


Ecotoxicology


- What do we know?
 - Pharmaceuticals and personal care products have been detected in some groundwater, surface water, and drinking water sources



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Ecotoxicology


- 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 effect aquatic organisms
- These effects are often not identified during toxicity studies in New Drug Applications
- Not likely to cause acute health effects



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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



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Ecotoxicology

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

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Ecotoxicology

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



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Animal Exposure Studies

- Knowledge of the ecotoxicity of pharmaceuticals is limited to a few substances in a few test species
 - Estrogen
 - Antibiotics
 - Antidepressants
 - Antiepileptics
 - NSAIDS
 - Fibrates
 - Statins
 - Beta blockers

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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

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Animal Exposure Studies

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

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Animal Exposure Studies

Estrogens

- 5.7% US streams surveyed had >5 ng/L 17 α -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



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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

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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

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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

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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

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Human Health Risk Assessment
Predicted Environmental Concentrations

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

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Human Health Risk Assessment
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 & Xagorarakis, Regulatory Toxicology and Pharmacology, 2010

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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

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Human Health Risk Assessment
Assessment of Sensitive Populations

RESULTS


- 99th percentile CDI:ADI less than 1×10^{-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

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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

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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

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Human Health Risk Assessment
Prescribed and Naturally Occurring Estrogens

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

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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



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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**

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