FOSSIL WATER

Cytotoxins in Drinking Water: A Water Quality Prediction Exercise of the Thames Catchment

Nicole Rowney

Masters of Science: Water Science Policy and Management

Environmental Toxicology and Chemistry, Vol. 28, No. 12, pp. 2733–2743, 2009

*** Research conducted in partial fulfillment of MSc****

Centre for Ecology & Hydrology
NATURAL ENVIRONMENT RESEARCH COUNCIL

OXFORD UNIVERSITY
CENTRE FOR THE ENVIRONMENT

UNIVERSITY OF OXFORD

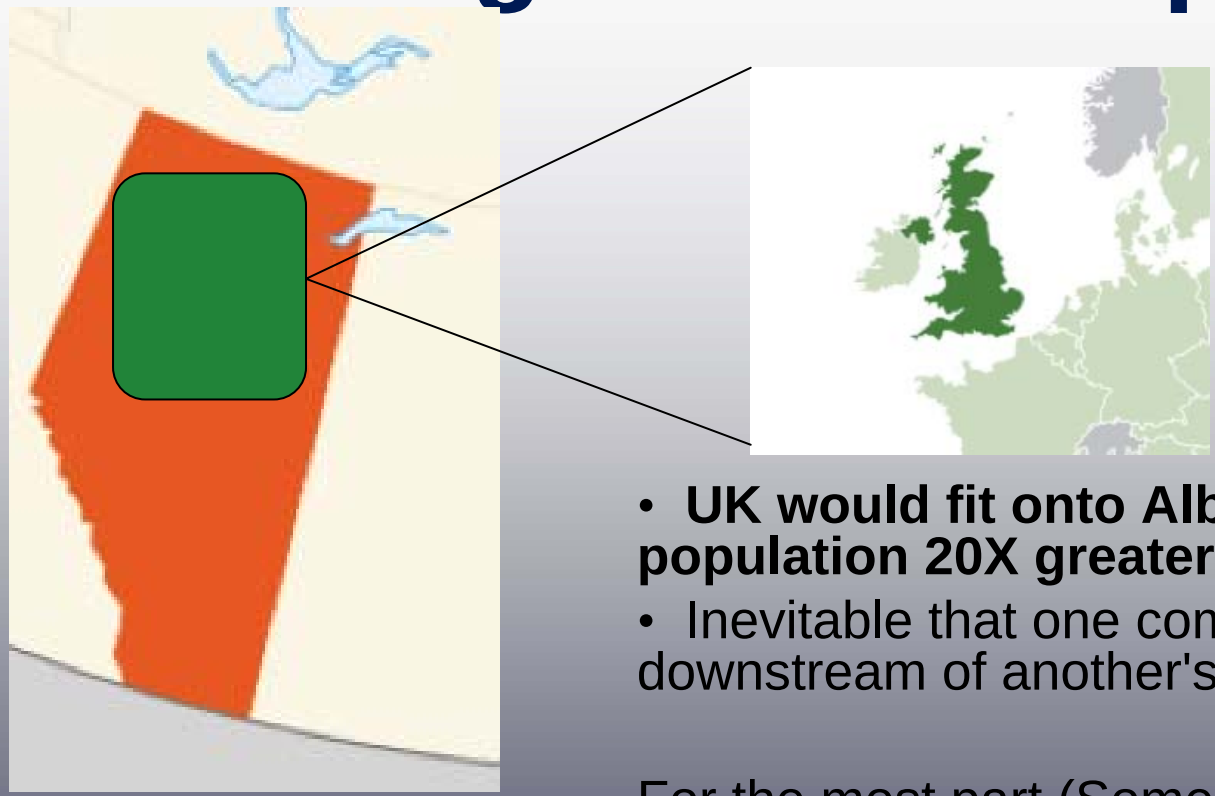
FOSSIL WATER

- Fossil Water provides turnkey solutions to water supply and treatment problems faced by community and industrial development.
- Our partners have been involved in several hundred water, wastewater and produced water facilities throughout North America.
- We believe in collaborative solutions that address the interests of all stakeholders within the communities we work in.
- We specialize in improving water quality in our headwaters, having led projects in Banff, Jasper, Okotoks, Cochrane and Bragg Creek (*inter alia*).

