Cytotoxic drugs present in aquatic systems and their occurrence in the environment

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The next generation of emerging compounds?

What are cytotoxic drugs?

We cant look at all the compounds – better to focus on the most toxic compounds; Anti-cancer drugs.

Anticancer drugs – Cytostatic (no DNA interaction) and cytotoxic which interacts with DNA and leads to cell death. Reported to exert teratogenic, genotoxic, mutagenic effects. Practically all eukaryotic organisms are vulnerable to damage.

1970's: US EPA discovered and published the first report specifically addressing pharmaceuticals in wastewater effluents (Garrison 1976)

In similar studies, aspirin, caffeine and nicotine were detected in sewage sludge influent and effluents (Hignite and Azarnoff 1977)

1994: detection of clofibric acid in river and tap water, Berlin. (Stan 1994)

1999: detection of endocrine disruptors that causes feminization in male fish (Snyder 1999)

Late 90's: 5FU detected at high concentration in wastewater from a 5-FU plant (Anheden 1996); Ifosfamide and cyclophosphamide have been found in sewage samples from hospitals and STP (Ternes, 1998)

Route of entry into the aquatic environment

Continuous induction

Urinary Excretion

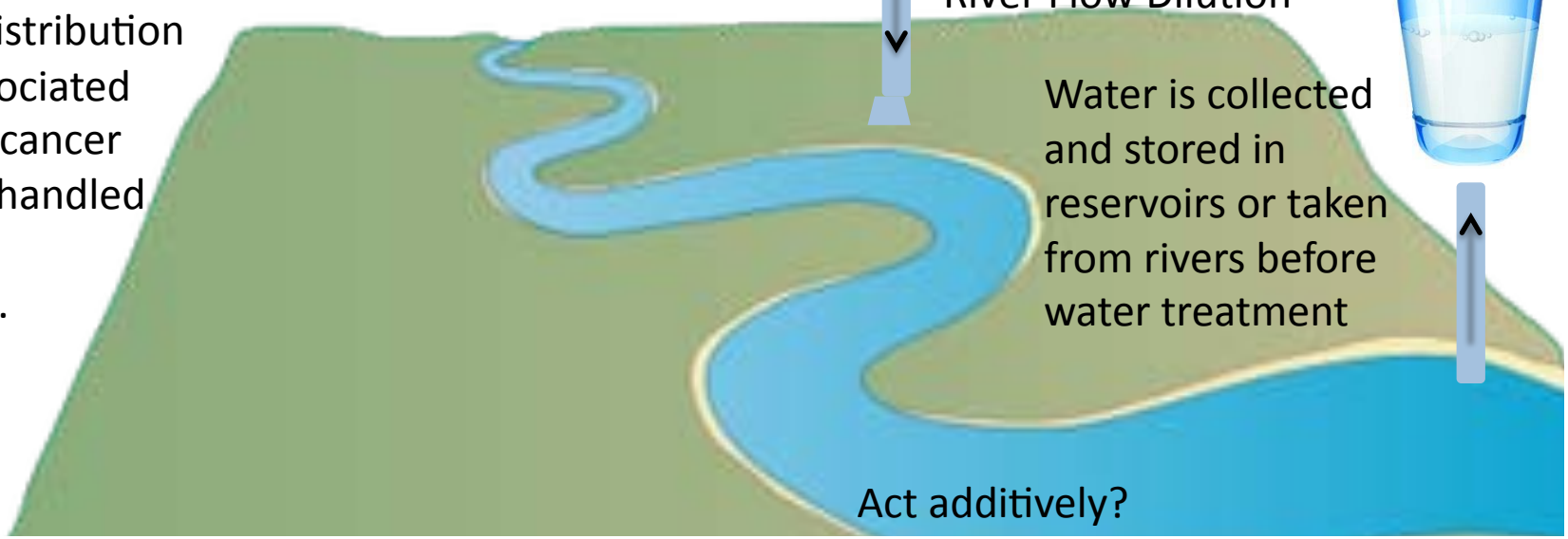
Sewage Treatment

Potential loss/transformation

Anti-cancer drugs are highly polar, non volatile and poorly biodegradable – escape sedimentation and biological and physical treatment in STP

Excretion can be related to the national population distribution and their associated STPs – much cancer treatment is handled in outpatient departments.

