Pharmaceuticals in the Environment –
A Review of P*h*RMA Initiatives

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1. Introduction

When patients consume pharmaceuticals, there may be some active pharmaceutical ingredient (API) that is not completely metabolised and is excreted by the patient. These small quantities of material are then transported to wastewater treatment systems where most of them are removed but some are discharged to receiving streams.

Recently, as a result of advances in analytical techniques, it has become possible to show that pharmaceuticals can be measured in wastewater, surface water (rivers and streams) and drinking water at low concentrations. There is substantial public concern about the possibility of health or environmental effects, compounded by debate about the effects of endocrine modulating chemicals and worries about resistance to antibiotics.

There is ongoing scientific work to establish the extent of the issues. P*h*RMA has been actively involved in industry efforts to develop models that can then be used to identify potential environmental exposures from pharmaceutical products entering the environment through patient use. When used with appropriate effects information, these exposure assessments may be used to assess potential risk to human health and the environment from trace levels of pharmaceuticals in drinking and surface waters. In addition, P*h*RMA has been proactively involved in efforts to develop: the science needed to understand and manage the technical aspects; the methodologies to better define the environmental fate characteristics of pharmaceuticals and the appropriate end-points for impacts on aquatic life and ecosystems; and the strategies needed to appropriately manage the issue. However, the state-of-the-art for this issue is developing rapidly, and considerable additional work needs to be done to ensure that this issue is understood, managed, and properly

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communicated to internal and external stakeholders, including employees, contractors, suppliers, customers, investors, governmental agencies, NGOs, and the public.

2. Background

The widespread detection of pharmaceuticals in environmental samples as a result of improved analytical capabilities and focused field surveys has led to concern over the potential risks associated with releases of pharmaceuticals into the environment. This concern has been driven by surface water sampling programs in the US, Europe and elsewhere that have all shown the presence of many different classes of pharmaceuticals. The high polarity and low volatility of most pharmaceuticals means that they are likely to be transported to and by the water compartment. The research published to date describes the sampling and analysis of surface water, groundwater, drinking water, and sewage treatment plant (STP) effluent, and the detection of pharmaceutical active ingredients and their degradation products, usually at concentrations much less than 1 µg/L. The pharmaceuticals reported in surface water include hormones (*e.g.*, synthetic and natural estrogens), antibiotics, blood lipid regulators, non-steroid analgesics and anti-inflammatory agents, beta-blockers, antiepileptics, antineoplastics, tranquilizers, and diagnostic contrast media. Although some pharmaceuticals are unlikely to be a risk to the aquatic environment because of low concentrations combined with low toxicity, other pharmaceuticals such as natural and synthetic sex hormones may pose potentially significant risks.

Attention has focused on pharmaceuticals used in both veterinary and human medicine; however the environmental exposure scenarios are quite different for these modes of entry. A comprehensive discussion of the issue of veterinary medicines in the environment, which may be introduced to the environment through a variety of direct and indirect, point and diffuse sources, is provided in Boxall *et al.*. In contrast, exposure of aquatic wildlife to human pharmaceuticals is most likely to occur from sewage treatment plant (STP) point source discharges and this exposure may therefore be at continuous, low concentrations. Despite this, most published aquatic toxicity data and risk assessments for pharmaceuticals are based on short-term acute studies. Concerns over the possible environmental effects of low level continuous aquatic exposure to human pharmaceuticals have led to significant revisions in European new drug regulatory submission requirements, where chronic aquatic toxicity tests have been adopted in the most recent environmental risk assessment guidance document for human pharmaceuticals produced by the European Medicines Agency in support of Directive 2001/83/EC.

3. Occurrence in the Environment

In the late 1980s, new, highly sensitive analytical methods for organic chemicals with polar and nonpolar properties were developed. These new analytical methods could detect and quantitate organic chemicals, including pharmaceuticals, at concentrations ranging from 1-100 nanograms/litre (ng/L). Some pharmaceutical chemicals can now be identified and quantified at sub-ng/L concentrations, i.e., down to 100 parts per quadrillion (to 0.1 ng/L).