Cytotoxins in Drinking Water

- To date, few predicted environmental concentrations studies on cytotoxic drugs have been documented.
  - What are cytotoxic drugs?
  - Why are they a concern and to who?
- Research question is unique to the UK, in particularly in the context of drinking water and additive effects of cytotoxins with analogous mechanisms of action.
  - Estimated that Cancer rates will increase by 1/3 in England by 2020 (TCR 2007).
  - Increase popularity of Chemotherapy treatment.
    - Common practice to undergo Chemotherapy at medical facility as an outpatient.
- Research endeavoured to initiate a proactive narrative in risk assessment, public health, safety and water quality regulation.

Background/Perspective…



Not to scale

- **UK would fit onto Alberta ~2.5x and has a population 20X greater.**
- Inevitable that one communities DW intake will be downstream of another's STP outfall.

For the most part (Some exceptions):

- Standard sewage treatment in the UK.
- Standard filtration/chlorination DW treatment.
  - *Minimal investment into aging infrastructure.*

Hypothesis and Methods

- **Cytotoxic drugs discharged into the Thames Catchments will enter drinking water at concentrations harmful to human health; A prediction study**.
  - Identify cytotoxic use in the UK (NICE,2006 report).
  - Determine consumption, excretion rates and calculate influent load.
  - Utilizing Low Flows 2000, Model PEC's under mean and low flow scenarios and assess.
  - Focus on DW abstraction points.
  - Calculate environmental exposure & compare to literature sited standards.

Low Flows 2000™ Highlights

- Model widely used by Environment Agency of England & Wales to predict statistical distribution of down-the- drain chemicals.
- Geo-referenced based model.
- Per capita loads from the population served by the STP (preset in the model), are combined with estimates of STP removal efficiencies to give effluent loads on the river.
  - *Model can be adjusted for flow scenarios (mean & low flow).*
- Effluent discharges are then combined with reach specific flow statistics to calculate in-river concentrations after mixing @ the point of discharge and correcting for upstream concentrations using a simple mass balance equation in Monte Carlo simulations.

Cytotoxins in Water

- This study considers the water quality implications for the Thames catchment arising from the routine discharge of chemotherapy drugs after use, down the drain and into the river.
- The review focuses on 13 different cytotoxic drugs from 3 drug families
  - alkylating agent,
  - antimetabolite,
  - anthracycline antibiotic
- A geographic-information-system-based water quality model was used to predict end use (DW) concentrations.
  - Low Flows 2000™
  - Model was informed by literature values on consumption, excretion, and fate data to predict raw drinking water concentrations at the River Thames abstraction points at Farmoor, near Oxford, and Walton, in West London.
- **To discover the highest plausible load values, the upper boundary values for consumption and excretion together with lower removal values for sewage treatment were used.**

Example: Alkylating Agents

- Alkylating cytotoxic drugs are nonspecific chemotherapy drugs used to stop tumor growth.
- They function by attaching an alkyl group onto the DNA helix inhibit or alter DNA replication resulting in mutation or cell death
- A potential outcome of alkylating agents' mutagenic capability is the possibility of teratogenic effects.
  - Unwanted side effects of alkylating agents include bone marrow suppression, fertility impairment, development of acute myeloid leukemia, and urinary disorders (Renwick et al, 2005).