River Flow Dilution



Water is collected and stored in reservoirs or taken from rivers before water treatment

Act additively?

Prioritization of anticancer drugs

HOSPITAL CONSUMPTION

High usage chemicals: Hydroxyurea, capecitabine, 5-fluoruracil, imatinib, gemcitabine, cyclophosphamide, mitotane, erlotinib, cytarabine, lapatinib, ifosfamide, carboplatin, methotrexate

URINARY EXCRETION

Methotrexate and pemetrexed have excretion rates > 75%

Capecitabine has excretion rate <5%

Hydroxyurea is the highest consumed anti-cancer drug and has an excretion rate between 45-75%

ENVIRONMENTAL FATE PROFILE

e.g. Mitotane has a high koc value and would have a high adsorption to soil, suspended solids or sediments and therefore the chemical is likely to be immobile in soil.

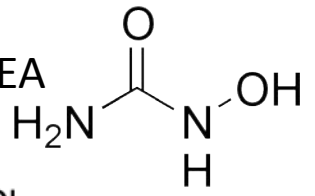
DEGRADATION

Biodegradation is significant in the STP for gemcitabine and 5-fluorouracil, whereas hydrolysis is significant for irinotecan.

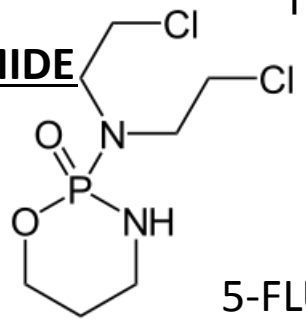
IMPACT ON THE ENVIRONMENT AND TOXICITY

MEASURED IN THE ENVIRONMENT

HYDROXYUREA

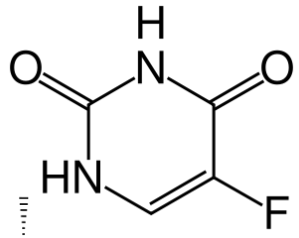


CYCLOPHOSPHAMIDE



CAPECITABINE

5-FLUOROURACIL

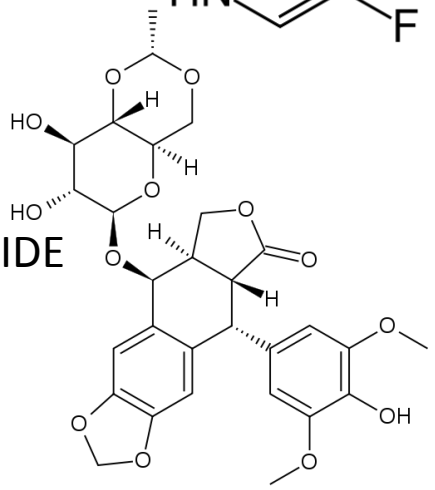


IMATINIB

PEMETREXED

METHOTREXATE

ETOPOSIDE



GEMCITABINE

IFOSFAMIDE

Quantification of environmental concentrations in WWTP influent, effluent and receiving waters

Previous methods suffer from low LOD, or require a high sample volume.

- Samples filtered and extracted using a combination of Strata-X and Florisil SPE cartridges
- Analysis was performed by LC-MS/MS with chromatographic separation on a Thermo Scientific Hypersil GOLD C18 (1.9µm 50 X 2.1mm) using a CHOOH-buffered H_2O/MeOH mobile phase.
- The mass spectrometer was operated in highly selective reaction monitoring mode and heated electrospray ionisation (HESI) by Quantification by internal standardisation was achieved using custom synthesised d4-cyclophosphamide
- Limits of detection were between 0.03-0.12ng/L and 0.05-0.09ng/L for cyclophosphamide and ifosfamide respectively.

