] Organisation for Economic Cooperation and Development. 1984. Alga, growth inhibition test, No. 201. In: OECD guidelines for testing of chemicals. Paris: OECD.

[OECD] Organisation for Economic Cooperation and Development. 1984. *Daphnia* sp., acute immobilisation test and reproduction test, No. 202. In: OECD guidelines for testing of chemicals. Paris: OECD.

[OECD] Organisation for Economic Cooperation and Development. 1998. *Daphnia magna* reproduction test, No. 211. In: OECD guidelines for testing of chemicals.

[OECD] Organisation for Economic Cooperation and Development. 1981. Dissociation constants in water, No. 112. In: OECD guideline for testing chemicals.

[OECD] Organisation for Economic Cooperation and Development. 1984. Fish acute toxicity test, No. 203. In: OECD guidelines for testing of chemicals. Paris: OECD.

[OECD] Organisation for Economic Cooperation and Development. 1981. Hydrolysis as a function of pH, No. 111. In: OECD guideline for testing of chemicals.

[OECD] Organisation for Economic Cooperation and Development. 1981. Inherent biodegradability: modified SCAS test, No. 302A. In: OECD guideline for testing of chemicals.

[OECD] Organisation for Economic Cooperation and Development. 1995. Partition coefficient (n-octanol/water): shake flask method, No. 107. In: OECD guidelines for testing of chemicals. Paris: OECD.

[OECD] Organisation for Economic Cooperation and Development. 2000. Phototransformation of chemicals in water - direct and indirect photolysis. In: Draft OECD guideline for testing of chemicals. 1-59

[OECD] Organisation for Economic Cooperation and Development. 1995. Water solubility, No. 105. In: OECD guideline for the testing of chemicals.

Ram JL, Crawford GW, Walker JU, Mojares JJ, Patel N, Fong PP, Kyozuka K. 1993. Spawning in the zebra mussel (*Dreissena polymorpha*): activation by internal or external application of serotonin. J Exp Zool 265(5):587-598.

Rexrode M, Armitage TM. 1987. Hazard evaluation division, standard evaluation procedure, *Daphnia Magna* life-cycle (21-day renewal) chronic toxicity test. EPA 540/9-86-141, PB87-209730. Washington: US EPA.

Sarojini R, Nagabhushanam R, Fingerman M. 1993. In vivo evaluation of 5-hydroxytryptamine stimulation of the testes in the fiddler crab, *Uca pugilator*: a presumed action on the neuroendocrine system. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 106C(2):321-325.

Somoza GM, Yu KL, Peter RE. 1988. Serotonin stimulates gonadotropin release in female and male goldfish, *Carassius auratus* L. Gen Comp Endocrinol 72(3):374-382.

Sullivan D. 1998. Fertilizing with biosolids. PNW 508. Corvallis: Oregon State University, Extension Service. p 1-12.

IV.H. Nonconfidential Appendices

IV.H.1. Appendix A

DULOXETINE DATA SUMMARY TABLE	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	At pH 4 21.6 g/L At pH 7 2.74 g/L At pH 9 0.331 g/L
Dissociation Constant	$pK_a = 9.34$
Log Octanol/Water Partition Coefficient	Log P_{ow} At pH 4 0.781 At pH 7 1.54 At pH 9 3.35
Vapor Pressure or Henry's Law Constant	Not determined, assumed to be nonvolatile. Thermogravimetric analysis indicates decomposition and melting do not occur until 160°C.
Sorption/Desorption (K_{oc})	2893 to 4296

DEPLETION MECHANISMS	
Hydrolysis	Half life at temperatures equal to or lower than 30°C is 1.5 to 3.5 months
Aerobic Biodegradation	No significant degradation in 8 days. Small radioactive degradation product indicates eventual degradation.
Soil Biodegradation	Not determined
Photolysis	Theoretical phototransformation is 100% loss within one month in pH 4, 7 and 9 aqueous buffers.
Metabolism	Human metabolism is extensive, <10% excreted as parent compound.