Alkylating Agents

- In this class, five alkylating agents oxaliplatin, temozolomide, cisplatin, carboplatin, and cyclophosphamide were examined.
- Information on their excretion suggests that 5 to 68% of the alkylating agent dosed is expelled from the body unchanged.
- STP removal ranges from 0-88%

Alkylating Agents

Table 2. Predicted alkylating agents likely to be present in sewage effluent in England based on 2005 maximum drug consumption values and Switzerland cyclophosphamide use. Predictions assume maximum excretion of unchanged drug and minimum sewage treatment plant removal rates

Drug	Family[a]	Maximum use in England[b]	Consumption (μg/capita/d)	Consumption (kg/UK[c]/pa)	Therapeutic dose	Excretion of original drug	Predicted influent load (ng/capita/d)	Sewage treatment plant removal	Predicted load (ng/capita/d)	Predicted effluent concentration (ng/L)[d]
Oxaliplatin	Alkylating agent	78.90	0.43	7.78	130 mg/m^2[e]	5–50% unchanged in urine[e,f]	216.76	54% activated sludge, 60% ultraviolet[g,h]	9.97E+01	4.99E−01
Temozolomide	Alkylating agent	152.20	0.84	15.00	150–200 mg/m^2[e]	5–10% unchanged in urine[e,i]	83.63	No removal[j]	8.36E+01	4.18E−01
Cisplatin[k]	Alkylating agent	199.00	1.09	19.61	75–120 mg/m^2[e,l]	27–65% unchanged in urine[e,l]	546.70	88% activated sludge[g]	1.20E+02	6.01E−01
Carboplatin[k]	Alkylating agent	1,458.60	8.01	143.74	200–300 mg/m^2[l]	32–65% unchanged in urine[l,m]	5,209.29	26% activated sludge[g]	4.38E+03	2.19E+01
Cyclophosphamide (Switzerland)	Alkylating agent	Not applicable	20.64	55.00	300 mg/m^2[l]	<20% unchanged in urine[n,o], 30–68% unchanged[p]	14,036.40	No removal[q,r,s]	1.40E+04	7.02E+01
Additive concentration									1.86E+04	9.36E+01

