Pharmaceuticals as *emerging substances* in surface waters used for the production of drinking water

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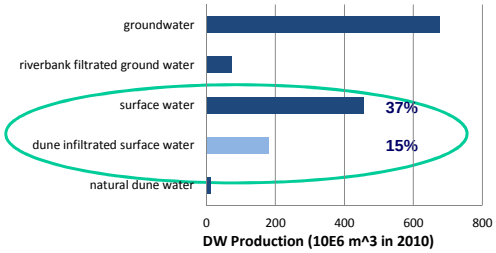
- Introduction
  - Drinking water production in the Netherlands
  - How pharmaceuticals became emerging substances
  - Why are pharmaceuticals relevant for dw companies?
- Monitoring of drinking water sources
- Human health risk assessment of pharmaceuticals in water

Drinking water production in the Netherlands

- 10 companies, 7.7 million connections
- Production 1.1 billion cubic meters /y



How pharmaceuticals became *emerging substances*

- 1970s: Recognition of possibility of emission
  - E.g. pharmaceuticals in wastewater Big Blue River, Kansas City, USA (Hignite & Azarnoff, Life Sciences, 1977).
  - However, significance remained unnoticed for long.
- 1990s: Increasingly sensitive analysis techniques: various pharmaceuticals in surface waters at ng-ug/L
- 2000s (in the Netherlands):
  - Association of River Waterworks (2000/1): Exploring desk study followed by monitoring projects with others
  - Studies on emission routes, fate in water cycle, methods to reduce emissions.
  - Cooperation between research institutes, water boards, dw companies, government and within ministries.
  - Monitoring by dw companies
  - National Institute for Public Health and the Environment (2003 & 2007): pharmaceuticals incompletely removed, very low concentrations present in drinking water.
  - Risk assessment studies
- 2012: Preparation of a policy letter to the parliament: removal of pharmaceuticals in the waste water chain

Pharmaceuticals stay *emerging* till their risk assessment is completed……We are on our way!

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Why are pharmaceuticals relevant for dw companies?

Sources: DW production philosophy

- Aim: 'impeccable' drinking water: chemically and microbiologically safe
- DW is a natural product; simple treatment should be sufficient
- Sustainable protection of surface water sources: prevention > removal > transformation / degradation

Drinking water:

- Safety of consumers if there might be a health risk (precautionary principle)
- Legislation:
  - Drinking Water Act: 1 ug/L anthropogenic contaminants
- Q 21 aims: common ethical standards of companies beyond legislation
- Public Perception: consumer worries about hormones, pharmaceuticals etc. in dw
- Environment: switch to bottled water high carbon footprint

→ Careful monitoring of sources and produced drinking water
→ Research on treatment techniques, toxicology, risk assessment
→ Thoughtful communication with customers about DW quality

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Monitoring of pharmaceuticals in dw sources: footprint of the population of the Rhine basin

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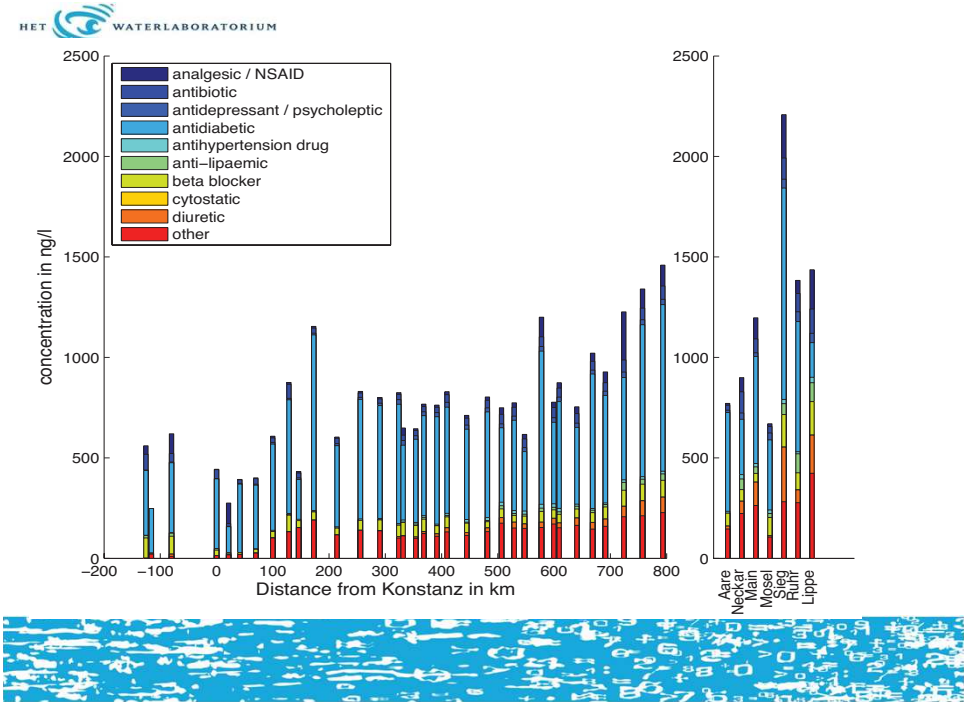

