

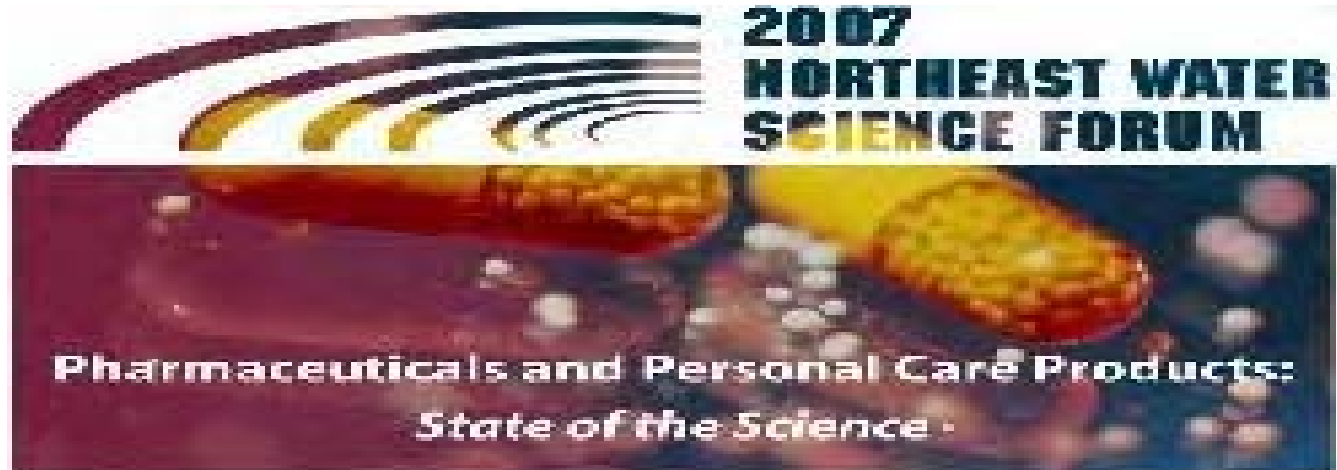
Can Drug Delivery Be A Solution to the Pharmaceuticals In the Environment Problem?

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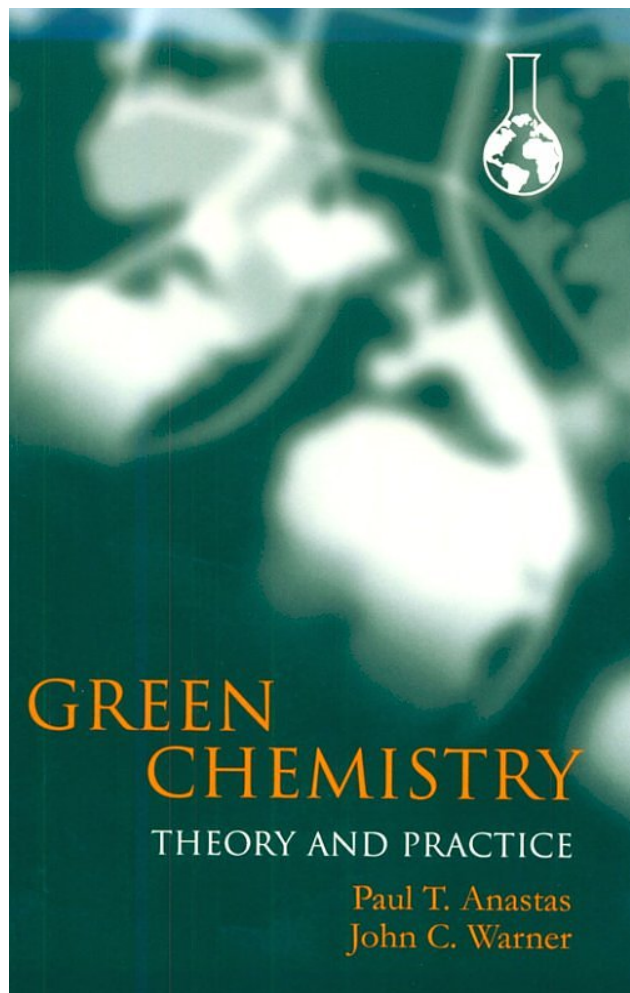
Portland, ME