Rowney et al. 2009

Eg: Alkylating Agent

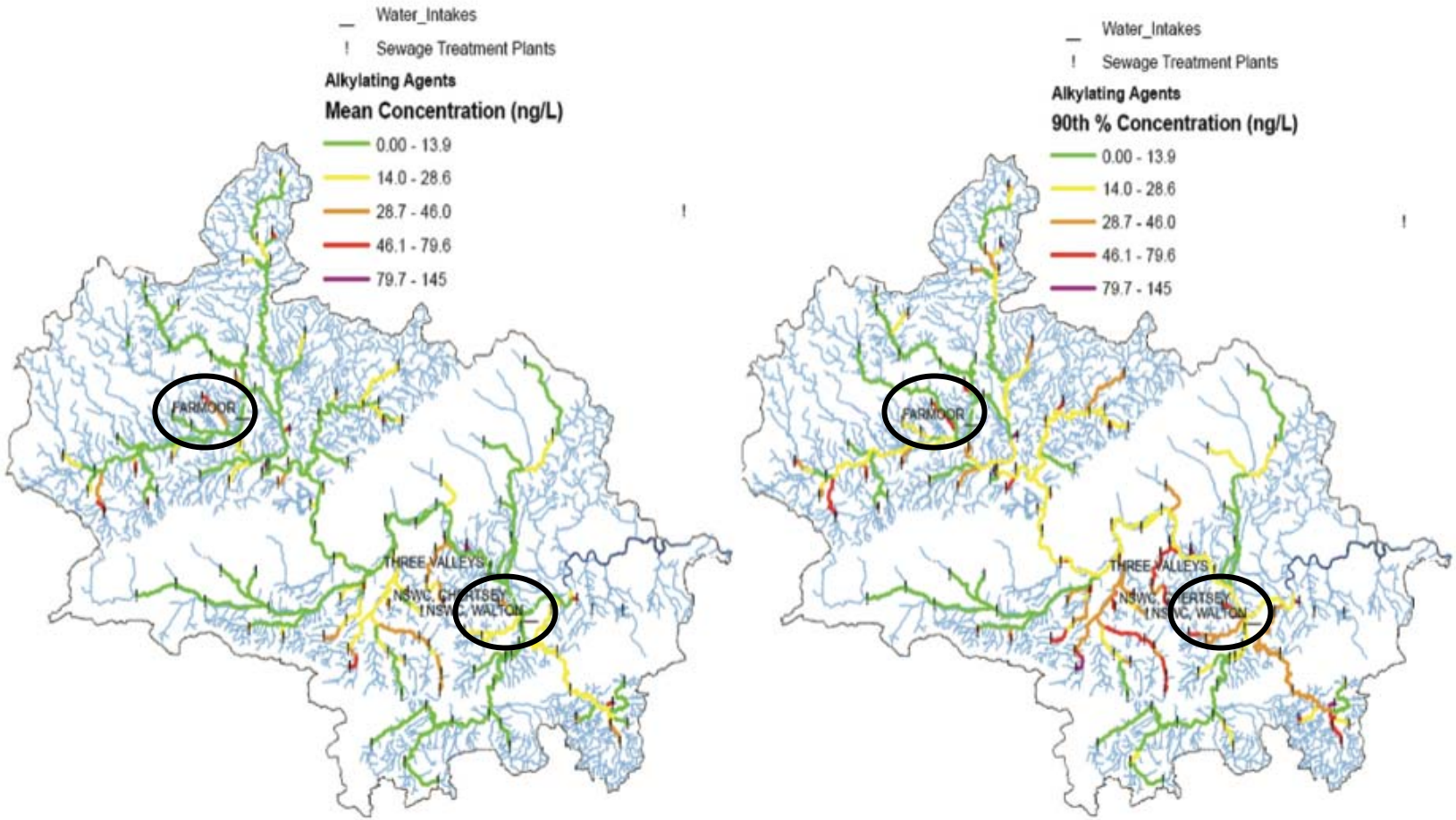


Fig. 1. Predicted alkylating agents in the Thames (United Kingdom) catchment showing mean and 90th percentile concentrations.

Thames Water: DW Treatment

- Although this risk assessment study is based only on raw drinking water concentrations, it is worth reviewing what is known about the efficacy of current water purification technology as used in the Thames region.
  - Water is held for several days in a reservoir followed by sand filtration, ozonation, a second filtration through granular activated charcoal and finally a chlorination/disinfection treatment (Evans et al, 2003).
- Although these techniques have been demonstrated to successfully eliminate many pharmaceuticals in laboratory tests, the extent does vary from compound to compound (Webb et al, 2003; Huber et al, 2005; Stackelberg et al, 2004; Ternes et al, 2002)
- **Unfortunately, little information exists on their performance with cytotoxic drugs.**

Drinking Water Risk Assessment

Table 5. Drinking water risk assessment at the Farmoor and Walton intakes on the Thames River (UK) during mean flow and 90th percentile

Family	Predicted environmental concentrations at intake (ng/L)	Drinking water exposure (µg/capita/d)	Ratio of exposure: Effect threshold (1.5 µg/d)[a]	Ratio of exposure: Effect threshold (0.15 µg/d)[b]	Ratio of exposure: Effect threshold (1.0 µg/d)[c]	Vulnerable groups: Dose ingested during pregnancy (36 weeks) (µg)
Drinking water risk assessment at the Farmoor and Walton intakes on the Thames River during mean flow conditions						
Alkylating agents						
Farmoor	6.97	0.01	9.29E-03	9.29E-02	1.39E-02	3.51
Walton	10.72	0.02	1.43E-02	1.43E-01	2.14E-02	5.40
Antimetabolites						
Farmoor	1.31	2.62E-03	1.75E-03	1.75E-02	2.62E-03	0.66
Walton	2.02	4.04E-03	2.69E-03	2.69E-02	4.04E-03	1.02
Anthracycline antibiotics						
Farmoor	0.03	6.44E-05	4.29E-05	4.29E-04	6.44E-05	0.02
Walton	0.05	9.92E-05	6.61E-05	6.61E-04	9.92E-05	0.02
Drinking water risk assessment at the Farmoor and Walton intakes on the Thames River during 90th percentile flow conditions						
Alkylating agent						
Farmoor	13.85	0.03	54.15	5.42E+00	3.61E+01	6.98
Walton	19.99	0.04	37.52	3.75E+00	2.50E+01	10.07
Antimetabolites						
Farmoor	2.61	0.01	287.36	2.87E+01	1.92E+02	1.32
Walton	3.76	0.01	199.47	1.99E+01	1.33E+02	1.90
Anthracycline antibiotics						
Farmoor	0.06	1.20E-04	1.25E+04	1.25E+03	8.33E+03	0.03
Walton	0.09	1.80E-04	8.33E+03	8.33E+02	5.56E+03	0.05

[a] European Medical Agency [66].
[b] Kroes et al. [67].
[c] Schulman et al. [68].

