AN INFORMATIC APPROACH TO ESTIMATING ECOLOGICAL RISKS POSED BY PHARMACEUTICAL USE

Mitch Kostich

August 24, 2005

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Overview:

Why worry about pharmaceuticals?

The data deficit

An informatics guided approach

Additional considerations

Acknowledgements

Ecological Exposure Research Division

Why worry about pharmaceuticals?

Pharmaceuticals in widespread use for humans, agricultural animals, aquaculture, pets

Often excreted in active form or as active metabolites

Found in WWTP influents, effluents, sludge, surface water, ground water, drinking water, fish, etc

Often >ng/L concentrations

Designed to have effects at low concentrations

Some (i.e. EE2) known to affect fish at ng/L in lab

Reasonable suspicion of contributing to intersex, etc.

The data deficit

The question: which drugs are likely to have detrimental effects at environmental concentrations

>2000 drugs approved for use in US

Little/no concentration or ecotox data for vast majority

Chemical analysis expensive

Chronic ecotox data even more rare + expensive

Too expensive to thoroughly study all drugs soon

Some subjectively of more concern than others

Need rational way to ‘triage’ drugs for further work

An informatics guided approach

Break problem down into components based on:

- different data sets involved
- different routes into environment
- different likely modes of environmental impact

Break out / order:

- Human retail prescription
- Human OTC
- Human institutional
- Agricultural animals
- Aquaculture
- Companion animals

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

An informatics guided approach

Environmental Risk Assessment of Medicinal Products for Human Use According to European Commission Recommendations

Gerd Huschek,[1] Peter D. Hansen,[2] Hans H. Maurer,[3] Dietmar Krengel,[1] Anja Kayser[1]

[1]IEQ Institute of Environmental Protection and Quality Assurance Dr. Krengel Ltd., Konsumhof 1–5, D-14482 Potsdam, Germany

[2]Department of Ecotoxicology, Technical University of Berlin, Franklinstrasse 29, D-10587 Berlin, Germany

[3]Department of Experimental and Clinical Toxicology, University of Saarland, D-66421 Homburg (Saar), Germany

Received 3 August 2003; revised 28 January 2004; accepted 13 February 2004

Abstract: Presented here, based on new recommendations of the European Commission, is an environmental risk assessment (ERA) of a selected group of pharmaceuticals for Phase I, environmental exposure assessment, and Phase II Tier A, initial environmental fate and effect analysis. This pharmaceutical group is composed of the 111 highest-selling human drug substances that have annual sales in Germany of more than 5,000 kg. The data required for this ERA came from analyzing: (1) sales annually (in kg or IU) of the 2671 active pharmaceutical drug substances (2001) on the German market in all medicinal products sold by pharmacies (with and without prescriptions) and used in hospitals in 1996–2001; (2) the use pattern of drug substances as categorized according to Anatomical Therapeutic Chemical (ATC) classification indexes ATC3 and ATC7; (3) data for excretion, toxicity, and metabolites of the 111 selected human drug substances; (4) the physico-

Environ Toxicol. 2004;19(3):226

Ecological Exposure Research Division

An informatics guided approach

Calculate likely worst case scenario for each drug

Assume most likely toxicity is mechanism based

- physical properties unlikely cause of tox at ng/L

Predict highest likely environmental concentration (PEC)

- public data on usage, ADME, physical properties
- estimate excretion, dilution, partition between matrices
- ‘worst case’ fudge factors to fill data gaps (raise PEC)
- assume some (~10%) flushed unchanged in every case

Concentrations as human dose equivalents per volume

An informatics guided approach

Predict ‘no effect’ concentration for fish (PNEC)

- public data on ADME, MOA, MOTox for many
- mostly mammalian data
- consider molecular/physiological conservation
- ‘worst known case’ fudge factors (lower PNEC)

