Evaluation of Potential Human Health Effects from Environmental Exposure to Human Pharmaceuticals

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Overview

►► Background
►► Pharmaceuticals – special aspects
►► Risk Assessment Components
►► Examples of results of assessments
►► Conclusions
Since the 1990’s there are increasing reports of the presence of very low levels of drugs, in surface waters, and sometimes in drinking water.

The prime focus has been on the detection of drugs and their environmental fate, and recently on impact to aquatic species.
- Increasingly sensitive methods for detection

There are relatively few reports concerning risk to human health from exposure via drinking water and or fish consumption.

People want “clean” water, including drinking water. Some equate this to “zero” drug presence.
- How to reach zero!

Regulatory agencies and the public need to know if there are harmful effects as a result of the low levels of medicines in drinking water.

Therefore, it is important to focus on defining and determining acceptable levels via risk assessment activities.
Terminology

- **API** - active pharmaceutical ingredient
- **NOEL (LOEL)** - no (low)-observed-effect level
- **NOAEL (LOAEL)** - no (low)-observed-adverse-effect level
- **POD** - point of departure - the NOAEL or LOAEL dose for an effect of concern. Used to conduct a risk assessment.
- **ADI** - Acceptable Daily Intake - daily dose that should not result in adverse health effects, including sensitive individuals
  - Usually applied to compounds with threshold effects
- **PNEC** - Predicted no effect concentration
  - Usually applied to surface water/aquatic organisms, but can be useful for human drinking water/fish consumption assessments
- **PIE** - Pharmaceuticals in the Environment
Pharmaceuticals – Data available

► Much data may exist for APIs used in chronic therapy.
  ▪ Extensive preclinical (in vitro or animal studies) batteries for
    ► pharmacology
    ► metabolism and pharmacokinetics
    ► safety assessment – including repeat dose/chronic effects,
      gene tox, cancer bioassays, developmental and reproductive
      effects, cardiovascular safety, etc.
  ▪ Extensive human experience for many drugs,
    ► Clinical trial experience / acute NOEL/NOAEL for pharmacologic
      effect
    ► Effects on some sensitive populations, e.g. renal impairment,
      children
    ► Post-market pharmacovigilence
    ► Epidemiology studies
    ► Drug interactions
Pharmaceuticals – Some data may not be available

► Older drugs
  - Preclinical datasets may be more limited for older APIs.
  - However, clinical experience may be substantial.

► Metabolites of APIs can enter the environment.
  - They are often more polar.
  - Studies of the API reflect also exposure to the metabolites.

► Some recent APIs may have limited datasets
  - No chronic data if supporting acute/short term use
    - e.g. emergency medicine (stroke, myocardial infarction), antibiotics, local anesthetics, diagnostic agents,
  - Select populations studied
    - single sex only
    - adults only – no children, infants
      - e.g., Alzheimer’s and senility drugs,
Pharmaceuticals – Special Aspects

► Physicochemical Properties
  - Most APIs/metabolites are somewhat polar. Not likely to bioconcentrate.
  - Most APIs are not volatile.
  - Some may sorb to sludge or sediment.

► Metabolism & Pharmacokinetic properties
  - Most pharmaceuticals are designed to be short-lived – t1/2 ~ 6-12 hrs
  - They are not expected to undergo significant accumulation.

► CMR (carcinogen, mutagen, reproductive toxicant) status
  - Most pharmaceuticals for chronic, non-cancer therapies are not carcinogenic, mutagenic, reproductive toxicants and/or or selective developmental toxicants.

► Protein therapeutics
  - Protein therapeutics are not well absorbed orally and not excreted as API.
  - They break down to normal amino acids.
  - They will not be of major concern for exposure via the environment.
Risk Assessment (RA)
Human Health RA for APIs

- Aim is to protect the general population, sensitive individuals

- Multi-step process
  - Hazard Identification
  - Dose-Response Assessment
  - Exposure Assessment
  - Risk Characterization

- Iterative process
  - Screening modes – may choose to use conservative defaults
  - Refined modes

- Most relevant pathways of exposure for PIE
  - Drinking water
  - Fish Consumption

- A variety of approaches can be used at each stage
Hazard Identification

► Determine the spectrum of effects of your compound

► Therapeutic effects and “Side Effects”, e.g.,
  - Lower blood pressure
  - Lower cholesterol
  - Contraception
  - Anxiety relief
  - Antipsychotic effects
  - Antibiotic
  - Hypoglycemic
  - Target organ toxicity
  - Embryo/fetal toxicity
  - Genotoxicity
  - Carcinogenicity
  - Reproductive toxicity
  - GI microflora
  - Allergen

► For many APIs the therapeutic effect will drive the risk assessment.