Efforts to improve the sensitivity of analytical methods for trace analytes in water will continue. As an example of the sensitivity of analytical methods for trace organics in water, the currently approved analytical method for 2,3,7,8-tetrachloro-p-dioxin can detect this chemical at less than 1 picogram/litre (pg/L) - 1000 times lower than 1 ng/L, nearly approaching the molecular level. As the sensitivity of analytical methods increases, it is likely that additional chemicals will be identified in ambient waters and that chemicals already found may prove to be more widespread.

4. Behavior in the Environment

Aquatic transport and transformation processes in the environment include sorption, ionization, volatilization, hydrolysis, oxidation-reduction, photolysis, biological transformation-degradation and precipitation-dissolution. These processes occur continuously in the environment and influence the presence and bioavailability of pharmaceuticals in aquatic ecosystems. Response of drugs to any of these pathways for partitioning, degradation or change in the environment could reduce their concentrations in the environment or remove them entirely and thereby reduce their potential to impact human health and aquatic life. Pharmaceutical compounds that are marketed in large quantities and are soluble or slightly soluble yet resistant to degradation through biological or chemical processes have the greatest potential to reach steady-state levels in the environment and be detected in surface and ground waters and potable water supplies.

5. Understanding the Risk to Human Health - Modeling as One Approach

The potential risk to human health associated with low levels of pharmaceuticals in the environment is a function of exposure and hazard. One way to assess this risk is to create a model to predict human exposure and evaluate the hazard present. However, models are merely predictive and are only as good as the input data and assumptions used. Models can be constructed, using the principles discussed above, to estimate the human health risk associated with pharmaceuticals in the environment.

Screening models can be used to evaluate large numbers of compounds, employing conservative assumptions and readily available data, in order to identify those compounds with the greatest potential risk. A P*h*RMA-sponsored risk assessment for 26 APIs has been published. Other assessments have been published as well.

Detailed deterministic or probabilistic models can then be used to provide more definitive risk estimates for those compounds, and/or classes of compounds, identified in the screening analysis. Deterministic models are used to simulate site-specific conditions in a particular area, while probabilistic models are used to estimate the percentage of the population exposed to various levels of risk.

A. Hazard

There is no universally accepted methodology to measure the human health hazard associated with low levels of pharmaceuticals in the environment. One approach could be to use the therapeutic dose with a safety factor of 1000. Another approach is to use EPA's Reference Dose (RfD) methodology. The RfD is the amount of a chemical that a person, including sensitive subgroups, can be exposed to on a daily basis without causing adverse health effects over a lifetime. The RfD is derived from the no observed adverse effect level (NOAEL) by consistent application of generally order-of-magnitude uncertainty factors.

One methodology developed and reported by pharmaceutical industry scientists is a model to establish human health predicted no effects levels (PNECs). Typically during the research and development of pharmaceuticals, a risk/benefit analysis is used by regulatory authorities to evaluate the safety of pharmaceuticals for the patient population. A certain amount of risk, e.g., side effects, is recognized as acceptable to receive the therapeutic benefits. This contrasts with the case where no benefit is presumed to be received by the exposed individual, such as the incidental exposure to pharmaceuticals through drinking water or fish consumption. The potentially exposed population is presumed to include healthy adults as well as susceptible sub-populations (e.g., children, the elderly, and infirm) in which the pharmacologic effect is considered undesirable. The database for a compound normally contains several toxic endpoints from which a point of departure should be determined to calculate the most restrictive reference value (or allowable daily intake - ADI). The point of departure for determining an ADI for chemicals is often either the highest dose resulting in no observed effects (no observed effect level or NOEL) or in no observed adverse effects (no observed adverse effect level or NOAEL) for a given toxic endpoint. For many APIs, however, a point of departure is the lowest dose resulting in an observable effect (lowest observed effect level or LOEL) or in an observable adverse effect (lowest observed adverse effect level or LOAEL). For an API, the therapeutic effect usually occurs at a dose considerably below those expected to result in toxicity.

B. Exposure

Human exposure to environmental concentrations of pharmaceuticals is believed to be primarily through ingestion of drinking water and, for compounds that bioaccumulate, through ingestion of meat or fish.