Then, Now and In the Future

- Then (and maybe now)-The solution is dilution
 - EPA/FDA mandated fate and effects studies
- Now (just starting)-End of Pipe solutions
 - POWWTF's
 - Chemical Treatments, such as TAML[®]/peroxide
 - Take-backs
- In the Future-Design solutions
 - Designing API's
 - Designing Drug Delivery Platforms

What is Green Chemistry?



“...the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products.”

*Source: Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998).

ISBN 0 19 850698 8

The Twelve Principles of Green Chemistry

1. **Prevent waste:** Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.
2. **Design safer chemicals and products:** Design chemical products to be fully effective, yet have little or no toxicity.
3. **Design less hazardous chemical syntheses:** Design syntheses to use and generate substances with little or no toxicity to humans and the environment.
4. **Use renewable feedstocks:** Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.
5. **Use catalysts, not stoichiometric reagents:** Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.
6. **Avoid chemical derivatives:** Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.

Paul T. Anastas and John C. Warner, *Green Chemistry: Theory and Practice* (New York, NY: Oxford University Press Inc., 1998).

ISBN 0 19 850698 8 as found on www.epa.gov/greenchemistry

The Twelve Principles of Green Chemistry (continued)

- 7. Maximize atom economy:** Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.
- 8. Use safer solvents and reaction conditions:** Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.
- 9. Increase energy efficiency:** Run chemical reactions at ambient temperature and pressure whenever possible.
- 10. Design chemicals and products to degrade after use: Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.**
- 11. Analyze in real time to prevent pollution:** Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.
- 12. Minimize the potential for accidents:** Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment

Pharmaceuticals In the Environment

Recently, there have been significant industry efforts to develop improved environmental risk assessment models in the United States and Europe. These **models are being used to identify potential risks of ... pharmaceutical products entering the environment through patient use.**

...is one of the leading companies in the Pharmaceutical Research and Manufacturers of America (PhRMA) working to provide guidance on disposal of unused products in a manner that minimizes environmental impact. Very low levels of ingredients of certain drug products have been detected in water by scientists at various locations around the world due to improved testing technologies. Reported concentrations of drug substances in water are extremely low, ranging from parts per trillion to parts per billion. ... has been **proactive in promoting a science-based examination of the issue and supports efforts to address existing gaps in knowledge associated with the very low concentrations of these substances in water.** We are partnering with PhRMA and working with scientific experts to better understand and analyze the impact of trace levels of pharmaceuticals on the environment.

Green Chemistry Performance

Metrics: E-Factor

Roger Sheldon, *Chem Tech*, 1994, **24**, 38

Table 1. Sectors of the chemical industry by quantity of byproduct per kg of product

<i>Industry Sector</i>	<i>Product tonnage</i>	<i>kg byproducts/ kg of product</i>
Oil refining	$10^6 - 10^8$	ca 0.1
Bulk Chemicals	$10^4 - 10^6$	<15
Fine Chemicals	$10^2 - 10^4$	5-50
Pharmaceuticals	$10^1 - 10^3$	25-100+