Model

- 2 parametric model to link population to concentrations of pharmaceuticals
  - Emission of pharmaceutical into the river (ng/person.day)
  - Decay length associated with degradation of pharmaceutical (km)
- Estimate parameters by minimizing differences between predicted and measured concentrations
- Data input:
  - Locations of sampling points along the catchment (GPS)
  - Measured concentrations of pharmaceuticals
  - Population data (Eurostat):
    - Gender
    - Age groups: <15; 15-65; >65; total
    - Nationalities: Swiss, Austrian, German, French, Belgian
  - Discharge data of the Rhine
- Compute best correlations between pharmaceuticals and demographic groups
- Highest correlation R^2 => most contributing group.

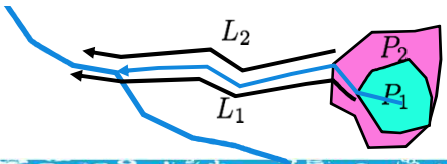

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Table 1. The most contributing demographic group per pharmaceutical

pharmaceutical	therapeutic class	most contributing group	pseudo-R^2	p-value
carbamazepin	anti-epileptic	male elderly	0.98	< 0.001
primidone	antidepressant	male elderly	0.98	< 0.001
temazepam	antidepressant	German	0.96	< 0.001
bezafibrate	antilipaemic	Germans	0.97	< 0.001
losartan	antihypertensia	male children	0.93	< 0.001
sotalol	betablocker	female children	0.97	< 0.001
lidocain	analgesic	female adults	0.94	0.001
bisoprolol	betablocker	male elderly	0.95	0.003
hydrochlorothiazide	diuretic	Germans	0.96	0.004
sulfamethoxazole	antibiotic	male elderly	0.95	0.009
oxazepam	antidepressant	female children	0.93	0.034
atenolol	betablocker	Swiss	0.84	0.05
lincomycin	antibiotic	Germans	0.76	0.065
metoprolol	betablocker	Swiss	0.77	0.077
iopromide	x-ray contrast agent	female adults	0.84	0.083
phenazone	analgesic	Germans	0.69	0.113
diazepam	antidepressant	French	0.77	0.361
atorvastatin	antilipaemic	Swiss	0.60	0.593
propanolol	betablocker	male children	0.70	0.62
trimethoprim	antibiotic	male adults	0.64	0.824
metformin	antidiabetic	male children	0.79	0.852
Average			0.85	< 0.001

- 12 of 21 pharmaceuticals have a p<0.05 significance correlation with a demographic group

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Pharmaceuticals in drinking water

- DW companies frequently monitor pharmaceuticals in drinking water
- This study: 26 analyses at one production site in 2 years
- Low concentrations detected in drinking water (29 / 41 pharmaceuticals detected)
- Most prominent:
  - Metformin (antidiabetic)
  - Caffein (stimulant, non-medical use)
  - Diclofenac (analgeic, NSAID)
  - Clofibrate (antilipaemic)

What do these concentrations mean in terms of exposure?

