The occurrence and phototransformation of controlled and chemotherapeutic drugs in aqueous environments in Taiwan

Angela Yu-Chen Lin

National Taiwan University

Graduate Institute of Environmental Engineering

+

Pharmaceuticals TOXICITY

Emerging contaminants Natural Attenuation

Sunlight Photochemistry *Chemical of Emerging Concern*

Sorption Water Reuse **Antibiotics** River Waters

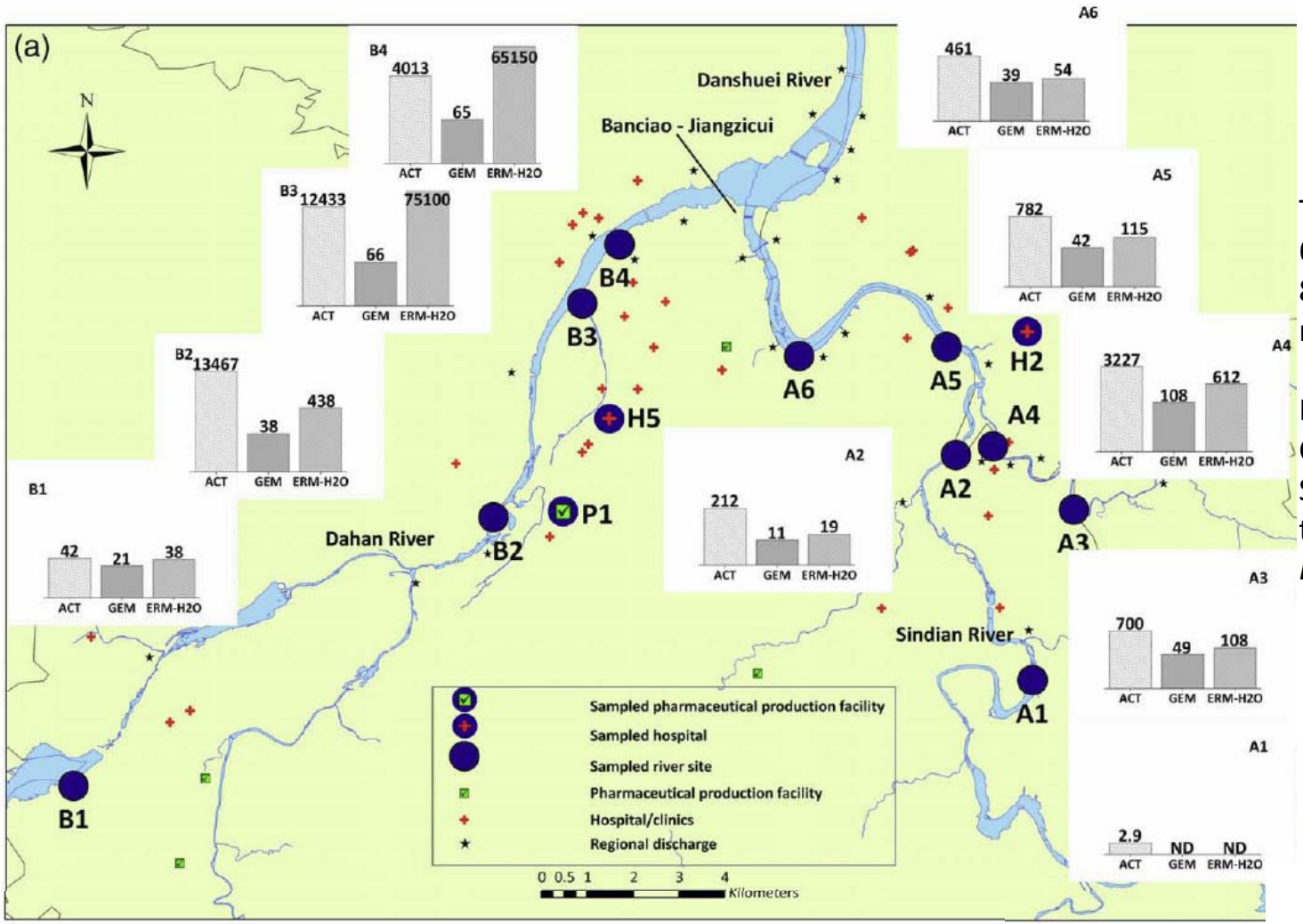
Storm Water Reuse Bicarbonate

Indirect Photolysis Hospital Wastewaters

Perfluorinated Chemicals Personal Care Products

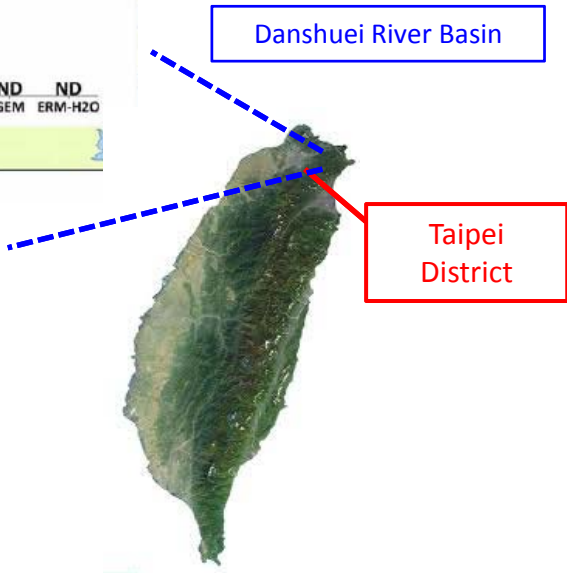
Estrogen Controlled Substances

National Taiwan University

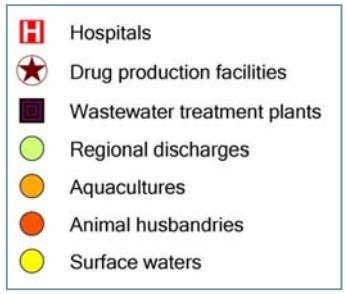


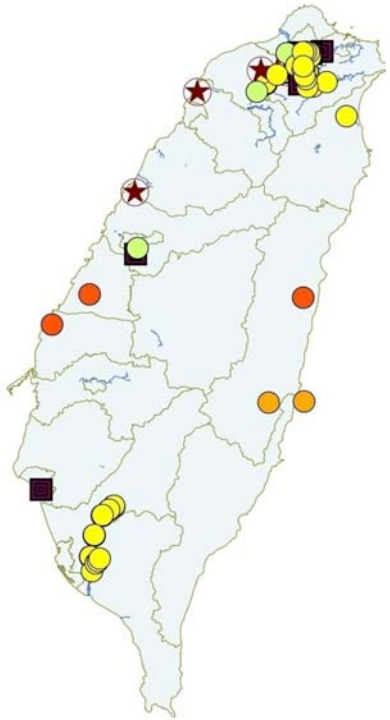
Taipei and its suburbs
6.4 million inhabitants
80 district hospitals and medical centers

BOD 30 mg/L,
COD 100 mg/L,
SS 30 mg/L,
true color 550 color unit,
E. coli 200000 CFU/100mL