► Philosophy - Pharmacologic effects are considered adverse for a non-patient population.
  - Prescription drugs should be prescribed by physicians to patients who will benefit from them.
Dose-Response Assessment and calculation of ADI

Many methods available for the dose-response assessment.
- Threshold – most commonly used
  - LOAEL/NOAEL + Uncertainty factors

Uncertainty factors (UF) often used to estimate ADIs
- ADI = POD/[UF1 x UF2 x ....UFn]
- Decide point of departure (POD) and UFs

Uncertainty factors that are typically used (factors 1-4 can range to 10x)
1. LOAEL to NOAEL
2. Duration of exposure
3. Interspecies extrapolation
4. Interindividual variability (sensitive populations)
5. Miscellaneous (e.g. data quality)
Uncertainty Factors - Considerations

Low effect to no effect - consider

- the description of the population
  - normal, healthy vs. person with medical disorder
- proportion of population affected at the POD dose
- who are likely to be the sensitive individuals?
  - Persons with impaired kidney, liver, immune function? Children? etc
- the severity of the POD effect;
  - Is the effect pharmacodynamic or is it toxic?

Duration of exposure - consider

- the nature of the effect and potential side effects
  - acute, transient vs. chronic, severe
- the pharmacokinetics of the compound, t1/2, etc.
  - does compound accumulate
Uncertainty Factors

Interspecies Extrapolation and Intraspecies variability - consider
► the effect, mechanism, relevance of species to humans
► the metabolism/pharmacokinetics in species - similar to man?
► the relative sensitivity of species,
► Use data-derived factors to replace default;

Miscellaneous - can range from less than 1 to 10 - consider
► completeness of dataset
► quality of data set
► route of administration
► no toxicity seen in well conducted studies at high doses
Establishing PNECs

PNEC_{Dw} - Concentration in drinking water that should not cause an adverse health effect in a specific set of persons, e.g. adults, children, etc. Derived from assumptions about the group of persons, e.g. daily water intake,

PNEC_{F} - Concentration in surface water that will maintain any residues in fish below limits of concern for fish ingestion.
## Establishing PNECs

### Parameters relating to adults and children

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Symbol</th>
<th>Receptor</th>
<th>Adult</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>kg</td>
<td>BW</td>
<td></td>
<td>70</td>
<td>14</td>
</tr>
<tr>
<td>Water consumption</td>
<td>L/day</td>
<td>IngRDW</td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fish consumption</td>
<td>kg/day</td>
<td>IngRF</td>
<td></td>
<td>0.0175</td>
<td>0.0065</td>
</tr>
<tr>
<td>Exposure frequency</td>
<td>days/year</td>
<td>EF</td>
<td></td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>Exposure duration</td>
<td>years</td>
<td>ED</td>
<td></td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>ADI averaging time</td>
<td>days</td>
<td>AT</td>
<td></td>
<td>10,950</td>
<td>2190</td>
</tr>
</tbody>
</table>

- PNECs for children are always lower than adult PNECs
  - by a factor of about 2.5 for drinking water,
  - a factor of about 1.9 for fish consumption
  - a factor of about 2.3–2.5 for drinking water + fish consumption
Establishing PNECs

Predicted no effect concentrations (PNEC) for children for three exposure scenarios: drinking water, fish consumption, and combined drinking water/fish consumption.