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Exposure to pharmaceuticals

Assumptions:

- 2 liter consumption/ day
- Life-long = 70 years
- Calculated with average and maximum concentrations

Life-long exposure:

- **Expressed in mg: all < 15 mg / 70 years**
- **Expressed in Daily Doses: all < 8% of 1 DDD**

***Exposure* is extremely low.**
But...., is there a *health risk*?

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Risk assessment of pharmaceuticals in water

Method for individual compounds
(World Health Organization(2006); Van Leeuwen (2000))

- Tolerable / Acceptable Daily intake (derived from NOAEL or LOAEL)
  - NO TDI or ADI => MRL for veterinary pharmaceuticals in milk (Versteegh et al., 2007)
  - No ADI nor MRL => DDD/100 (De Jongh et al, (2012)
  - Adapted approach for genotoxic carcinogens
  - Uncertainty factors (1-10), e.g. interspecies, intra species, adequacy of studies or database, nature and severity of effect, subchronic to chronic exposure
- Calculation of (provisional) Guideline value
  Parameters:
  - Bw: 60 or 70 kg bodyweight
  - P: Fraction allocated to dw 10%
  - C: 2 liter consumption/day
- Calculation of Margin of Exposure (MoE)
  - <1 : risk not excluded
  - 1-10: further assessments warranted
  - >10: risk of adverse health effects negligible

$$TDI = \frac{\text{NOAEL or LOAEL or BMDL}}{\text{UF and/or CSAF}}$$

where:

NOAEL	=	no-observed-adverse-effect level
LOAEL	=	lowest-observed-adverse-effect level
BMDL	=	lower confidence limit on the benchmark dose
UF	=	uncertainty factor
CSAF	=	chemical-specific adjustment factor

The guideline value (GV) is then derived from the TDI as follows:

$$GV = \frac{TDI \times bw \times P}{C}$$

where:

bw	=	body weight (see below)
P	=	fraction of the TDI allocated to drinking-water
C	=	daily drinking-water consumption (see below)

Margin of Exposure (MoE) = conc / pGLV

Performed with average and maximum concentrations

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Risk assessment of pharmaceuticals in water

- All MoE >30 => risk of adverse health effects negligible
- Average concentrations: MoE > 2000
- Maximum concentrations: MoE > 31
- NB: outcome strongly dependent on used pGLV
  e.g. carbamazepin: pGLV: 1; 12 or 50 ug/L
  => MoE 31, 372 or 1550.

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How to include mixtures?

- Often RA only performed for individual compounds
- WHO: applied uncertainty factors are large enough to cover possible mixture effects.
- Mixture toxicity concepts:
  - Concentration Addition (CA; similarly acting compounds)
  - Independent Action (IA; dissimilarly acting compounds)

$$\sum_{i=1}^{n} \frac{c_i}{EC x_i} = 1$$

$$E(c_{mix}) = 1 - \prod_{i=1}^{n} [1 - E(c_i)]$$

- Example: De Jongh et al (2012): CA used in RA of metabolites and similarly acting pharmaceuticals
- Boobis (2007), Backhaus (2011): Multi-component mixtures of dissimilarly acting compounds usely do not deviate much from CA or IA.
- Application of CA gives provisional impression of combined exposure and risk assessment of multiple pharmaceuticals

Apply Concept of Concentration addition to all detected pharmaceuticals (although with different mechanisms of action)

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Combined exposure to pharmaceuticals

- Problem: max. concentrations were never together in 1 sample: unrealistic worst case.
- Data set large enough => average concentrations give more realistic values
- Including mixtures in assessment of exposure and risks:
  - Life-long combined exposure to pharmaceuticals via dw << 1 DDD (“mixture pill”)
  - Risk of adverse health effects can be considered negligibly low.

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To conclude

- Pharmaceuticals in the water cycle deserve and receive attention as *emerging substances*
- Monitoring of dw sources in combination with modeling and statistical tools provides information on:
  - contamination patterns
  - links between human activities in catchments and water quality

Risk assessment

- Pharmaceuticals present at ng/L concentrations in dw.
- DW complies with Drinking Water Acts and ethical limits.
- Life-long exposure extremely low compared with therapeutic doses.
- RA: risk of adverse health effects of life-long exposure can be considered negligibly low.
- Application of CA confirms this picture for combined exposure.
- Inclusion of mixtures in RA methodology research deserves more attention to support RA in applied fields.

Thanks for your attention!