ENVIRONMENTAL EFFECTS	
Microbial Inhibition	EC50 36.5 ppm NOEC 2 ppm
Acute Toxicity	*Daphnia magna* (48 hr) EC50: 2.4 ppm NOEC: 1.1 ppm *Oncorhynchus mykiss* (96 hr) EC50: 1.3 ppm NOEC: 0.45 ppm *Pseudokirchneriella subcapitata* (72 hr) $EC_{biomass}50$: 0.064 ppm $NOEC_{biomass}$: 0.011 ppm $EC_{growthrate}50$: 0.20 ppm $NOEC_{growthrate}$: 0.029 ppm
Chronic Toxicity	Full Life-Cycle Toxicity Test with *Daphnia magna* (21 days) LOEC: 0.037 ppm NOEC: 0.011 ppm MATC: 0.020 ppm $EC_{survival}50$: 0.45 ppm $EC_{reproduction}50$: 0.28 ppm

IV.H.2. Appendix B: Report Summary

Report Title: Duloxetine Hydrochloride - Determination of the Water Solubility of a Test Substance Following OECD Guideline 105

Study #: 1982.6114

Study date: June 2001

Methods:

The aqueous solubility of duloxetine hydrochloride was determined in pH 4, 7, and 9 aqueous buffers. Duloxetine hydochloride was added to 250 mL round bottomed flasks containing 100 mL of the buffer solutions. Test samples were agitated on a shaker table in a 30°C environmental chamber for equilibration periods of 24, 48 or 72 hours. After the equilibration period, the flasks were moved to an environmental chamber at 20°C for 24 hours with continued shaking. Duplicate samples were taken from the flasks and centrifuged at 25,848 g for 20 minutes. The supernatants were analyzed for duloxetine by HPLC.

Results:

The length of the equilibration time at 30°C did not affect the water solubility. Solubility decreased with increasing pH.

	Mean water solubility of duloxetine hydrochloride at 20°C (g/L)
pH 4	21.6
pH 7	2.74
pH 9	0.331

IV.H.3. Appendix C: Report Summary

Report Title: Duloxetine Hydrochloride - Determination of the Dissociation Constant for a Test Substance Following OECD Guideline 112

Study #: 1982.6115

Study date: June 2001

Methods:

The dissociation constant of duloxetine was determined at 20°C by a titration method using a Brinkman Titrino Workcell Version 4.0, Metrohm titrator. Two concentrations of duloxetine hydrochloride were prepared in CO_2-free water: 2.98 mM and 0.596 mM. The 2.98 mM solution was titrated with 0.150 mL aliquots of 0.1 M hydrochloric acid. The 0.596 mM solution was titrated with 0.020 mL aliquots of 0.1 M sodium hydroxide. The software program recorded the cumulative milliliters added and the resulting pH after each addition.

Results:

The dissociation constant (pK_a) was determined from the titration curve with 0.1 M sodium hydroxide. Titration with 0.1 M hydrochloric acid did not result in a titration curve. The mean pK_a for duloxetine hydrochloride was determined to be 9.34 at 20°C.

IV.H.4. Appendix D: Report Summary

Report Title: Duloxetine Hydrochloride – Determining the Partitioning Coefficient (n-Octanol/Water) of a Test Substance by the Flask-Shaking Method Following OECD Guideline 107

Study #: 1982.6127

Study date: June 2001

Methods:

The octanol/water partition coefficient (P_{ow}) of duloxetine hydrochloride was determined at pH 4, 7, and 9. A stock concentration of 201 mg/L duloxetine hydrochloride was prepared in buffer-saturated n-octanol. Solutions were prepared in duplicate for each pH using the volume ratios of 1:16, 1:8, and 1:4 of n-octanol-saturated buffer to duloxetine n-octanol stock. The mixtures were placed in centrifuge tubes with Teflon®-lined caps and rotated for five minutes at 20°C, centrifuged and re-equilibrated. Each phase was then analyzed by HPLC.

Results:

The partition coefficients were dependent on pH but independent of concentration.