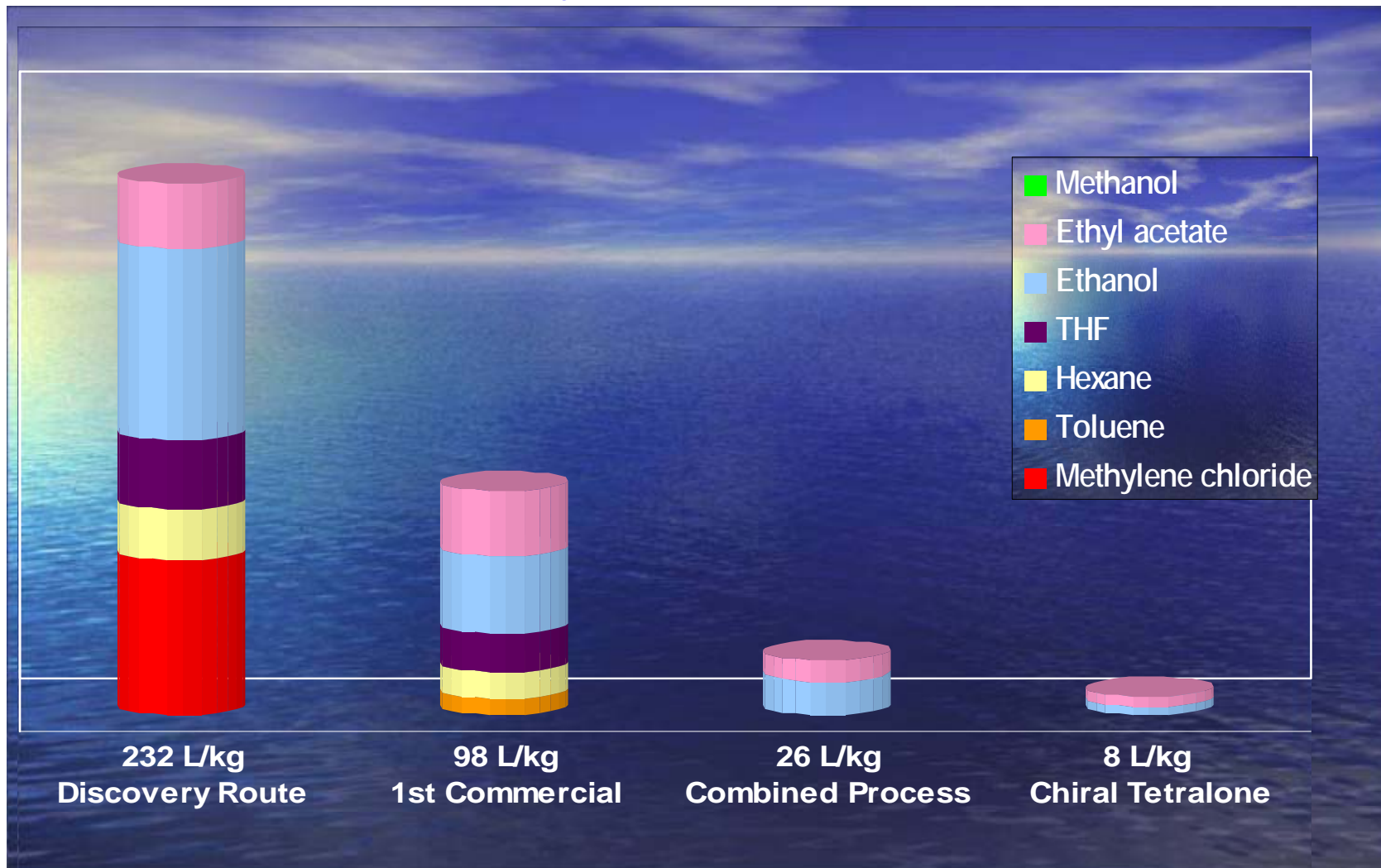
Note: For pharmaceuticals these E-Factors are calculated based on fine chemical inputs, i.e., from the loading dock

Waste Prevention Opportunity

API Pharma Model

- 2006 Worldwide Rx expenditures **\$650 Billion/yr** (IMS)
- Assume \$1.50/day cost and 100mg/day dose, then 475 billion doses/yr => **47,500,000 kg API produced per year.**
- With pharma E factors typically 25-100+ kg of waste/kg API (Sheldon 1994) => **1– 5 billion kilos of waste per year**
- An E factor of 10-20 (achievable using **green chemistry** principles in process design) => **0.5-1 billion kilos of waste per year**
- **Equivalent to preventing as much as 4 billion kilos of waste per year**
 - 75-80% solvent, 20-25% chemicals
- Cost of disposing of 1 kg waste: \$1-5/kg
- Cost of buying 1 gal of solvent \$1-5/gal
- Cost of buying a kilo of RSM \$50-200+/kg