Major Pharmaceutical Contamination Sources





Wastewater treatment plants

Hospitals

Drug production facilities

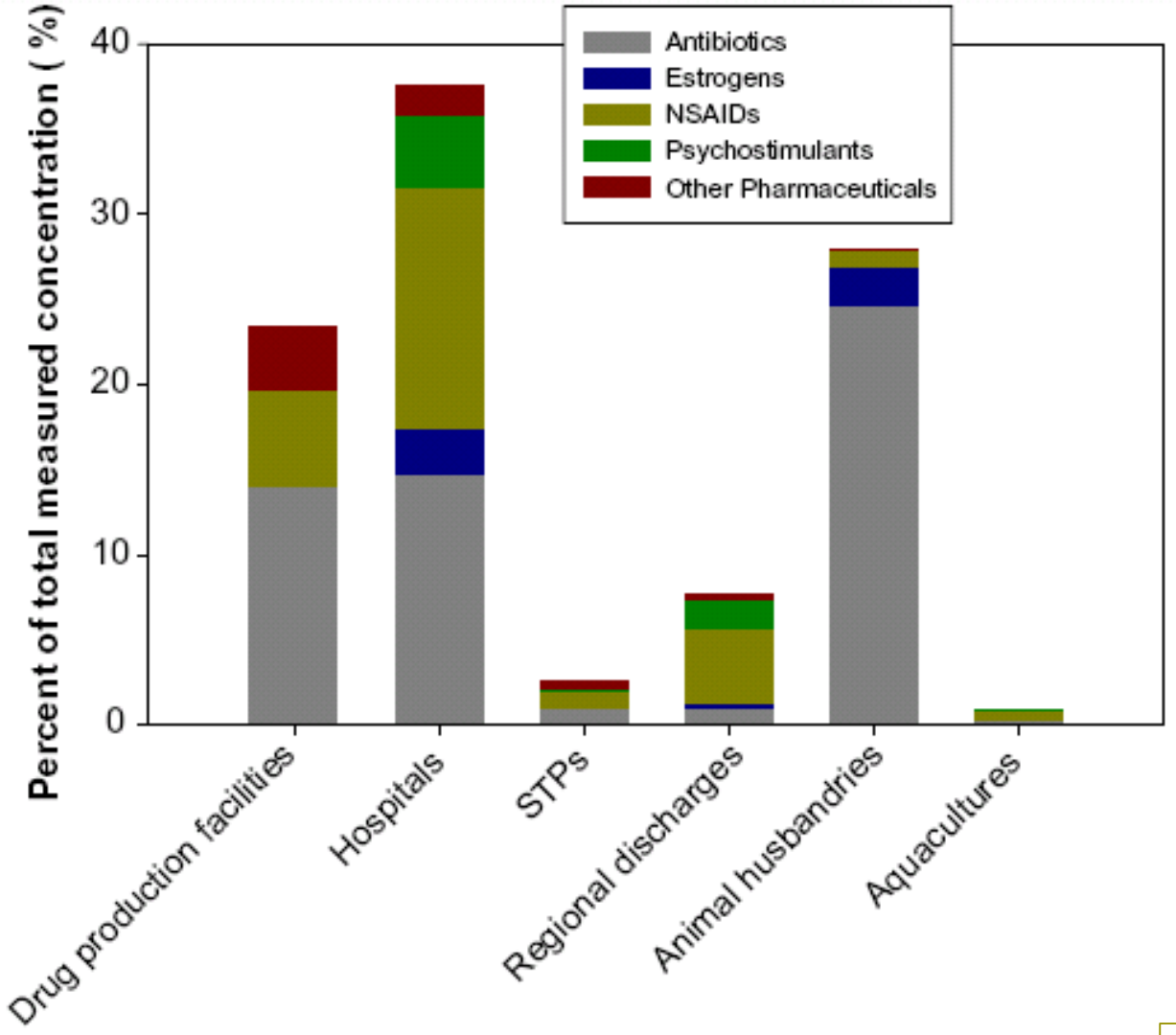
Animal husbandries

Aquacultures

Regional discharge

Ref: Lin et al. 2008 Chemosphere

The portion of pharmaceuticals found at six potential contamination sources.



effluent standards
BOD 30 mg /L, COD100 mg /L, S.S 30 mg/L, true color 550 color unit, E. coli 200,000 CFU/100 mL)

Ref: Lin et al. 2008 Chemosphere

Removal (in groups) in 4 WWTPs in Taipei Region

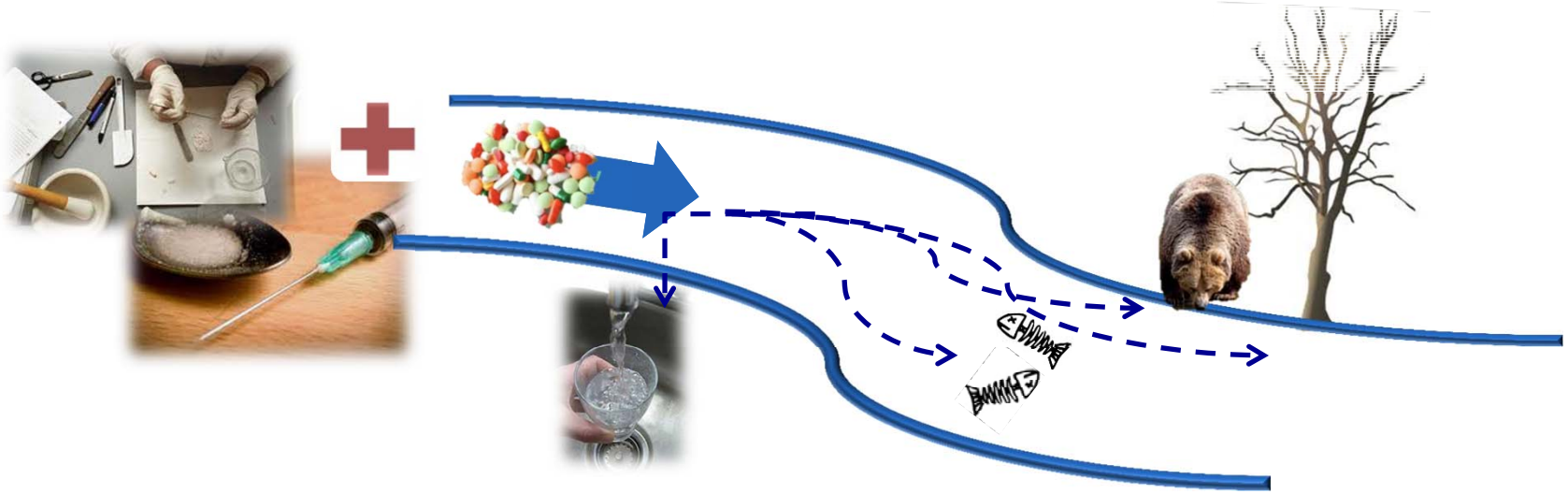
Therapeutic classes	WWTP 1 % RE	WWTP 2 % RE	WWTP 3 % RE	WWTP 4 % RE
Sulfonamide antibiotics	82	20	44	26
Tetracycline antibiotics	70	80	66	91
Lincosamide antibiotics	NR	52	59	100
Macrolide antibiotics	NR	NR	77	NR
Penicillin antibiotics	NR	100	NR	NR
Cephalosporin antibiotics	75	100	36	92
Imidazole antibiotics	NR	61	NR	55
Quinolone antibiotics	11	25	80	35
Chloramphenicol antibiotics	NR	57	23	89
Other antibiotics	36	23	57	51
Estrogens	100	100	NR	100
β-blockers	76	58	69	66
Psychostimulants	99	85	96	100
Vasodilators	52	23	43	NR
Psychiatric drugs	26	40	NR	40
NSAIDs	97	93	72	89
Lipid regulators	81	14	55	NR