Quantum Ultra MS-MS and an Accela LC

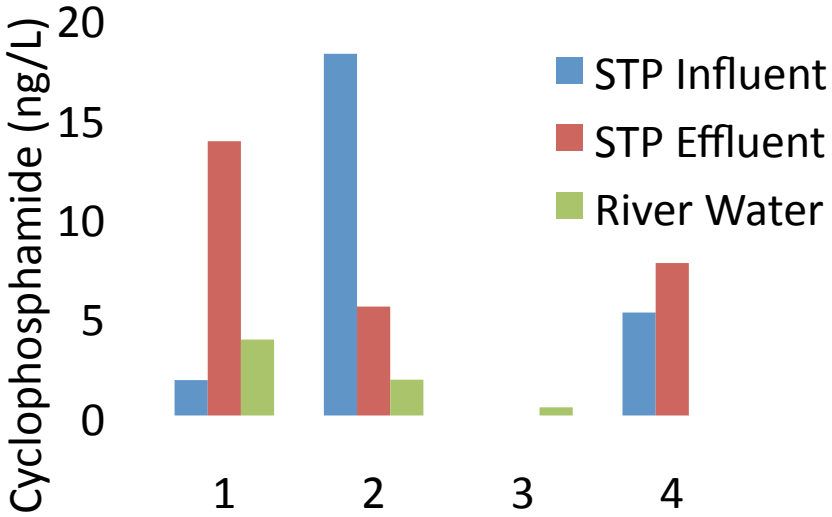
River Ribble catchment

Darwen, Calder, Ribble

It flows through Settle, Clitheroe, Ribchester and Preston, before emptying into the Irish Sea between Lytham St. Annes and Southport.

The main tributaries of the Ribble are the Hodder, Calder, River Darwen and the River Douglas.

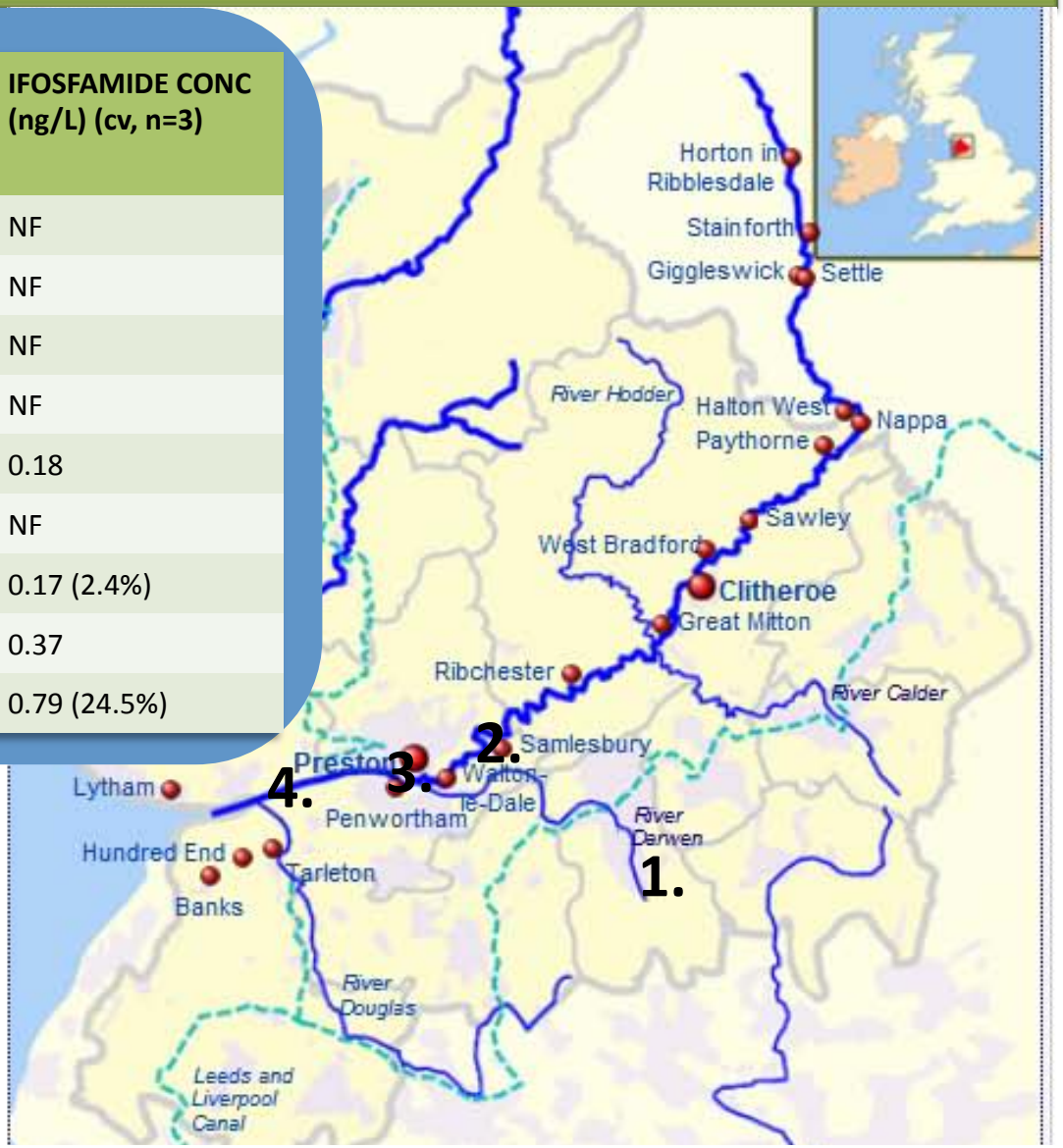
Livestock farming in the upper part of the catchment. Industrialised urban areas such as Blackburn in the middle part of the catchment



