Environmental risk of pharmaceuticals

Caroline Moermond

Centre for Safety of Substances and Products (VSP)
What is RIVM?

- National Institute for Public Health and the Environment
- 1500 staff, situated in Bilthoven
- Independent (by law!!), scientific advisor
- Not allowed to work for industry
- Three domains:
  - Environment and Safety
  - Public Health and Health Services
  - Infectious Diseases and Vaccinology
Who am I?

Caroline Moermond
- European Registered Toxicologist
- MSc Environmental Hygiene (WUR); aquatic ecology, ecotoxicology, environmental chemistry
- PhD related to the same three subjects (WUR)
- Since 2006: Centre for safety of substances and products (RIVM-VSP) – Environmental safety of substances and products.
- First as environmental risk assessor, now as senior policy advisor on pharmaceuticals and environment.
  - Regulatory assessment of pharmaceutical ERA’s
  - Guidance development
  - NL and EU policy advice
- Member of the Environmental Risk Assessment Working Party and Drafting group for new guideline at the European Medicines Agency (London)
The Drugs We Wash Away
Male fish mutating into females because of our antidepressants

Environment

30 miljoen om meer medicijnresten uit water te zuiveren

Relatie met autisme

Onderzoeker Michaela Dobbelaere ondervindt medische introductie van medicijnresten in waterproefstallingen

Chemicals from the contraceptive pill have been blamed...
Pharmaceuticals are toxic

- Paracetamol is applied as snake poison
- Warfarin is a rat poison
- Botox is the most powerful (natural) poison we know

- "The dose differentiates a poison from a medicine"
Pharmaceuticals and ecology

- Acute effects (mortality) mostly not relevant
- Continuous exposure to very low concentrations: no acute mortality, but population relevant, more subtle effects like reproduction or behaviour
  - Hormones (ethinylestradiol) → sex change in fish
  - Pain killers (diclofenac) → tissue damage in fish
  - Antibiotics (trimethoprim) → effects on algae/plants, but also antimicrobial resistance?
  - Antidepressants (fluoxetine) → behavioural changes in fish and invertebrates
Pharmaceuticals and drinking water

- Dutch drinking water complies with all quality standards
- Pharmaceuticals are measured in drinking water
  - Advanced analytical methods: very low concentrations
  - However, also the mixture of compounds is safe
- Pharmaceuticals present in drinking water sources
  - Intensive treatment needed for surface water
  - Less intensive treatment of groundwater
- Presence of X-ray contrast media causes additional treatment needs
  $\Rightarrow$ source control possible?
- Future development
  - Climate change $\Rightarrow$ fluctuations in the amount of water in rivers and canals
  - More elderly people, medicalisation of society
Legislation: marketing authorization (1)

- European Directives, implemented in NL law
- No reference to other environmental legislation like Water Framework Directive and groundwater Directive

- Environmental Risk Assessment since 2006
- ERA is product based – different dossiers (and conclusions) for different products with the same active substance
- No ERA for ‘old’ (legacy) pharmaceuticals
- No assessment of antimicrobial resistance
Legislation: marketing authorization (2)

- Different procedures for marketing authorization:
  - Centralized
  - National
  - Decentralized
  - Mutual recognition (=Wederzijdse erkenning)

- Depending on the procedure, a rapporteur member state is chosen
Legislation: marketing authorization (3)

- Human pharma’s:
  - ERA is performed, but not part of the benefit/risk analysis and thus cannot be a ground to refuse marketing authorization.

- Veterinary pharma’s:
  - ERA is part of the benefit/risk analysis.
  - Decision tree in phase 1 of ERA: only for food producing species (e.g., not for companion animals)
  - When a risk is identified: risk mitigation measures
    - Dilution of manure, use only once per year, keep animals away from water courses during XX days, etc.
  - ERA also for generics (based on products already on the market)
What is a risk?

High hazard
What is a risk?

High hazard
What is a risk?

Risk = the possibility of an effect occurring

Risk depends on effect and exposure

Hazard does not depend on exposure

→ Persistent, Bioaccumulative and Toxic compounds, e.g., PFOS, PCBs
→ Moxidectin is one, too!

→ For pharmaceuticals, a hazard and a risk assessment are performed
Risk assessment: basic framework

Exposure assessment

- Emission
- Distribution
- Exposure levels

Data evaluation

- Data set

Effects assessment

- Single species toxicity data
- Extrapolation
- No effect levels

Risk characterisation

\[
\frac{\text{PEC}}{\text{PNEC}}
\]
Pharmaceutical

Toilet

Sewage treatment plant (STP)

Surface water

Soil

Patient
Intensively reared animals

Storage tank

Pasture animals

Aquaculture
Exposure assessment of EE2 in surface water

17α-ethinylestradiol or EE2
- contraceptive, synthetic estrogen
- dose: 20-35 µg/p/d for 21 d (or more)

Data: Hannah et al., 2009
# Measurements in rivers and PECs (ng/L)

## Measurements ($n = 360$)

<table>
<thead>
<tr>
<th></th>
<th>min</th>
<th>median</th>
<th>90P</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>~0.2 ng/L</td>
<td>–</td>
<td>0.43</td>
<td>4.6</td>
</tr>
</tbody>
</table>