% RE-% removal

NR-not removed

Ref: Lin et al. 2009 J. Hazardous Materials

The Problem



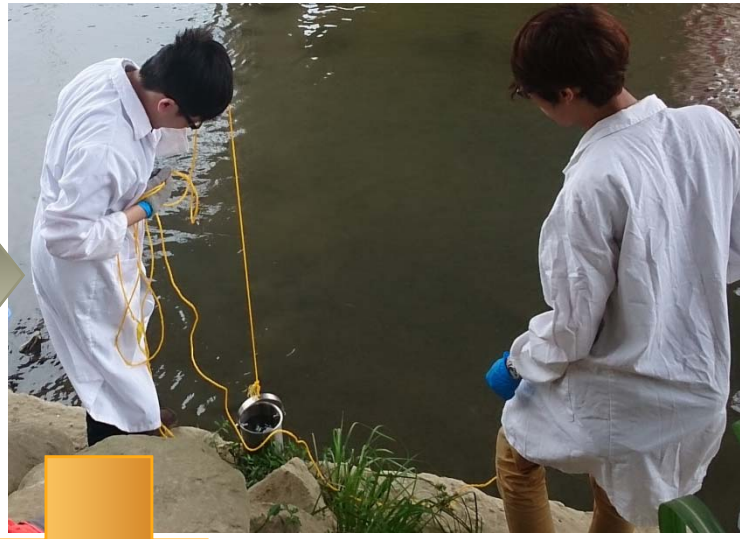
- Occupational exposure to chemotherapeutics and controlled substances has long been recognized as a potential health hazard.
- Exposure is not limited to the pharmacies and hospitals.
- Exposure can occur through environmental waterways.
- Major sources for controlled substances:

(1) substances abuse by individuals (2) use as prescription medication for treatment of acute and chronic pain

Cancer has been the main cause of death in Taiwan for several years. (28.1% in 2010)

Year	Billion NT dollar spent	Growth rate
2000	3.40	-
2001	3.86	13.4%
2002	4.81	24.7%
2003	5.29	10.1%
2004	6.89	30.3%
2005	8.24	19.6%
2006	9.76	18.4%
2007	11.28	15.6%
2008	13.31	17.9%
2009	15.07	13.3%
2010	18.57	23.00%

Source: Bureau of National Health Insurance, Taiwan



Taipei region

Compounds	Hospital wastewaters (n=7)		Rivers (n=13)		WWTP	
	Number of sites > MDL	Range[a] (ng/L)	Number of Sites > MDL	Range[a] (ng/L)	Influent (ng/L)	Effluent (ng/L)
Controlled drugs						
Ketamine	7	18.1 - 10027	13	0.5 - 415	1535	2453
Methamphetamine	7	12.4 - 241	12	0.2 - 256	267	15.6
Codeine	7	4.5 - 700	6	1.3 - 14.8	41.0	56.0
Methadone	6	1.7 - 202	4	0.2 - 4.3	3	4
Meperidine	6	89 - 1520	1	2	ND	ND
Morphine	4	35.8 - 2353	1	35.9	38.0	29.0
Cocaine	2	6.3 - 134	0	ND	1.2	0.6
Cytotoxic chemotherapy drugs						
5-Fluorouracil	7	48.4 - 1477	12	5.0 - 69.3	281	80.0
Cyclophosphamide	6	20.0 - 1169	11	3.1 - 12.9	12.0	15.2
Ifosfamide	4	13.0 - 88.5	8	1.9 - 8.9	8.3	10.4
Paclitaxel	4	4.2 - 12.5	0	ND	ND	ND
Methotrexate	2	6.1 - 298	0	ND	ND	ND