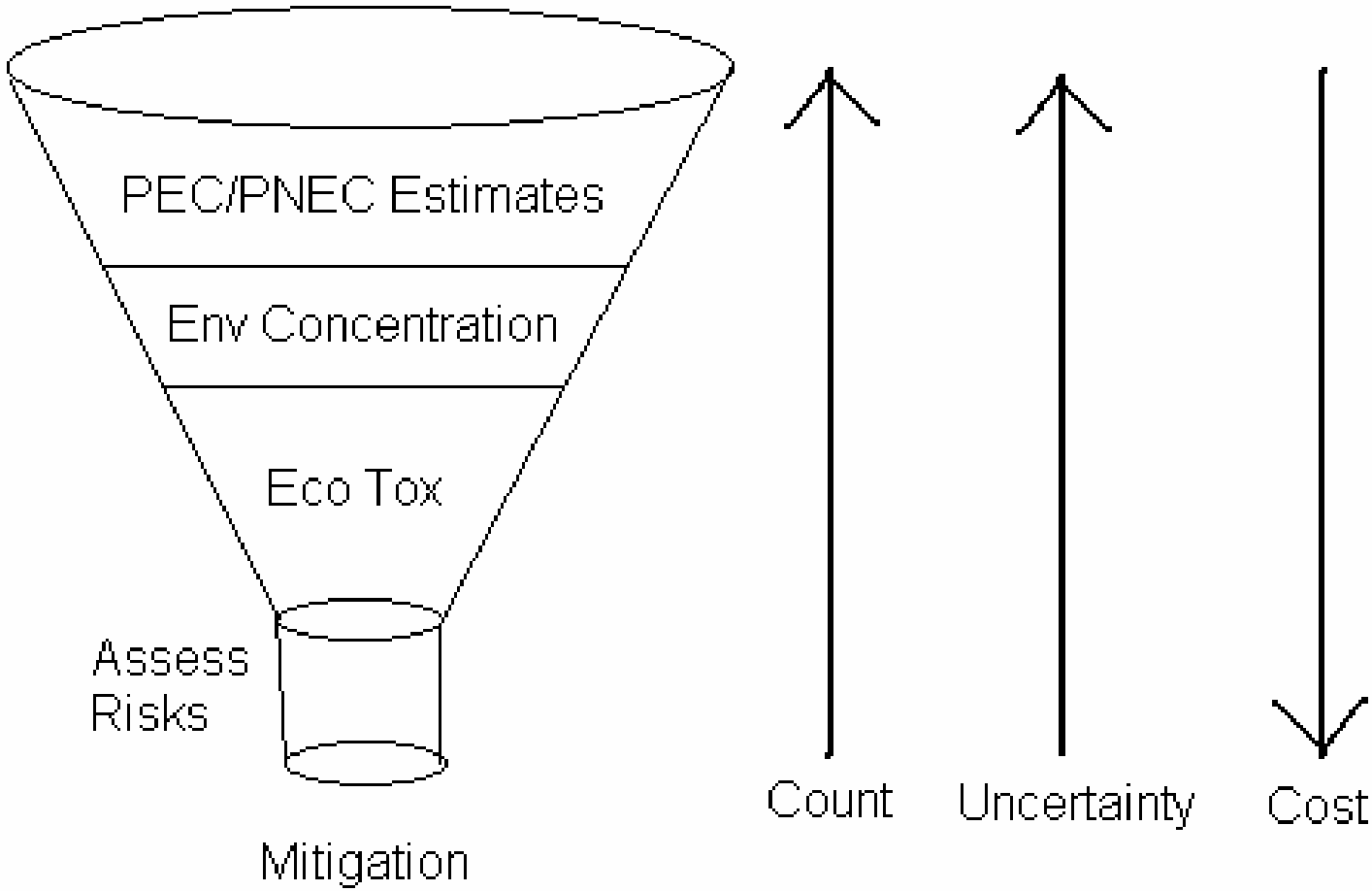
Ratio PEC/PNEC used to rank drugs for study