The concentration of drug substances in drinking water depends on the following factors:

- the quantity of drug substance consumed by a given population;
- the extent to which the drug is metabolised in the body;
- available dilution in public sewer systems and in receiving waters;
- removal and partitioning in STPs and receiving waters; and,
- degree of removal by drinking water treatment technologies.

Drug sales data available from IMS Health can provide the total mass of individual drug substances across all product lines. Since IMS data are not readily available except through commercial license agreements, many published studies use prescription sales data to characterize drug sales. However, it is difficult to estimate the mass of drugs sold from prescription data, because of the many different drug products and since the number of scripts typically does not include drugs dispensed in hospitals or nursing homes. Furthermore, there are several reasons why drug sales data may not translate into accurate drug use data: (1) drugs may be discarded in toilets or household trash (a small amount); (2) average sales data may not reflect geographic or seasonal variability in consumption; and, (3) only a portion of the drug substance may be delivered to the body, e.g., transdermal dosage forms.

After ingestion, human drugs undergo Phase I metabolism, which includes oxidation, reduction or hydrolysis; followed by Phase II metabolism, which involves conjugation (e.g., addition of glucuronic acid, sulphate, acetic acid or amino acid). Depending upon the drug, these processes can yield various proportions of unchanged drug substance, active or inactive metabolites, or conjugates. There is evidence that conjugates can be converted back to the parent drug or metabolite through bacterial hydrolysis in a STP. The reduction in pharmacological activity following metabolism can range from zero to essentially 100 percent depending on the drug.

Drug substances excreted into the public sewer are diluted by the available wastewater flow. The average total STP influent flow in the US is 121.4 billion liters per day, which is used to estimate the expected introductory concentration for FDA. Regional and seasonal variability in STP flow is expected as a result of differences in water consumption per capita, industrial water use, weather conditions, etc. STP effluent is further diluted by the receiving water – a factor of 1:10 is often used to account for dilution in the environment. As described in Section 2, a number of degradation and partitioning mechanisms can act on drug substances in both an STP and the environment.

Conservative estimates of environmental concentrations of a drug substance can be calculated from the total mass of drug substance sold and the available dilution from STP and receiving water flow as described above. These estimates can be refined by considering metabolism and the various STP and environmental degradation and partitioning mechanisms.

C. Characterizing Risk

The estimation of potential impact of human pharmaceuticals to human health from environmental exposures typically uses two concepts: the predicted environmental concentration (PEC) and the predicted no effect concentration (PNEC). The PEC element is based on the physical, chemical and biological fate properties of the molecule, as well as hydrological information on STP effluent flows and surface water flows. The PNEC element estimates concentrations at which potential effects on human health might occur. In general, if the PEC is less than the PNEC (PEC/PNEC < 1) the risk is deemed acceptable. This approach to environmental risk assessment is called the risk characterization ratio method.

7. Modeling as One Approach Understanding the Risk to the Environment

As with the risk to human health, the potential risk to the environment presented by the presence of pharmaceuticals is a function of hazard and exposure.

A. Potential for and Evaluation of Acute Hazards

Pharmaceutical companies sometimes conduct acute toxicity studies to support environmental assessments that are filed with NDA and MAA applications or to support internal programs. Acute toxicity to aquatic receptors is usually assessed by evaluation of several common species including typically a fish (usually fathead minnows, bluegills or rainbow trout), an invertebrate (usually a daphnid such as Daphnia magna) and an algal species. These acute toxicity studies last up to 96 hours. The endpoints measured may include growth and/or growth rate (algae), immobilisation (Daphnia), and morbidity and/or mortality (fish) and are often expressed as a concentration that elicits an effect in a specified percentage of the test group. For substances that may be expected to partition into soils or sediments, studies in terrestrial species, such as earthworms, may be conducted.

Generally speaking, there is little potential for an acute environmental hazard to exist from the presence of pharmaceuticals that find their way into the environment through use by humans because the levels are so low. As for the potential for an acute environmental hazard to be presented from pharmaceutical manufacturing, there are regulatory and industry practices in place that minimise the risk. Environmental agencies have in place permitting programs that control acutely toxic manufacturing discharges.