Risk Assessment

- Exposure values compared to TTC and NSRL standards found in literature and used by regulatory agencies.
  - European DW Directive does not contain WQ thresholds for Cytotoxins.
- Ratio of exposure for selected combined alkylating agents:
  - 40X below TTC (EMEA, 2006)
  - 25X below NSRL (Schulman et al, 2002)
  - 4X below TTC (Kroes et al, 2004)

- **NOTE: There are over 50 cytotoxic drugs used daily in the UK - this study looked @ combined concentration of 13.**

Risk Assessment cont'

- Unclear how different regulatory authorities would assess the risk of inadvertent exposure to combinations of cytotoxic drugs.
- Argued that risk assessments based on therapeutic dose benchmarks are not suitable for genotoxic drugs *(ie: chemotherapy agents)* (Webb et al, 2003).
  - Primarily because: **there is no threshold dose below which no carcinogenic effects may occur** (Ladou, 2003).

Risk: Sub-group populations

- Threshold benchmarks are typically not established for sub-group population let alone combinations of cytotoxic drugs.
  - Therefore pregnant women, their fetuses, breast feeding infants remain an important group for risk evaluation.
- Nonetheless, Collier (2007) took a pharmacological exposure approach to assess the cumulative risk of individual pharmaceutical contaminants in potable water to pregnant and pediatric patients.
  - All cytotoxic drugs (ifosfamide, cyclophosphamide & methotrexate) were categorized as contraindicated in pregnant or breastfeeding mothers.
  - Time calculated to reach a minimum clinical dose did not pose an immediate risk, it is known that sub-clinical doses can result in cellular physiological and morphological effects (Pomati et al, 2006)
- Cytotoxic drug exposure may induce changes that manifest later in life.
  - Such manifestations include short stature and cardiovascular anomalies such as those in prenatal and pediatric cancer survivors in chemotherapy-treated patients (Chow et all, 2007; Mone et al, 2004)
- **Therefore, subclinical chronic exposure of cytotoxic drugs to special subgroup populations could also potentially cause long-term physiological changes and therefore pose a risk.**

Conclusion

- Inadvertent exposure to cytotoxic drugs through drinking water in the Thames area requires further research.
- Cancer rates predicted to increase - the prevalence of increasing use of cytotoxic drugs will likely correlate.
- The ability of a proportion of cytotoxic drugs to pass through sewage treatment unchanged, the limited dilution in the Thames, and the abstraction of this water for drinking purposes even during low flows are also grounds for further research.
- Inadequate information on cytotoxic removal during drinking water treatment.

Conclusion

- The modeling exercise suggested that at Walton during low flows and using high (*but plausible loadings*) the inlet concentrations of one group of cytotoxic drugs were close to some of the proposed safety margins.
- Of course, this risk is still based on informed speculation as no monitoring of these drugs at abstraction points, or tap water, has yet occurred.
- However, given the apparent increasing consumption of these drugs, the projected increase in population in the southeast of England, and the possibly hotter and drier summers of the future, the issue warrants further investigation.
- The risk to healthy adults from this exposure is low. However due to their developmental vulnerability, special subgroup populations such as newborn babies may be at an elevated risk

FOSSIL WATER

Thank you.

nicolerowney@fossilwater.ca

Centre for Ecology & Hydrology
NATURAL ENVIRONMENT RESEARCH COUNCIL

OXFORD UNIVERSITY
CENTRE FOR THE ENVIRONMENT

UNIVERSITY OF OXFORD