	Mean P_{ow} (range)	Log P_{ow}
pH 4	6.05 (5.76 to 6.39)	0.781
pH 7	34.7 (33.2 to 36.3)	1.54
pH 9	2250 (2110 to 2320)	3.35

IV.H.5. Appendix E: Report Summary

Report Title: Duloxetine hydrochloride - Determination of the Inherent Biodegradability and Adsorption of a Test Substance by the SCAS Test, Modified from OECD Guideline 302A

Study #: 1982.6123

Study date: June 2001

Methods:

[^{14}C]Duloxetine hydrochloride was used to determine the kinetics of adsorption to sewage sludge and the aerobic biodegradability of duloxetine in activated sludge.

For adsorption determination, duplicate 500 mL flasks containing 200 mL 0.01 M $CaCl_2$ and 2500, 1250, 625, or 313 mg/L sludge solids were incubated with 1.01 mg/L [^{14}C]duloxetine hydrochloride. The flasks were stirred in an environmental chamber at 22 ± 3°C for four hours. At timepoints 0, 1, 2, and 4 hours, 30 mL homogenous samples were taken from each flask. Samples were split with one portion being extracted and analyzed for parent material by HPLC/RAM and LSC and the other portion centrifuged to isolate the supernatant for assay of parent material. The organic carbon content of the sludge was also determined.

For assessment of biodegradation potential, duplicate 500 mL flasks containing 250 mL of sewage sludge with 2500 mg/L solids were incubated with 1.00 mg/L of [^{14}C]duloxetine hydrochloride. The flasks were stirred in an environmental chamber at 22 ± 3°C. The flasks were stoppered and connected to a volatiles trapping system. Samples (20 mL) were taken from the flasks at 0, 8, 24, 72, 96, 120, 144, and 192 hours. The volatiles traps were sampled at 96 and 192 hours. Sludge samples were analyzed by HPLC/RAM following extraction of the whole sample. Volatile trap samples were assayed by LSC.

Results:

Adsorption of duloxetine hydrochloride to solids reached a plateau by 2 hours incubation with the sewage sludge. The adsorption coefficients ($K_{d(sludge)}$) at 4 hours were calculated to be 1166, 1269, 1197, and 1731 for 2500, 1250, 625, and 313 mg solids/L, respectively. The adsorption coefficients expressed as a function of the organic carbon content ($K_{oc(sludge)}$) of the activated sludge were calculated to be 2893, 3150, 2970, and 4296.

During the biodegradation study, duloxetine concentrations dropped from 91.3% at 0 hour to 62.1% by 8 hours. There was no further decline in duloxetine concentration over the remaining 8 days. Therefore, this initial decline is most likely attributable to extraction inefficiency as duloxetine becomes more tightly bound to the sludge solids. After 8 days, a small degradation peak was observed accounting for approximately 1.5% of the total radioactivity. The presence of this degradation product indicates the eventual biodegradability of duloxetine.

IV.H.6. Appendix F: Report Summary

Report Title: Duloxetine Hydrochloride – Determination of the Abiotic Degradation of the Test Substance by Hydrolysis at Three Different pH Values Following OECD Guideline 111

Study #: 1982.6120

Study date: June 2001

Methods:

Preliminary Test:

A hydrolysis study with duloxetine was conducted in three aqueous buffers, pH 4, 7, and 9. Duloxetine hydrochloride was added to the buffers for a final concentration of 10 mg/L (expressed as duloxetine free base). Aliquots of each solution were incubated in 50 mL volumetric flasks in a 50°C water bath for 5 days. All flasks were wrapped in foil. Analysis for duloxetine concentration was performed on days 0 and 5.

Definitive Test:

A hydrolysis study with duloxetine was conducted in the same three aqueous buffers above. Two 200 mL aliquots of each solution containing 10 mg/L duloxetine were incubated in volumetric flasks for 28 days in a 40°C water bath. A third 200 mL aliquot was incubated for 35 days at 30°C. All flasks were wrapped in foil. At days 0, 3, 7, 10, 12, 14, 17, 20 and 28 samples were removed from the 40°C incubation for analysis. Samples were taken from the 30°C incubation at days 0, 3, 7, 10, 12, 17, 28, and 35.