Sertraline Process – Reduction in Solvent Usage vs. Synthetic Route



Design of Environmentally Friendly Drugs

- Risk: Expectation could be established that favorable environmental properties can be easily designed into new drugs
- *Environmental Health Perspectives*, ..Stewardship of Drugs... November 2002, US EPA author:
 - “Drug Design: New drug design (chemical structure and properties) and formulation ... should factor in new considerations for “environmental friendliness” ... maximizing ... susceptibility to biodegradation ... to yield innocuous end products.”
- Futures:
 - Unclear

The Challenge to the Pharmaceutical Scientist

- We design drugs to be biologically active
- We want the active drug to be stable under all synthesis conditions
- We want the active drug to be stable in storage
- We want the active drug to be stable during manufacture of the dosage form
- We want the dosage form to be stable during its shelf life
- But when the patient excretes it we want it to degrade completely to benign or inert materials
- We currently lack the scientific knowledge to achieve the last want and meet all the others as well

Lipinski's Rule of Five

- Lipinski's Rule of Five states that, in general, an orally active drug has:
 - Not more than 5 [hydrogen bond](#) donors (OH and NH groups)
 - Not more than 10 hydrogen bond acceptors (notably [N](#) and [O](#))
 - A [molecular weight](#) under 500 g/mol
 - A [partition coefficient](#) log P less than 5
- Reference: C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings*, Adv. Drug Del. Rev., **2001**, 46, 3-26. ([DOI:10.1016/S0169-409X\(00\)00129-0](https://doi.org/10.1016/S0169-409X(00)00129-0))

Purposeful Degradation

Klicke, et.al., Pharm. Tech., 48, February 2005

Data and Review

Toward a Generic Approach for Stress Testing of Drug Substances and Drug Products

Silke Klicke,* Pim G. Muijselaar, Joop Waternivall,† Thomas Eichinger, Christiana Korn, Thijs K. Gording, Alexander J. Debets, Carl Sijger-van de Orsland, Cas van den Dijk, Govert W. Smeets, and Gerhardus J. De Jong

The Impurity Profiling Group has developed a generic approach for conducting stress testing on drug substances and drug products. The proposed strategy is evaluated and verified with historical data and new experiments. Results demonstrate that the proposed approach is reasonable and generates relevant, generally predictive results for the development of a stability-indicating method.

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- Drugs are designed to be resistant to degradation from
 - Oxidation
 - Photochemistry
 - Heat
 - Acid/water
 - Base/water
- To ensure adequate shelf life
Any impurity >0.1% (or any PGI > 1.5 mcg/day) is a regulatory issue

Drug Delivery Can Be Green

- Bioavailability Enhancements
 - Solubility-limiting bioavailability
 - Permeability-limiting bioavailability
 - CYP Inhibitors
- Drug Particle Optimization
 - Crystal engineering
 - Nano particles
- Targeted Delivery
 - Embryonic technology
- Molecular Self Assembly
 - Embryonic technology
- Designing less stable drugs that are stabilized in a formulation matrix.
 - Shelf life and inventory control implications

Targeting Using Drug Delivery Technology

Drug Delivery Without Targeting



Target

Broad systemic distribution requires high dose for efficacy and leads to off-target side effects