River Ribble catchment

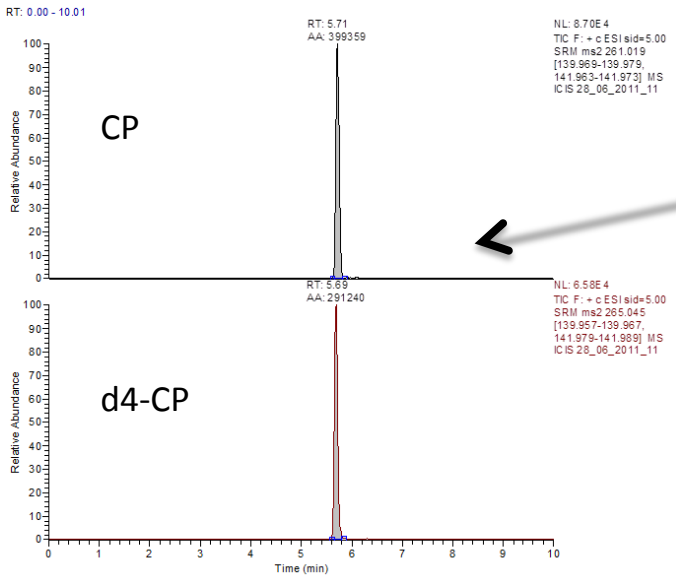
Darwen, Calder, Ribble

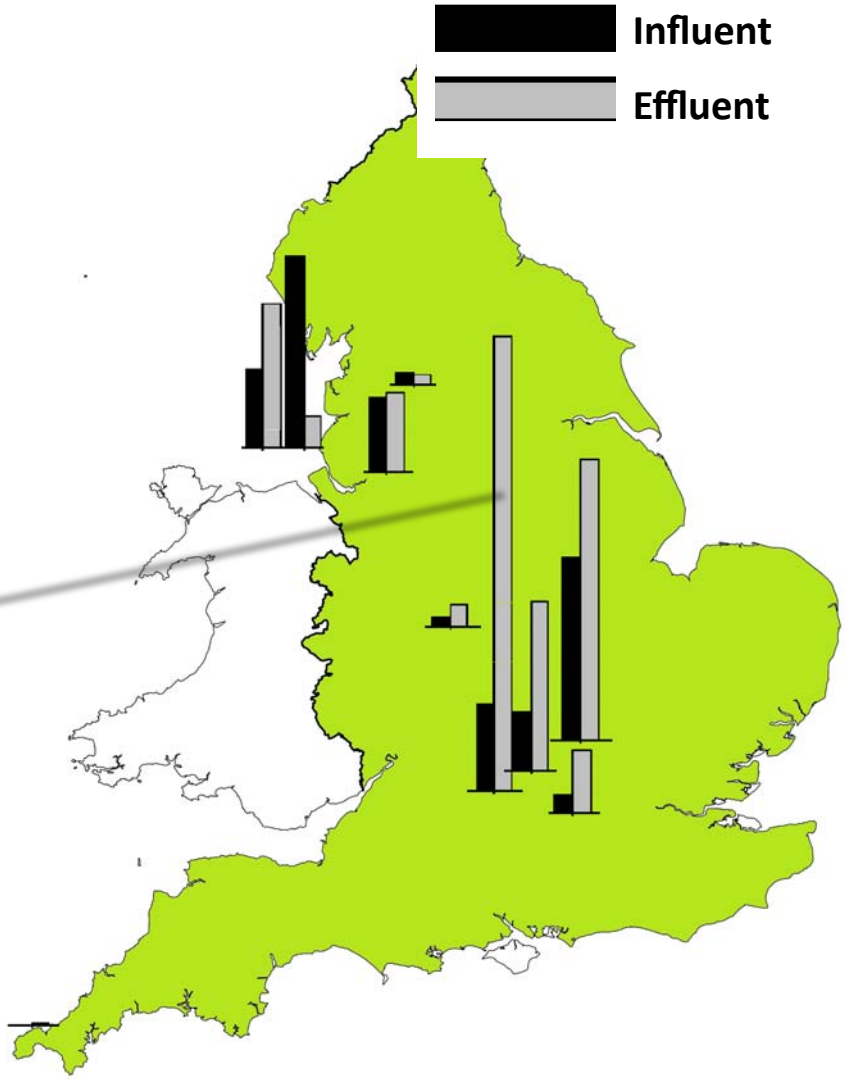
NO.	SAMPLE TYPE	FLOW ML/DAY	CYCLOPHOSPHAMIDE CONC (ng/L) (cv, n=3)	IFOSFAMIDE CONC (ng/L) (cv, n=3)
1.	STP Influent	13.8	1.78 (3.5%)	NF
1.	STP Effluent	13.8	13.80 (11.0%)	NF
1.	River Water	14.0	3.82 (5.4%)	NF
2.	STP Influent	72	18.2 (12.4%)	NF
2.	STP Effluent	72	5.48 (2.9%)	0.18
2.	River Water		1.80 (10.8%)	NF
3.	River Water	4100	0.41 (21.0%)	0.17 (2.4%)
4.	STP Influent	59.2	5.18 (4.2%)	0.37
4.	STP Effluent	59.2	7.67 (7.6%)	0.79 (24.5%)



STP influent and effluent samples
UK SURVEY

- 24 hr composite influent and effluent samples taken across England
- Mean 5.7 ng/L
- Range 0.1 – 22.7 ng/L





Conclusions and further research

Cyclophosphamide was detected in most samples, corresponding to its relatively high consumption and persistence (i.e. Low removal rates from STPs)

Cyclophosphamide concentrations were greater in the final effluent than the raw influent, suggesting the 'release' of cyclophosphamide possibly as a metabolite complex, during the wastewater treatment process.

The researchers estimated that an adult drinking more than three pints of water a day would receive a weekly dose of between 300 ad 30,000 times lower than recommended safety levels.

They warn that a developing foetus would also be exposed to drugs in the womb.

There is no evidence to show that drinking water treatment removes all these drugs, so while we are not wanting to alarm people, it would be foolish to assume there is no risk.