<table>
<thead>
<tr>
<th>Compound</th>
<th>ADI (μg/kg/day)</th>
<th>PNEC&lt;sub&gt;DW&lt;/sub&gt; (ng/L)</th>
<th>PNEC&lt;sub&gt;F&lt;/sub&gt; (ng/L)</th>
<th>PNEC&lt;sub&gt;DW+F&lt;/sub&gt; (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>340</td>
<td>5.0E + 06</td>
<td>2.4E + 08</td>
<td>4.9E + 06</td>
</tr>
<tr>
<td>Albuterol</td>
<td>2.8</td>
<td>4.1E + 04</td>
<td>2.0E + 06</td>
<td>4.0E + 04</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>29</td>
<td>4.2E + 05</td>
<td>2.1E + 07</td>
<td>4.1E + 05</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1.6</td>
<td>2.3E + 04</td>
<td>1.1E + 06</td>
<td>2.3E + 04</td>
</tr>
<tr>
<td>Codeine</td>
<td>2</td>
<td>2.9E + 04</td>
<td>1.4E + 06</td>
<td>2.9E + 04</td>
</tr>
<tr>
<td>Dehydronifedipine</td>
<td>100</td>
<td>1.5E + 06</td>
<td>5.1E + 06</td>
<td>1.1E + 06</td>
</tr>
<tr>
<td>Digoxigenin</td>
<td>0.07</td>
<td>1.0E + 03</td>
<td>1.1E + 05</td>
<td>1.0E + 03</td>
</tr>
</tbody>
</table>

(Schwab et al., 2005)
Exposure Assessment

Approaches to exposure assessment include:

► Direct measurement in drinking water
► Surrogate measurement, e.g. surface water near drinking water plant intakes
► Model to predict concentrations –
  ▪ several available
    ► EUSES, GREAT-ER – EU
    ► PhATE – US
  ▪ Run as worst case, or consider use of probabilistic modeling.
## Measured (MEC) and Predicted (PEC) concentrations

<table>
<thead>
<tr>
<th>Compound</th>
<th>Kolpin et al., 2002</th>
<th>Others</th>
<th>Max. P hATE PECs, low flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max. conc. or 1/2 RL *</td>
<td>Max. conc.</td>
<td>Drinking water</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>10,000</td>
<td>1,950</td>
<td>220,000</td>
</tr>
<tr>
<td>Albuterol</td>
<td>15</td>
<td>352</td>
<td>120</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>580</td>
<td>338</td>
<td>4400</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>30</td>
<td>30</td>
<td>3600</td>
</tr>
<tr>
<td>Codeine</td>
<td>1000</td>
<td>123</td>
<td>1100</td>
</tr>
<tr>
<td>Dehydronifedipine</td>
<td>30</td>
<td>2.0</td>
<td>1100</td>
</tr>
<tr>
<td>Digoxigenin</td>
<td>4.0</td>
<td>ND</td>
<td>6.3</td>
</tr>
</tbody>
</table>

- All conc. In ng/L
- MEC = Measured environmental concentration
- PEC = Predicted Environmental Concentration
- RL = Reporting Limit
Risk Characterization – MEC:PNEC or PEC:PNEC

Schwab et al, 2006
Risk Assessment – Other Publications

Assessment of the Potential Health Risk of Human Pharmaceuticals in the Environment; Binks, S.; Olson, M.; Cunningham, V. (GSK) (presented at SOT, 2006 & DIA)

► Evaluated 30 APIs; considered drinking water and fish ingestion scenarios

► All had human health risk ratio’s significantly lower than one

► For most of compounds studied, safe levels of exposure were directly to related therapeutic dose

► Because of their ionic nature most pharmaceuticals do not have significant potential for bioaccumulation
Risk Assessment – Other Publications


All concluded that environmental exposure to human pharmaceuticals poses little human health risk.
References on Human Health Risk Assessment


References – continued


Extra slides

►► Extra slides
Establishing PNECs

Drinking water consumption:
\[ \text{PNEC}_{\text{DW}} = 1000 \times \text{ADI} \times \text{BW} \times \text{AT} \times \text{IngR}_{\text{DW}} \times \text{EF} \times \text{ED} \]

Fish intake:
\[ \text{PNEC}_F = 1000 \times \text{ADI} \times \text{BW} \times \text{AT} \times \text{BCF} \times \text{IngR}_F \times \text{EF} \times \text{ED} \]

Drinking water + fish consumption:
\[ \text{PNEC}_{\text{DW+F}} = 1000 \times \text{ADI} \times \text{BW} \times \text{AT} \times (\text{IngDW} + \text{BCF} \times \text{IngR}_F) \times \text{EF} \times \text{ED} \]