Drug Delivery With Targeting



Localized drug leads to improved efficacy and safety with lower dose

ACS Green Chemistry Institute Pharmaceutical Roundtable

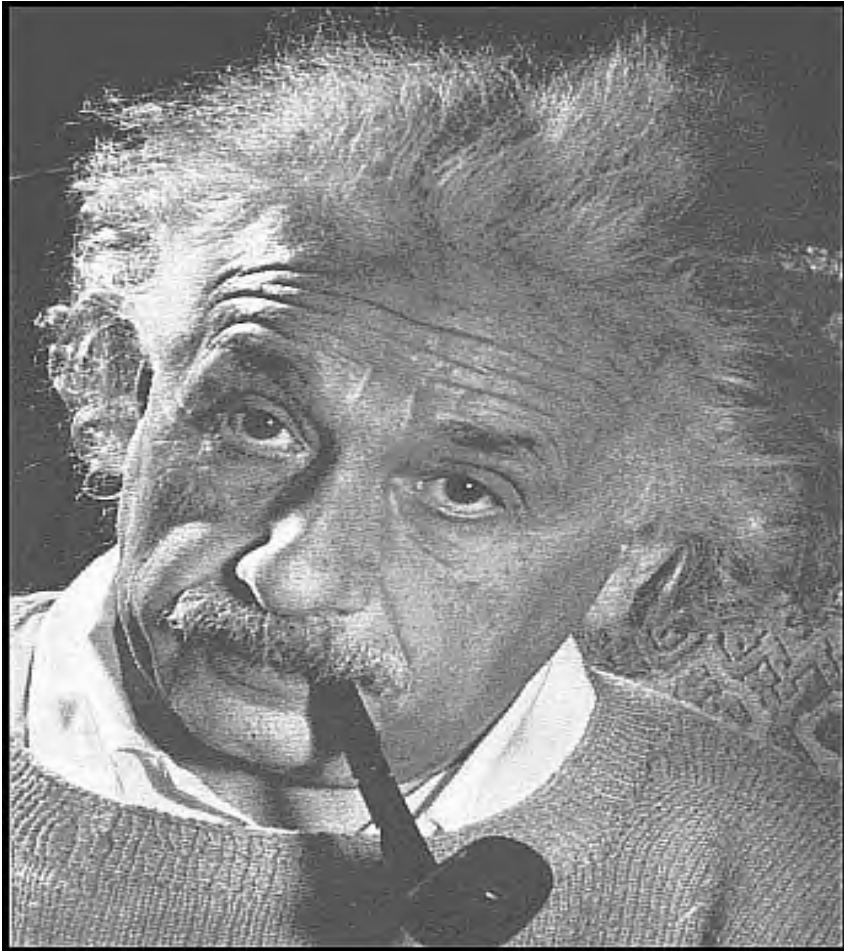
Current Membership as of August 1, 2007

The Lilly logo is written in a red, cursive script.The GSK logo features the lowercase letters 'gsk' in white inside an orange-to-yellow gradient oval, with the text 'GlaxoSmithKline' in grey to its right.The Pfizer logo consists of the word 'Pfizer' in white, italicized, sans-serif font inside a blue oval.The Schering-Plough logo features a red stylized 'sp' symbol followed by the text 'Schering-Plough' in grey.The Merck logo features a teal stylized 'M' symbol followed by the word 'MERCK' in bold, black, uppercase, sans-serif font.The AstraZeneca logo features the text 'AstraZeneca' in purple, with a stylized purple 'Z' symbol to its right, and the tagline 'life inspiring ideas' in a smaller purple font below.The Johnson & Johnson logo is written in a red, cursive script.

Membership is open to all pharmaceutical research, development, and manufacturing companies. The Roundtable will be strongest when all global pharmaceutical corporations are members.