B. Potential for and Evaluation of Chronic Hazards

There are several methods that are currently approved by regulatory agencies for the conduct of chronic aquatic toxicity studies. The most commonly used are the Daphnia 21-day toxicity study and the prolonged toxicity study in fish. Currently, such studies are conducted relatively infrequently due to the relatively low introduction concentrations of drug substances into the environment, the tendency for many drugs to be metabolized to relatively more water-soluble and less active metabolites, and because they are primarily produced by batch vs. continuous manufacturing operations. There is however, considerable interest in the development of improved methods for aquatic toxicity assessments of chronic effects. In addition, the EMEA Guidelines for environmental risk assessments for new pharmaceuticals now requires a base set of chronic ecotoxicity studies in lieu of the previously required acute studies.

C. Characterizing Risk

The estimation of potential impact of human pharmaceuticals to aquatic life mirrors the procedure used for human health risk characterization: the predicted environmental concentration (PEC) and the predicted no effect concentration (PNEC). Here, the PNEC element estimates concentrations at which potential effects on aquatic life might occur. In general, if the PEC is less than the PNEC (PEC/PNEC < 1) the risk is deemed acceptable. This approach to environmental risk assessment is called the risk characterization ratio method.

C. Links

EMEA *Guideline on the environmental risk assessment of medicinal products for human use*; The European Agency for the Evaluation of Medicinal Products, London, England, June 2006 Doc. Ref. EMEA/CHMP/SWP/4447/00
http://www.emea.eu.int/pdfs/human/swp/444700en.pdf

FDA-CDER. *Guidance for industry - environmental assessment of human drugs and biologics applications*, FDA Center for Drug Evaluation and Research, Rockville, MD, USA (CMC6 Revision 1), 1998, http://www.fda.gov/cder/guidance/index.html)

The Swedish Association of the Pharmaceutical Industry (LIF) (http://www.fass.se)

Pharmaceuticals and Personal Care Products (PPCPs) as Environmental Pollutants
http://www.epa.gov/esd/chemistry/pharma/

Monograph, Toward a Green Pharmacy (US EPA)
http://www.epa.gov/esd/chemistry/pharma/images/green1.pdf

Antibiotic Resistance (US FDA)
http://www.fda.gov/oc/opacom/hottopics/anti_resist.html

Endocrine Disruption (WHO)
http://www.who.int/pcs/emerg_site/edc/global_edc_TOC.htm

US PhRMA Position on Pharmaceuticals in the Environment
http://www.phrma.org/mediaroom/press/releases///13.03.2002.366.cfm

P*h*RMA P*h*ATE Model:Screening Analysis of Human Pharmaceuticals in US Surface Waters
http://pubs.acs.org/cgi-bin/article.cgi/esthag/2004/38/i03/pdf/es034430b.pdf

Human pharmaceuticals in US surface waters: A human health risk assessment
http://dx.doi.org/ doi:10.1016/j.yrtph.2005.05.005

Effects of Human Pharmaceuticals on Aquatic Life: Next Steps
http://pubs.acs.org/subscribe/journals/esthag/40/i11/pdf/060106viewpoint_cunningham.pdf

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Zuccato *et al.* 2004. E. Zuccato, S. Castiglioni, R. Fanelli, R. Bagnati and D. Calamari, Pharmaceuticals in the environment: changes in the presence and concentrations of pharmaceuticals for human use in Italy. In: K. Kümmerer, Editor, *Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks* (Second Edition), Springer, Berlin, Germany (2004), pp. 45–53.