Results:

Preliminary Test:

The percent duloxetine remaining after 5 days at pH 4, 7, and 9 was 56.4%, 75.9%, and 60.7%, respectively.

Definitive Test:

The following first order hydrolysis rate characteristics for duloxetine were calculated.

pH	°C	Initial [Duloxetine] on Day 0 (mg/L)	[Duloxetine] at end of test (mg/L)	Hydrolysis Rate Constant (Day^{-1})	Half Life (Days)
4	30	10.4	6.07	0.0165	41.88
7	30	10.0	8.05	0.0069	100.62
9	30	10.0	7.43	0.0096	72.48
4	40	9.98	2.92	0.0440	15.73
7	40	10.2	5.67	0.0219	31.69
9	40	9.84	4.21	0.0306	22.64

IV.H.7. Appendix G: Report Summary

Report Title: Duloxetine Hydrochloride - Determination of the Ultraviolet-Visible Absorption Spectrum in Aqueous Solution Following OECD Proposed Guideline for Phototransformation of Chemicals in Water

Study #: 1982.6130

Study date: June 2001

Methods:

Solutions of 0.0015 M duloxetine hydrochloride were prepared in pH 4 and pH 7 buffers and in unbuffered pure reagent water. A solution of 0.0003 M duloxetine hydrochloride was prepared in pH 9 buffer. The absorption spectra of the test solutions were measured using a Hewlett-Packard Model 8453 UV-Vis spectrophotometer. Absorbance peaks recorded in the wavelength range for natural sunlight (i.e. 295 to 800 nm) were used to calculate the propensity for phototransformation of duloxetine.

Results:

Absorbance peaks were observed in the range of 295 to 325 nm. The molar absorption coefficient was determined for each peak and using these values it was calculated that within 30 days, 100% of duloxetine would be phototransformed at pH 4, 7, and 9 and in pure reagent water.

IV.H.8. Appendix H: Report Summary

Report Title: Duloxetine Hydrochloride - Activated Sludge Respiration Inhibition Following OECD Guideline 209

Study #: 1982.6126

Study date: June 2001

Methods:

Duloxetine hydrochloride was incubated with synthetic sewage feed and activated sludge (1.5 g/L solids concentration) in a volume of 500 mL in 1000 mL beakers. There were five treatment levels consisting of one replicate each. Four treatment levels of 3,5-dichlorophenol were incubated as above as a reference control for the study. There were two controls consisting of synthetic sewage feed and activated sludge only and an abiotic control with synthetic sewage feed only. The nominal concentrations of duloxetine (expressed as free base) were 2, 6, 18, 54, and 162 mg/L. The stock solution (500 mg/L) used to make the test concentrations was analyzed by HPLC and determined to be 498 mg/L duloxetine (free base). The nominal concentrations of 3,5-dichlorophenol were 3.0, 10, 30 and 100 mg/L. After 3 hours and 25 minutes of incubation during which the test systems were aerated, homogenous samples from each replicate and control were collected. The pH was measured and the dissolved oxygen was monitored over 10 minutes in a Strathkelvin Instruments oxygen system while the samples were continuously stirred in a water bath. From these measurements, the oxygen consumption rate was calculated for each treatment level and control.

Results:

The temperature of the test solutions was maintained between 18.5 and 21.9°C during the incubation and the water bath used during the oxygen measurements was maintained at approximately 21°C. The pH in all treatments was between 7.27 and 7.59. The respiration rates for the control vessels were 29.3 and 31.1 mg O_2/L/hr. The abiotic control respiration rate was -1.8 mg O_2/L/hr. The respiration rates for the reference compound were 26.9, 15.4, 3.5 and 0.6 mg O_2/L/hr for 3.0, 10, 30, and 100 mg/L, respectively. The EC50 of 3,5-dichlorophenol was calculated to be 11.1 mg/L which is within the acceptable limits (5.0 to 30 mg/L) as specified in the OECD 209 Guideline. Respiration rates for the treatment levels were 30.7, 21.8, 26.0, 7.7 and -0.8 mg O_2/L/hr for 2, 6, 18, 54, and 162 mg/L duloxetine, respectively. The no-observed effect concentration for duloxetine was 2 mg/L and the EC50 was calculated to be 36.5 mg/L.

