The Adverse Effects of Pharmaceuticals in Water Supplies

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Ecotoxicology:
The study of how chemicals affect the environment and the organisms living in it.
Ecotoxicology

• What do we know?
  – Pharmaceuticals and personal care products have been detected in some groundwater, surface water, and drinking water sources
  – Some active pharmaceutical ingredients (APIs) persist in the aquatic environment at low concentrations
  – They are continuously released into the environment
  – Some have been found to adversely affect aquatic organisms
  – These effects are often not identified during toxicity studies in New Drug Applications
  – Not likely to cause acute health effects

Ecotoxicology

• What don’t we know?
  – The extent to which these detected personal care products and pharmaceuticals affect wildlife, and whether they affect human health
Ecotoxicology

- Understanding potential risks to aquatic wildlife and humans is complicated by:
  - Multiple routes of exposure
  - Exposure to multiple contaminants
  - Low level chronic exposures

Ecotoxicology

- How do we assess the affects?
  - Animal exposure studies
  - Environmental risk assessments
  - Human health risk assessments

Animal Exposure Studies

- Knowledge of the ecotoxicity of pharmaceuticals is limited to a few substances in a few test species
  
<table>
<thead>
<tr>
<th>Substance</th>
<th>Class</th>
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<tbody>
<tr>
<td>Estrogen</td>
<td>NSAIDS</td>
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<tr>
<td>Antibiotics</td>
<td>Fibrates</td>
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<tr>
<td>Antidepressants</td>
<td>Statins</td>
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<tr>
<td>Antiepileptics</td>
<td>Beta blockers</td>
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</tbody>
</table>
Animal Exposure Studies

• Mechanisms of toxicity may differ between acute and chronic low-dose exposures
• Need to determine if subtle effects are occurring
  Growth Sex ratio
  Fertility Reproductive behavior
• Must use ecologically relevant endpoints
  Growth impairment Delayed reproduction
  Delayed development

Antibiotics
• Some detected antibiotics persist in environment
• Development of antibiotic-resistant bacteria is of large concern
• Bacterial breakdown products of some pharmaceuticals are toxic

Antidepressants
• SSRIs bioaccumulate in the environment
• Long-term exposure has resulted in delayed development in fish and metamorphosis in frogs

Estrogens
• 5.7% US streams surveyed had >5 ng/L 17α-ethinylestradiol
• 2 ng/L partial life-cycle exposure caused sex reversal
• 5 ng/L life-long exposure caused 56% reduction in fertility of F1 generation
• 0.2 ng/L for life-long exposure caused 20% reduction in hatching success
Environmental Risk Assessments

• Risks are characterized by comparing estimated environmental exposure concentrations with estimated environmental toxicity concentrations.
• Efforts are being made to use the more ecologically relevant toxicity endpoints for determining environmental toxicity concentrations.

Human Health Risk Assessments

• Few studies have addressed the affects of trace levels of pharmaceuticals in the environment on human health.
• Recent studies with new twists:
  – Predicted environmental concentrations
  – Assessment of sensitive populations
  – Prescribed vs. naturally occurring estrogens

Human Health Risk Assessment: Predicted Environmental Concentrations

• Evaluated 44 active pharmaceutical ingredients (22 general pharmacological classes) for impact on human health due to exposures from:
  • Drinking water
  • Fish consumption

From Cunningham et al. Regulatory Toxicology and Pharmacology, 2009
Human Health Risk Assessment

Predicted Environmental Concentrations

• Pharmaceutical Environmental Concentrations (PEC) in water were predicted using with modeling
  • Insufficient measured concentrations available
  • Quantities discharged include products by sale from all sources
• Predicted No Effect Concentrations (PNEC) were developed
  • Standard EPA drinking water and fish consumption assumptions were used
• PEC:PNEC was used to assess risk

RESULTS
• PEC:PNEC were less than 1 for all pharmaceuticals evaluated

CONCLUSIONS
• The evaluated pharmaceuticals do not pose a threat to human health when in drinking water

SIGNIFICANCE
• Predicting PECs with models allows assessment on non-detect pharmaceuticals in water

Assessment of Sensitive Populations

• Evaluated risk of meprobamate, carbamazepine, and phenytoin exposures
  • Accidental exposures to stream water and fish consumption
  • Ingestion of drinking water

From Kumar & Xagoraraki, Regulatory Toxicology and Pharmacology, 2010
Human Health Risk Assessment
Assessment of Sensitive Populations

- Chronic Daily Intakes (CDIs) calculated using
- Default exposure parameters for recreational exposure, fish consumption, and drinking water ingestion
- Pharmaceutical concentrations in stream and drinking water were measured values in literature
- Acceptable Daily Intakes (ADIs) developed from subpopulation-specific toxic endpoints
- CDI:ADI was used to assess risk

RESULTS
- 99th percentile CDI:ADI less than 1x10^-4

CONCLUSIONS
- The evaluated pharmaceuticals do not pose a threat to human health

SIGNIFICANCE
- Characterize risk using subpopulation-specific toxic endpoints

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Human Health Risk Assessment
Prescribed and Naturally Occurring Estrogens

- Compared exposure to estrogens in drinking water with:
  - Exposures to natural estrogens in diet
  - Acceptable daily intakes (ADIs)

From Caldwell et al., Environmental Health Perspectives, 2010
Human Health Risk Assessment
Prescribed and Naturally Occurring Estrogens

• Estrogen concentrations in drinking water were predicted
  • Endogenous estrogens from diet and naturally produced
  • Prescribed endogenous estrogens
  • Prescribed synthetic estrogen
• Drinking water exposures determined using predicted concentrations and default intake rates

Human Health Risk Assessment
Prescribed and Naturally Occurring Estrogens

• Estrogen exposure in the diets were evaluated using
  • Milk consumption of young children
  • Adult female eating omnivorous diet
• ADIs were those available in the literature

RESULTS
• Child exposure to total estrogens in drinking water is about 150 times lower than exposure from milk
• MOS for total estrogens in drinking water ~2 times lower than MOS for prescribed estrogens
• MOS for children for total estrogen in drinking water ranged from 28-5120
Human Health Risk Assessment
Prescribed and Naturally Occurring Estrogens

CONCLUSIONS
• Prescribed and total estrogens in US drinking water are not causing adverse effects, including sensitive subpopulations

SIGNIFICANCE
• Used Predicted Environmental Concentrations and toxicity benchmarks for sensitive subpopulations

Summary
• Current human health risk assessments are not identifying problems with exposures to pharmaceuticals in water
• Environmental risk assessments will be of better value as our understanding of the significance of exposures to pharmaceuticals in water improves
• Animal exposure studies are showing that aquatic biota are at risk with exposures to pharmaceuticals in water