Pharmaceuticals in the Environment – A Review of P*h*RMA Initiatives

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Prepared for
4th Japan – U.S. Governmental Conference on Drinking Water Quality Management and Wastewater Control

PhRMA

Issue

- Pharmaceutical products are being detected in the environment
- Concern has been expressed that human health and aquatic life impacts might result from environmental exposure to pharmaceutical compounds

PhRMA

P*h*RMA Perspective

- A science-based approach:
  - is required to understand and address concerns resulting from presence of pharmaceutical compounds in the environment
  - will identify gaps in existing knowledge that require further investigation regarding the potential for impacts

PhRMA

Benefits of a Science Based Approach to PIE

- Provide confidence to the industry, communities and governments that safety of pharmaceuticals in the environment is well understood
- Identify any issues requiring further investigation regarding existence and significance of potential impacts

PhRMA

Characteristics of Pharmaceuticals

- Pharmaceuticals are often ionic, which influences their environmental fate.
- Ionic, hydrophilic behavior is not typical of chemicals usually evaluated for environmental fate and effects.
  - Many environmental models developed for non-ionic chemicals are not applicable to ionic, multifunctional compounds; their use
    - may lead to incorrect interpretations of test results
    - may lead to improper classifications

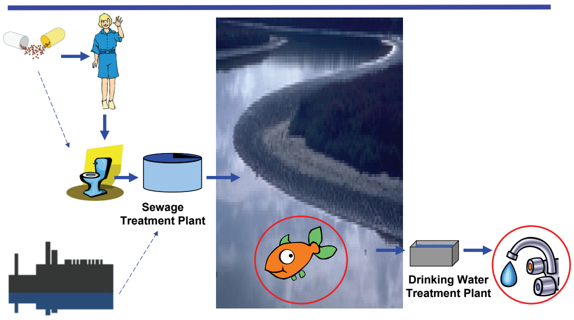
PhRMA

Characteristics of Pharmaceuticals

- Pharmaceuticals enter the environment continuously.
- Sources are geographically diffuse and may be influenced by regional use patterns.
- Compounds in the environment may be parent, metabolites or conjugates.
- Compounds may be present in mixtures with other pharmaceuticals, organic and inorganic pollutants, etc.
- Science challenges exist, e.g., testing methods, mixtures, chronic eco-toxicity endpoints

PhRMA

Pharmaceuticals in the Environment



Patient Use is the Primary Pathway Human Pharmaceutical Compounds Enter the Environment

A Science-based Approach: A step-wise progression

- **Understand the potential for exposure**
- Assess potential impacts to man
- Assess potential impacts to environmental species

PhRMA

The P*h*ATE Model™

Needs:

- Evaluate potential distribution of pharmaceutical compounds in the environment
- Assess the significance of reported concentrations to humans and aquatic life

Action:

- Develop tool to estimate concentrations of pharmaceutical compounds in the environment

PhRMA

P*h*ATE™ Model Development (2001)

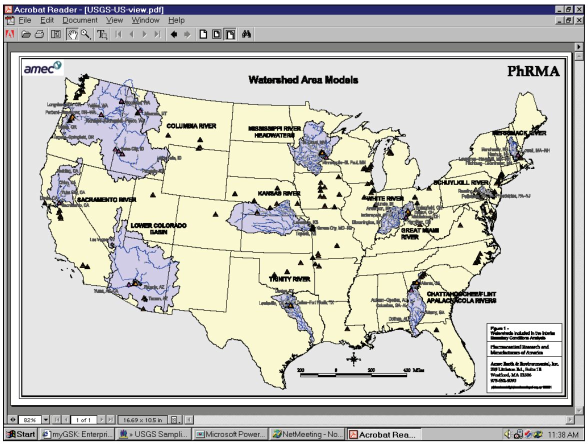
- Watershed (drainage basin of receiving waterbody)
  – a geographic area in which water, sediments and dissolved materials drain to a common outlet
- Approach allows better understanding of the cumulative impact of human activities
- Many regions moving toward watershed based water quality management

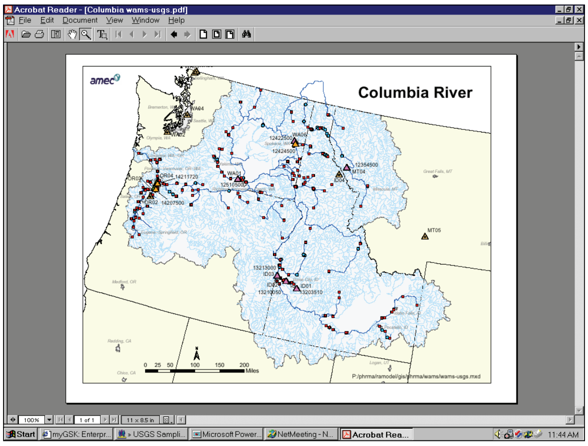
PhRMA

P*h*ATE™ Model Development (2001)