Semi-quantitative w/ subjective components

Focuses efforts on likely dangers and key uncertainties

Updateable data matrix can feed alternative scorings

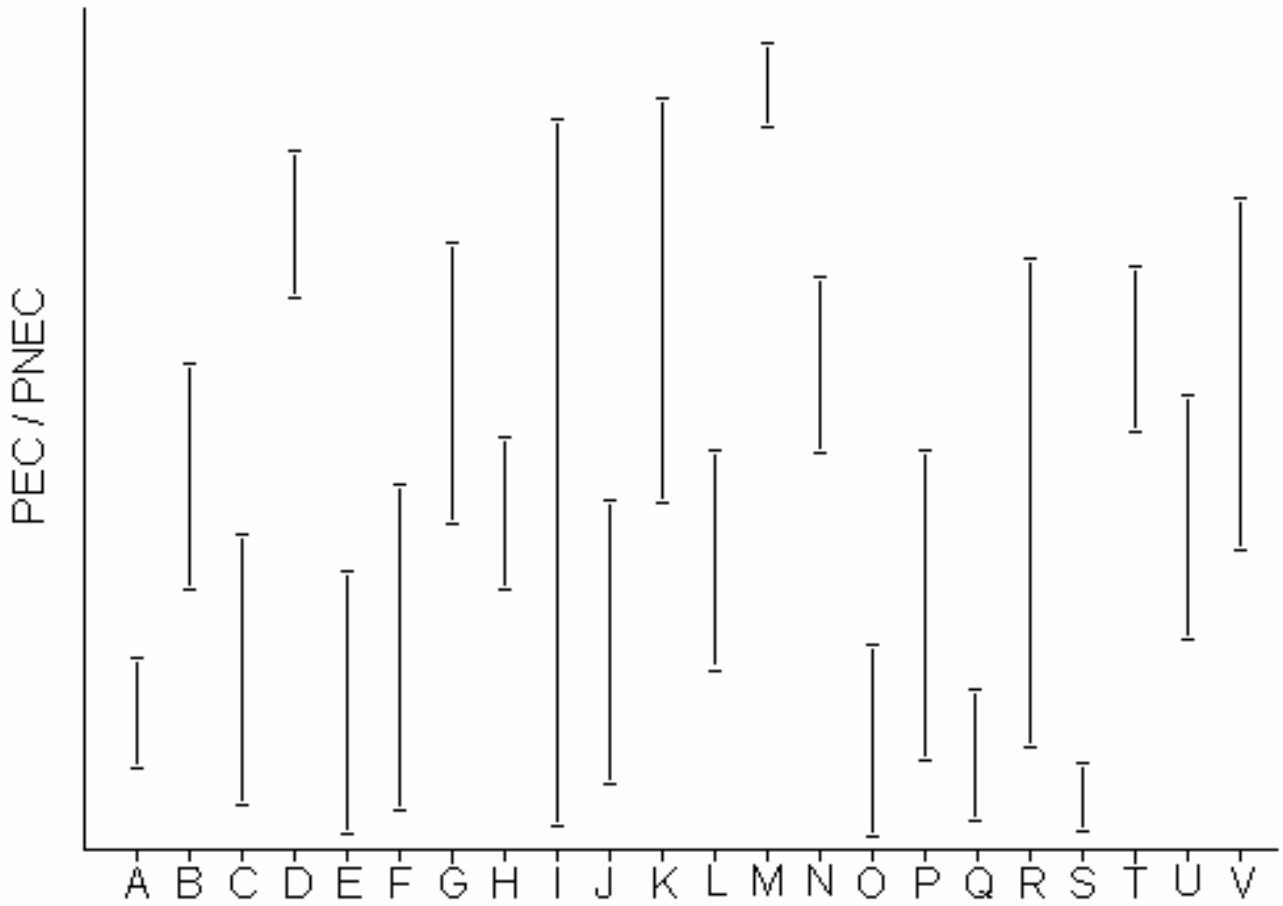
An informatics guided approach



RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

An informatics guided approach

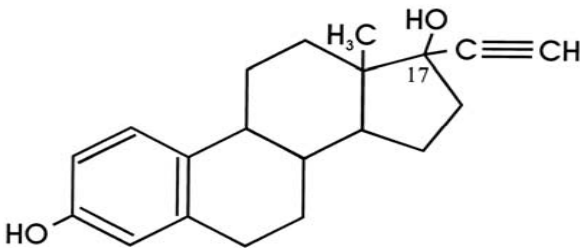


Ecological Exposure Research Division

Additional considerations

Poster child is ethynylestradiol (EE2):

- ecological concentrations known to cause effects in lab
- only part of total EDC activity
- any remediation would likely aim more broadly
- widely prescribed with frequent and regular use
- unusually potent with well conserved MOA
- designed to block critical species function (repro)
- how many other drugs fit this mold?

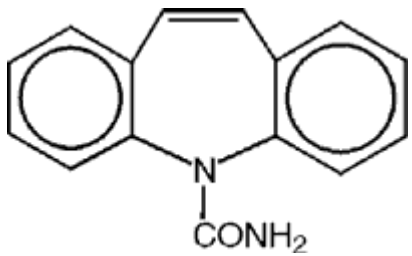


Ecological Exposure Research Division

Additional considerations

Carbamazepine hard to explain:

- usage stats not that high (not in top 200 lists)
- only 2-3% excreted unchanged
- main metabolite is active, but not looked for
- chronic high dose administration
- very stable in environment?
- perhaps the most ubiquitous drug in environment
- survives drinking water treatment
- but not very potent; what about drug combos?



RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions

Acknowledgements

Jim Lazorchak

Greg Toth

Christian Daughton

Susan Glassmeyer

Marc Mills

Ecological Exposure Research Division