IV.H.9. Appendix I: Report Summary

Report Title: Duloxetine Hydrochloride - Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) Under Static-Renewal Conditions

Study #: 1982.6125

Study date: June 2001

Methods:

The acute toxicity of duloxetine to rainbow trout was assessed according to OECD guideline 203. Juvenile trout (mean weight 0.75 g, mean length 42 mm) were exposed to mean measured concentrations of duloxetine of 0 (control), 0.45, 0.89, 1.9, 3.8, 8.6, and 17 mg/L (here and below expressed as duloxetine free base) for 96 hours. A total of 10 fish were exposed to each treatment level in a volume of 15 L. At 48 hours, the fish were transferred to fresh exposure solutions. Daily mortality and behavioral changes were recorded.

Results:

Temperature in the test system was maintained between 13 and 14°C. The pH and dissolved oxygen ranged from 6.7 to 7.4 and 6.2 to 10.2 mg/L, respectively. At 96 hours the cumulative mortality at concentrations ≥1.9 mg/L was 100%. There was no mortality in lower treatment levels or the control. Lethargic swimming behavior was observed in the 0.89 mg/L. The 96 hour LC50 was determined to be 1.3 mg/L duloxetine with 95% confidence intervals of 0.89 to 1.9. The 96 hour no-observed-effect concentration was 0.45 mg/L duloxetine.

IV.H.10. Appendix J: Report Summary

Report Title: Duloxetine Hydrochloride - Acute Toxicity to Daphnids (*Daphnia magna*) Under Static Conditions

Study #: 1982.6116

Study date: June 2001

Methods:

The acute toxicity of duloxetine to daphnids was assessed according to OECD guideline 202. Daphnids (≤24 hours old) were exposed to mean measured concentrations of duloxetine of 0 (control), 0.10, 0.52, 1.1, 2.1, 4.2 and 8.5 mg/L (expressed as duloxetine free base) for 48 hours. Four replicates were included at each treatment level. Each replicate contained five animals in 200 mL of test solution. The test solutions were prepared with fortified well water (initially pH 8.0, conductance 550 µmhos/cm, total hardness as $CaCO_3$ 180 mg/L, and total alkalinity as $CaCO_3$ 120 mg/L). At 24 and 48 hours, water quality measurements were made and the number of immobilized daphnids in each replicate was recorded.

Results:

During the testing period the temperature ranged from 19 to 21°C, the pH from 7.9 to 8.2 and the dissolved oxygen from 8.6 to 10.3. No immobilization or other adverse effects (e.g. lethargy) were observed in treatment levels ≤1.1 mg/L duloxetine and the control. Immobilization occurred in 35, 100 and 100% of daphnids exposed to 2.1, 4.2 and 8.5 mg/L duloxetine, respectively. The surviving daphnids in the 2.1 mg/L group were observed to be lethargic. The 48-hour EC50 and 95% confidence limits were calculated to be 2.4 mg/L and 1.1 to 4.2 mg/L duloxetine, respectively. The no-observed-effect concentration was 1.1 mg/L duloxetine.