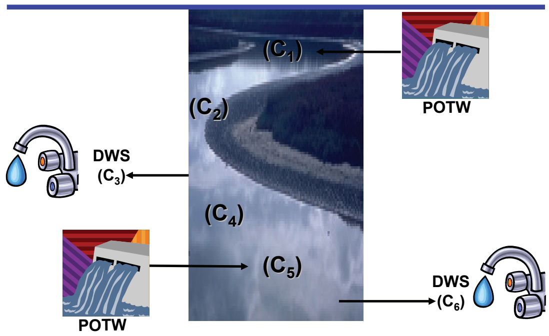
- Model predicts concentrations of pharmaceuticals in the environment due to patient use
- Model was developed by P*h*RMA PIE Task Force and AMEC Earth and Environmental
- Third party reviewers:
  - Dr. Josh Cohen, Harvard School of Public Health
  - Dr. Steve Chapra, Tufts University

PhRMA

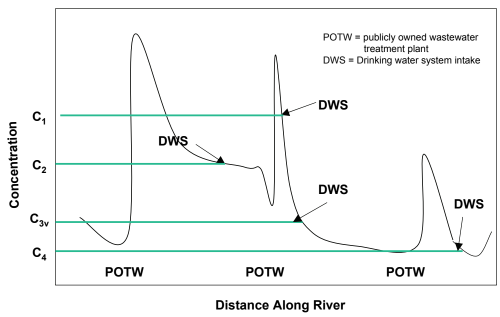




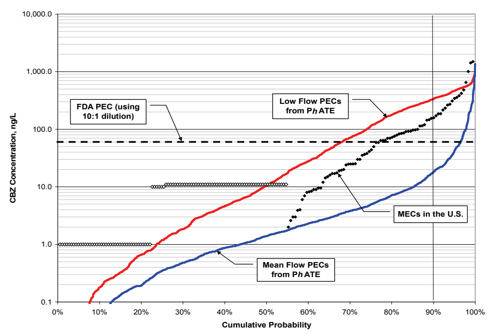
Watershed Evaluation



Determination of Concentration Profiles



Example P*h*ATE™ Output: carbamazepine



Model-related publications

- USGS Paper:
  - –Kolpin, *et al.*, **Pharmaceuticals, Hormones, & Other Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance**, *Environ. Sci. Technol.*. 2002, **36,** 1202-1211.
- P*h*ATE™ Papers:
  - –Cunningham, V.L. **The PhATE™ Model: Estimating the Distribution of Pharmaceuticals in the Environment,** *Southwest Hydrology*, November/December 2003, 20-21
  - –Anderson, P.D.; D'Aco, V.J.; Shanahan, P.; Chapra, S.C.; Buzby, M.E.; Cunningham, V.L.; DuPlessie, B.M.; Hayes, E.P.; Mastrocco, F.J.; Parke, N.J.; Rader, J.C.; Samuelian, J.H.; Schwab, B.W. **Screening analysis of human pharmaceutical compounds in U.S. surface waters**. *Environ. Sci. Technol.* 2004, **38**, 838-849.
  - –Cunningham, V. L.; Constable, D. J.; Hannah, R. E. **Environmental Risk Assessment of Paroxetine**, *Environ. Sci. Technol.* 2004**, 38,** 3351-3359.
  - – Cunningham, V.L.; Buzby, M.; Hutchinson, T.; Mastrocco, F.; Parke, N.; Roden, N. **Effects of Human Pharmaceuticals on Aquatic Life: Next Steps,** **E***nviron. Sci. Technol.* 2006**, 40**, 3456 - 3462

A Science-based Approach: A step-wise progression

- Understand the potential for exposure
- **Assess potential impacts to man**
- Assess potential impacts to environmental species