## Modelled values with model used in authorisation process

- 20 µg/p/d: 0.078 (min) – 0.86 (max)
- 30 µg/p/d: 0.12 (min) – 1.3 (max)

### Proposed Environmental Quality Standard in WFD:

0.035 ng/L!!!
Human pharmaceuticals – test data set

Physico-chemical and ‘fate’ tests

- Octanol-water partitioning ($K_{ow}$)
- Adsorption to soil / STP sludge
- Ready biodegradability test
- Aerobic transformation in water/sediment system

Toxicity tests

- Algae, growth inhibition test
- *Daphnia* sp., reproduction test
- Fish, early life stage toxicity test
- Activated sludge, respiration inhibition test
Risk assessment

Data evaluation

Data set

Exposure assessment

Exposure

Distribution

Exposure levels

Risk characterisation

PEC/PNEC

Effects assessment

Single species toxicity data

Extrapolation

No effect levels
Ecosystem representatives

Primary producers
green algae

Primary consumers
Daphnia, water flea

Secondary consumers
fish
Test species are representatives
We pick species from three trophic levels:
primary producers, primary consumers, secondary consumers

1 alga
1 Daphnia
1 fish

1000-s of species of green algae, brown algae, red algae, gold algae, cyanobacteria, diatoms, bacteria, ...

450 species of water fleas and >1,000,000 other invertebrate species

552 fish species in European waters amphibians, otters, birds...?
Aquatic ecosystem?

- algae
- crustacea
- fish
Derivation of PNEC – veterinary pharma’s

PNEC = Predicted No Effect Concentration

\[ \text{PNEC} = \frac{\text{lowest L(E)C50 or NOEC}}{\text{AF}} \]

Use of assessment/extrapolation factor, covering:

- intra- and interspecies variation
- extrapolation short-term to long-term toxicity
- intra- and inter-laboratory variation
- lab-to-field extrapolation

Three short term studies: AF = 1000 on LC50
Three long term studies: AF = 10 on NOEC
Risk assessment: basic framework

Data evaluation

Exposure assessment

Data set

Exposure

Distribution

Exposure levels

Effects assessment

No effect levels

PEC

PNEC

Single species toxicity data

Extrapolation

Risk characterisation
Risk characterisation

- PEC - Predicted environmental concentration
- PNEC - Predicted no effect concentration

Risk Characterisation Ratio or Risk Quotient = PEC/PNEC

- PEC/PNEC < 1 No risk for the compartment is anticipated
- PEC/PNEC > 1 A potential risk for the compartment is anticipated

- Refinement possible
Environmental risk assessment

- A risk is identified, and then....???
- Risk mitigation measures?
Case: Fluoxetine

- “Prozac”
- ~ 1 million people use antidepressants in NL

- Effects on behaviour at 30 ng/L
- Is behaviour population-relevant?
- Are infochemical effects population-relevant?
- Should they be taken up in standard testing protocols?

- Fluoxetine in the Rhine river: Maximum concentration 750 ng/L

- Do we have a problem??
Pharmaceuticals in the environment: the Dutch situation

- Scattered monitoring data
- Pharmaceuticals present in surface water, ground water, and (rarely) in drinking water
- Of 80 compounds analyzed, 29 were regularly found

Pharmaceuticals in Dutch surface water in 2014 (µg/L)

Source: Moermond et al., 2016 (RIVM report)
Pharmaceuticals in the environment: the Dutch situation

- Scattered monitoring data
- Pharmaceuticals present in surface water, ground water, and (rarely) in drinking water
- Of 80 compounds analyzed, 29 were regularly found
- For 22 of these 29 compounds, ‘safe concentrations’ were available in literature; no formal environmental quality standards
- 5 out of 22 compounds have a risk to the aquatic environment
Pharmaceuticals in the environment: the Dutch situation

Source: Moermond et al., 2016 (www.rivm.nl)
Pharmaceuticals in the environment: the Dutch situation

- Is this the tip of the iceberg, or is this all?

Source: Moermond et al., 2016 (RIVM report)
Pharmaceuticals in the environment: the Dutch situation

To put things into perspective:
- Lack of data on exact emissions to surface water
- Rough estimate: at least 140 tonnes API/year (without X-ray contrast media), but likely much higher
- Emissions of plant protection products to water: 17 tonnes/year
  - Concentrations of plant protection products often exceed formal environmental quality standards
- Plant protection products and pharmaceuticals are both made to be biologically active

Source: Moermond et al., 2016 (RIVM report)
Production: the example of Hyderabad
Production: the example of Hyderabad

- Up to 31 mg/L ciprofloxacin in the effluent from a WWTP from a large number of production plants
- In the receiving river, levels of up to 6.5 mg/L ciprofloxacin were measured.
- Also upstream lakes, groundwater and well water are contaminated with cocktails of APIs.
- Resistance? Yes, plenty of it.
Questions?
Case study:
In groups, identify possible measures that can help to reduce the amount of pharmaceuticals.

Try to identify measures in each phase of the pharmaceutical chain.
MEDICIJNRESTEN UIT WATER

BEZOEK DE INTERACTIEVE WEBSITE VOOR VERDERE TOELICHTING: HTTP://JAMDOTS.NL/VIEW/239/MEDICIJNRESTEN-UIT-WATER