IV.H.11. Appendix K: Report Summary

Report Title: Duloxetine hydrochloride - Acute Toxicity to the Freshwater Green Alga *Pseudokirchneriella subcapitata*, Following OECD Guideline #201

Study #: 1982.6118

Study date: June 2001

Methods:

A static toxicity test was conducted to evaluate the effects of duloxetine hydrochloride on the green alga, *Pseudokirchneriella subcapitata*. There were six treatment levels containing duloxetine hydrochloride and three replicates at each treatment. The initial measured concentrations in the treatments were 0.0053, 0.011, 0.029, 0.070, 0.20 and 0.47 mg/L duloxetine (concentrations and all results below are expressed as the free base). There were six replicates for the control. To each replicate, approximately one million algal cells were added to 100 mL of appropriately treated Algal Assay Procedure medium in sterile 250 mL flasks to give an initial cell concentration of 10,000 cells/mL. The cells were cultured under continuous illumination at 400 to 490 footcandles and continuous shaking for 72 hours. The pH and conductivity during the test ranged from 7.4 to 8.2 and 80 to 90, respectively. The temperature was 24°C. At 24, 48, and 72 hours, a sample was removed from each flask and the cells were counted using a hemocytometer. These measurements were used to calculate the growth rate and biomass for each replicate.

Results:

After 72 hours, the concentration of duloxetine in all treatments was <10% of the nominal concentration. An additional replicate in the 0.029 mg/L treatment in which no cells were added also contained less than 10% of the initial concentration after 72 hours. Thus the disappearance of duloxetine was probably due in large part to photolysis. There is no established method to maintain constant exposure concentrations in algal toxicity studies if test material declines over the study. After 72 hours the control growth rate was 1.61 $days^{-1}$ (standard deviation = 0.020) and for treatment concentrations ≥0.070 mg/L the rate was significantly reduced (≤1.51 $days^{-1}$). Thus, the no-observed-effect concentration (NOEC) for growth rate was 0.029 mg/L. The median effective duloxetine concentration on reduction of growth rate (EC50) was 0.20 mg/L with 95% confidence limits of 0.088 to 0.31 mg/L. After 72 hours, the biomass (the area under the growth curve) of the control cells was 10,500 cells·days/mL. At 0.47 mg/L duloxetine biomass was significantly reduced. Based on these results, the NOEC for biomass would be 0.20 mg/L. However, duloxetine concentrations ≥0.029 mg/L duloxetine caused >10% reduction of biomass. Thus, the NOEC for biomass was considered to be 0.011 mg/L rather than 0.20 mg/L. The EC50 at 72 hours was calculated to be 0.064 mg/L with 95% confidence limits of 0.019 to 0.23 mg/L. Biomass was the most sensitive endpoint and, therefore, the most conservative EC50 and NOEC for this study were initial duloxetine concentrations of 0.064 and 0.011 mg/L, respectively.

IV.H.12 Appendix L: Report Summary

Report Title: Duloxetine Hydrochloride - Full Life-Cycle Toxicity Test with Water Fleas, *Daphnia magna* Under Flow-Through Conditions, Following FIFRA Guideline 72-4, OECD Guideline #211, and OPPTS Draft Guideline 850.1300.

Study #: 1982.6129

Study date: June 2001

Methods:

Daphnia magna, ≤24 hours old, were exposed to duloxetine hydrochloride for 21 days in a flow-through exposure system. There were six treatment levels and a control with four replicate vessels in each treatment. Each replicate vessel held 10 daphnids in a volume of 1.4 L. Test solutions were delivered to the vessels at a rate of six vessel volumes per 24-hour period to provide a 90% solution replacement rate of approximately 9 hours. The mean measured concentrations in the treatments were 0 (control), 0.011, 0.037, 0.080, 0.14, 0.26 and 0.50 mg/L duloxetine (expressed here and below as the free base) prepared in fortified well water. Conditions during the exposure were 19 to 22°C and a light:dark cycle of 16:8 hours at 30 to 70 footcandles. The number of immobilized adult daphnids and observations of abnormal behavior were recorded daily. Assessments of offspring released were determined beginning on day 7 and three times per week through day 21.