Human Health Screening Analysis

- Analysis included 26 USGS human health pharmaceuticals
  - Non-steroidal analgesics, non-steroidal anti-inflammatory
  - Opiate analgesic
  - Bronchodilator
  - H2 receptor antagonists
  - Antimicrobial, antibiotics, antibacterial
  - Calcium blocker, ACE inhibitor, anti-hypertensives
  - Serotonin uptake inhibitors, anti-depressive
  - Hypoglycemic
  - Anti-coagulant
  - Cardiac glycoside
  - Anti-hyperlipidemic
- Compounds studied excluded hormones which are being evaluated separately due to the complexity of that evaluation

Human Health Screening Analysis

- Identified measured environmental concentrations for compounds reported in published articles (MEC)
- Used P*h*ATE™ in screening mode to predict concentrations in environment — **PEC**
- Developed predicted no effect concentrations (PNEC)
  - Considered drinking water and fish consumption exposure pathways — **PNEC**
- Evaluated MEC/PNEC and PEC/PNEC ratios

Human Risk Assessment

Conclusion:

"Results of this human health assessment indicate that no appreciable human health risk exists from the presence of these trace residues in surface water and drinking water."

Schwab, B. W., *et al.* **Human pharmaceuticals in US surface waters: A human health risk assessment**, *Reg. Tox. Pharmacol.* 2005, **42,** 296-312

Other Human Health Publications

- Christensen, F.M. (1998) **Pharmaceuticals in the environment – A Human Risk?,** Reg. Toxicol. & Pharmacol., 28, 212-221.
- Schulman, et al., (2002) **A human health risk assessment of pharmaceuticals in the aquatic environment***,* Human & Ecological Risk Assessment, 8 (4), pp. 657-680.
- Mons, M.N., (2003) **Pharmaceuticals and drinking water supply in the Netherlands**, Kiwa N.V. Water Research.
- Webb, et al., (2003) **Indirect human exposure to pharmaceuticals via drinking water***,* Toxicology Letters, 142, 157-167.

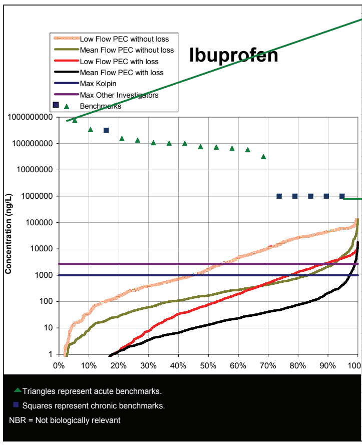
All concluded that environmental exposure to human pharmaceuticals poses little human health risk.

A Science-based Approach: A step-wise progression

- Understand the potential for exposure
- Assess potential impacts to man
- **Assess potential impacts to environmental species**

Aquatic Life Data Base - P*h*ACT™

- Includes English language, peer-reviewed literature
  - chronic and acute effects to aquatic organisms
  - fate and transport and treatment removal
- Bibliographic information entered for 1028 articles
  - 610 chronic and acute effects
  - 618 fate and transport / treatment
- Status
  - data from 583 articles have been entered
  - data from remaining 445 articles will be entered by 2007
  - data from 30-40 new articles entered each quarter