Email gcipr@acs.org or

http://chemistry.org/greenchemistryinstitute/pharma_roundtable.html



“The significant problems we face today cannot be solved at the same level of thinking we were at when we created them”

- Albert Einstein

Some Pharma Related PIE References

Human Pharmaceuticals in the Aquatic Environment: A Challenge to Green Chemistry

Sushil K. Khelasi* and Terence J. Collins*


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Contents		
1. Introduction	2	4.4.4. Neurotoxic Compounds: Antiepileptics
1.1. Pharmaceuticals: A Perspective	2	4.4.5. Neurotoxic and Endocrine-Disrupting Drugs
1.2. Population Growth, Increasing Age Structure, and Healthcare Spending in the U.S.	3	4.4.6. Blood Lipid-Lowering Agents: Fibric Acid
1.3. Entry of Pharmaceuticals into the Aquatic Environment	4	4.4.7. Blood Lipid-Lowering Agents: Statins
1.4. Generic Treatment Plant (GTP) Effluents: Temporal and Spatial Distributions and the Fate of Pharmaceuticals in Environmental Waters	5	4.4.8. Beta Blockers
1.5. Pharmaceutical Contamination in Drinking Water	8	4.5. Aquatic Toxicology of Pharmaceutical Wastewater
1.6. Possible Health Effects of Chronic Exposure to Pharmaceuticals	7	5. Minimal Clearance of Pharmaceuticals in the Environment: Photodegradation
2. Pharmaceuticals of Environmental Concern: Their Pharmacokinetics and Pharmacokinetics (PK/PD)	7	5.1. Phenytoin as a Model Parental Medication of Pharmaceuticals
2.1. Metabolic Transformations	7	5.2. Direct and Indirect Photolysis
2.2. High Volume Drugs	8	5.2.1. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
2.2.1. Acetaminophen/Paracetamol	8	5.2.2. Colic Acid
2.2.2. Cardiovascular Drugs	8	5.2.3. Alendronate
2.2.3. CNS Drugs	10	5.2.4. Selective Serotonin Reuptake Inhibitors (SSRIs)
2.2.4. Chemotherapy: Cancer Drugs	12	5.2.5. Carbamazepine
2.2.5. Respiratory Drugs	15	5.2.6. Steroid Hormones
2.2.6. Endocrinology Therapeutics	16	5.2.7. Antibiotics
2.2.7. Anticancer Drugs	18	6. Oxidative Transformations of Pharmaceuticals in Water
3. Fluorinated Pharmaceuticals	18	6.1. Non-Green-Chemistry Methods
3.1. The Role of Fluorine in the Stability and Bioavailability of Pharmaceuticals	18	6.1.1. Chlorination
3.2. Fluorine Substitution in the Development of Pharmaceuticals	19	6.1.2. Treatment with Chlorine Dioxide
4. Toxicity of Human Pharmaceuticals	20	6.2. Green-Chemistry Methods
4.1. Environmental Risk Assessment	21	6.2.1. O_3 , H_2O_2 , and Cu^{2+}/H_2O_2 Oxidation
4.2. Human Health Risk Assessment of Pharmaceuticals	21	6.2.2. Catalytic Oxidation with Fe-TAML Hydroxyl Peroxide
4.3. Aquatic Toxicology from Chronic Exposure	22	7. Management of Human Pharmaceuticals in the Environment
4.4. Aquatic Toxicology of Pharmaceuticals	22	7.1. Regulation of Pharmaceuticals
4.4.1. Steroid Hormones	23	7.1.1. Safety Testing of Pharmaceuticals
4.4.2. Antibiotics	23	7.2. Preventing the Entry of Pharmaceuticals into the Aquatic Environment
4.4.3. Neurotoxic Compounds: Antiepileptics	24	7.2.1. Pharmaceutical Return Program
		7.2.2. Advanced Wastewater Treatment and Incineration of Solid Waste
		7.3. Ecofriendly Pharmaceuticals
		7.3.1. Development of "Green" Drugs
		7.4. Paving the Ours of Responsibility on Industry
		8. A Green Chemistry Perspective
		8. Acknowledgment
		9. References

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**Pharmaceuticals in the Environment:
PhRMA Initiatives**

Mary Buzby,
Director, Environmental Technology
Merck & Co., Inc.

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MASS-A&WMA Technical Conference
April 6, 2006

Human Pharmaceuticals: Assessing the Impact on Aqueous Ecosystems,
Richard T. Williams (Ed), SETAC Press, 2005

THANK YOU

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