Results:

Water quality parameters monitored during the test included pH (7.9 to 8.2), conductivity (500 µmhos/cm), total hardness (180 mg/L as $CaCO_3$), and total alkalinity (110 to 120 mg/L as $CaCO_3$). After 21 days mean percent survival in the treatments was 95, 100, 93, 93, 100, 100, and 38% in the control, 0.011, 0.037, 0.080, 0.14, 0.26 and 0.50 mg/L duloxetine, respectively. The EC50 for survival was calculated to be 0.45 mg/L. After 21 days, the mean body length of daphnids exposed to ≥0.037 mg/L duloxetine was significantly reduced from the control average of 5.1 mm. The mean dry weight of daphnids exposed to ≥0.14 mg/L was significantly reduced compared to the control average of 1.1 mg. After 21 days the mean cumulative number of offspring released per female daphnid in the treatments was 161, 166, 140, 131, 113, and 72 for control, 0.011, 0.037, 0.080, 0.014, and 0.26 mg/L duloxetine, respectively. The reproduction for the 0.50 treatment was not analyzed in the statistics because of the significant survival effect. Offspring numbers in treatment levels ≥0.037 were significantly different from the control. The no-observed-effect concentration and the EC50 for reproduction were calculated to be 0.011 and 0.28 mg/L duloxetine, respectively.

IV.H.13. Appendix M: Curriculum Vitae of Preparers

Alison Nimrod Perkins

Lilly Research Laboratories, Greenfield, IN

Ph.D.	Pharmacology/Toxicology, University of Mississippi	1996
B.S.	Chemistry, Tulane University	1988

Previous Experience: Research Scientist, University of Mississippi in the National Center for Natural Products Research (1997 to 1999). Supervised technical staff of the Biological Core. This group was responsible for screening extracts and pure compounds from natural products for various biological activities. Primary effort included development of new assays. Author on several publications and abstracts in the natural products arena as well as environmental toxicology. Guest lecturer for undergraduate and graduate level courses in pharmacology and toxicology.

Current Responsibility: Senior Toxicologist, Environmental Science and Hazard Communication. Conducts research in environmental toxicology of pharmaceutical products. Prepares environmental risk assessments for animal and pharmaceutical products for submission to the FDA and Europe. Prepares guidelines for production facilities for containment of active products.

Professional Activities:

Editorial Board: Environmental Toxicology and Chemistry
Member: Society of Environmental Toxicology and Chemistry
Reviewer: ETC, Journal of Natural Products, Journal of Biomolecular Screening

Roger D. Meyerhoff

Lilly Research Laboratories, Greenfield, IN

Ph.D.	Fisheries/Pharmacology & Toxicology, Oregon St. Univ.	1980
M.S.	Fisheries/Limnology & Water Pollution, Oregon St. Univ.	1976
B.S.	Fisheries and Wildlife Biology, Univ. Calif. at Davis	1974

Previous Experience: Senior Toxicologist, Research Scientist, and Senior Research Scientist for Lilly Research Laboratories in Environmental Toxicology (1980 to 1994). Conducted acute and chronic environmental toxicology studies with over 20 aquatic and terrestrial species and coordinated aquatic and terrestrial field studies. Author of a number of abstracts and papers on the results of these studies and lecturer on environmental risk assessment to undergraduates and graduate students at several universities. Has prepared risk assessments for pesticides, animal products, and pharmaceutical products to support submissions to the EPA, FDA, and Europe since 1982.

Current Responsibility: Head, Environmental Science and Hazard Communications. Is responsible for the personnel and operation of this department. Environmental Science and Hazard Communications supports production facilities and registration of new products by conducting toxicology studies (inhalation, aquatic, wildlife, microbes, environmental chemistry) and writing material safety data sheets, caution statements, and risk assessments for human and environmental exposures. The department also provides studies to support shipment of new materials in the European Community.

Professional Activities:
Chairman (1993-1995), SETAC Foundation for Environmental Education
President (1991-1992), Society of Environmental Toxicology & Chemistry (SETAC)
Board of Directors (1987-1993), SETAC
Member (1991-Present), PhRMA Environmental Working Group
Member (1987 - Present), An. Health Inst. Sci. Com., Env. Working Group
Member (1985-1987), National Agricultural Chemical Association
Subcommittee on Environmental Toxicology and Chemistry

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