Value (ng/L)	Endpoint	Benchmark	Comment
753200000	Algae: Growth	EC80	
342200000	Algae: Growth	EC50	
315000000	Algae: Growth	EC50	
155500000	Algae: Growth	EC20	
134100000	Invertebrate: Immobilization	EC80	
108000000	Invertebrate: Immobilization	EC50	
102700000	Algae: Growth	EC10	
101200000	Invertebrate: Immobilization	EC50	
76400000	Invertebrate: Immobilization	EC20	
75000000	MIXTURE - Invertebrate: Immobilization	NOEC	Mixture
72900000	Algae: Growth	EC5	
66000000	Invertebrate: Immobilization	EC10	
58400000	Invertebrate: Immobilization	EC5	
32000000	MIXTURE - Invertebrate: Immobilization	NOEC	Mixture
22000000	Plant: Growth	EC50	
10000000	Invertebrate: Bud production	NOEC	NBR
4000000	Plant: Growth	EC50	
1000000	Plant: Wet Weight	NOEC	
1000000	Plant: Frond Number	NOEC	
1000000	Plant: Chlorophyll a	NOEC	
1000000	Plant: Chlorophyll b	NOEC	
1000000	Plant: Carotenoids	NOEC	
1000000	Plant: Wet Weight	EC10	Equal to NOEC
1000000	Plant: Frond Number	EC10	Equal to NOEC
1000000	Plant: Chlorophyll a	EC10	Equal to NOEC
1000000	Plant: Chlorophyll b	EC10	Equal to NOEC
1000000	Plant: Carotenoids	EC10	Equal to NOEC
1000000	Plant: Wet Weight	EC25	Equal to NOEC
1000000	Plant: Frond Number	EC25	Equal to NOEC
1000000	Plant: Chlorophyll a	EC25	Equal to NOEC
1000000	Plant: Chlorophyll b	EC25	Equal to NOEC
1000000	Plant: Carotenoids	EC25	Equal to NOEC
1000000	Plant: Wet Weight	EC50	Equal to NOEC
1000000	Plant: Frond Number	EC50	Equal to NOEC
1000000	Plant: Chlorophyll a	EC50	Equal to NOEC
1000000	Plant: Chlorophyll b	EC50	Equal to NOEC
1000000	Plant: Carotenoids	EC50	Equal to NOEC
600000	MIXTURE - Phytoplankton: Abundance	LC100	Mixture
600000	MIXTURE - Phytoplankton: Diversity	LOEC	Mixture
600000	MIXTURE - Zooplankton: Abundance	LOEC	Mixture
600000	MIXTURE - Plant: Growth	LOEC	Mixture
600000	MIXTURE - Zooplankton: Diversity	LOEC	Mixture
600000	MIXTURE - Fish: Mortality	LOEC	Mixture
60000	MIXTURE - Fish: Mortality	LOEC	Mixture
60000	MIXTURE - Plant: Growth	LOEC	Mixture
10000	Cyanobacteria: Growth	EC72	Stimulated growt
10000	Invertebrate: Polyp Structure	LOEC	NBR
10000	Invertebrate: Ingestion rate	LOEC	NBR
10000	Invertebrate: Polyp Regen.	NOEC	NBR
10000	Invertebrate: Polyp Regen.	NOEC	NBR
6000	MIXTURE - Fish: Mortality	NOEC	Mixture

Other P*h*RMA PIE Publications

- Till (2005) The detection of pharmaceutical compounds in surface water is a matter of significant interest to the pharmaceutical industry. *Sci. Tot. Environ.* In press.
- Till (2005) Pharmaceutical data do not elude researchers. *Environ. Sci. Technol.* (Oct 1 2005, p 292a)
- Carbamazepine risk assessment (SETAC presentations, Nov. 2005, May 2006)
- Cunningham *et al.* Human Health and Environmental Risk Assessment of Carbamazepine in Surface Waters of North America and Europe, submitted for review
- Analgesics case study (SETAC poster, Nov, 2005); manuscript in preparation
- Do pharmaceuticals in surface waters pose a risk to human health? In submission process
- Environmental risk assessment of EE2 in EU and US - manuscripts in preparation
- Landfill Disposal of Medicines as a Potential Surface Water Pathway – WEF presentation, August 2007, manuscript in preparation

PhRMA

Summary

- The industry is committed to assessing the significance of pharmaceuticals in the environment using science- based approaches.
- The human risk assessment concluded that, for the compounds investigated to date, no appreciable risk to human health exists.
- The industry is evaluating published data on aquatic life impacts and formulating an approach to assess the potential for impacts to ecosystems.
- The industry is committed to collaborating with other stakeholders

PhRMA

Contributors

- Pharmaceutical Research and Manufacturers of America
  - Aquatic Life Working Group
  - Human Health Working Group
  - Environmental Assessment Working Group
  - Unused Medicines Working Group
- Vince D’Aco, Quantum Management Group, Inc.
- Paul Anderson and Beth DuPlessie, AMEC
- Lial Tischler, Tischler & Kocurek

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