[a] minimum to maximum detected values

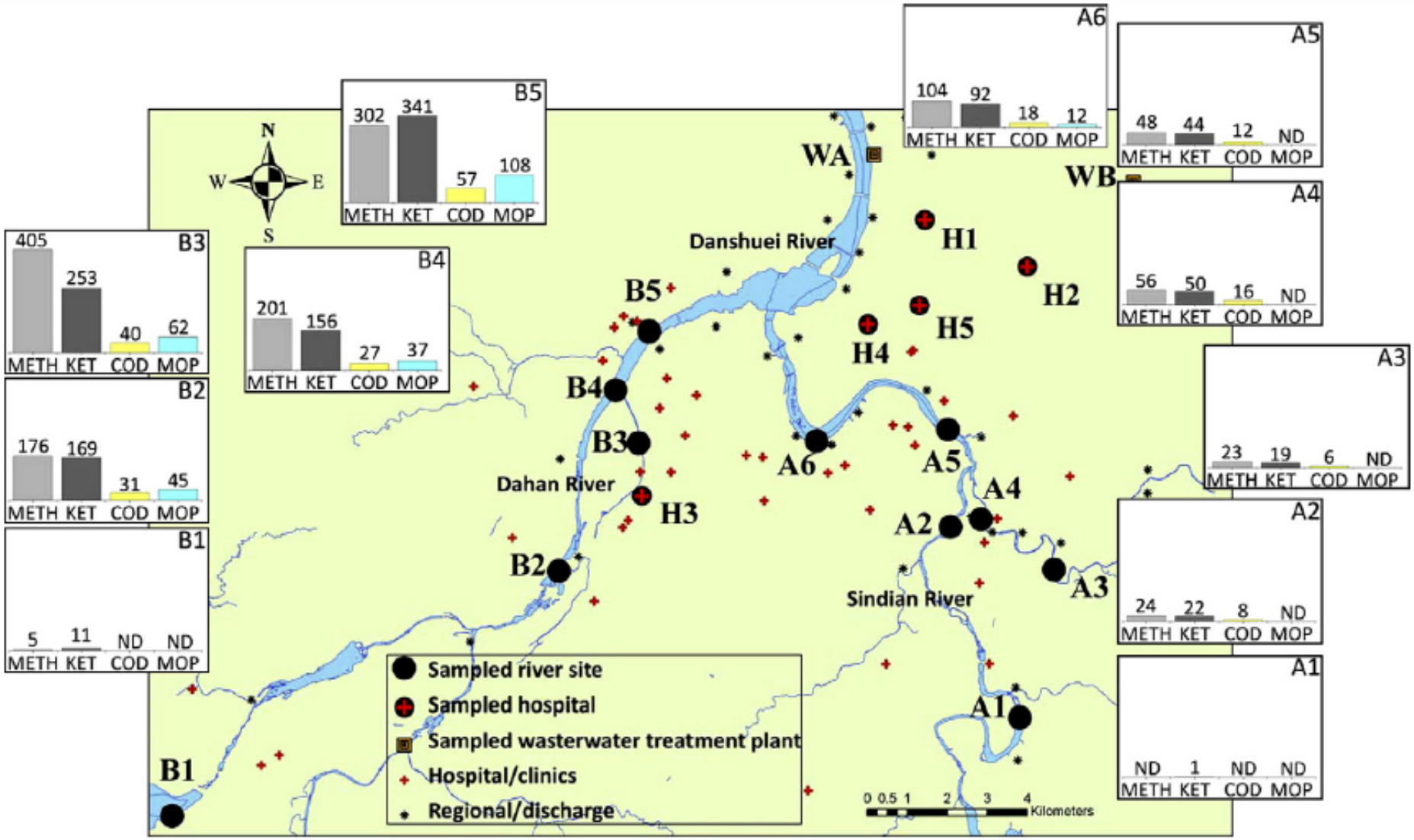
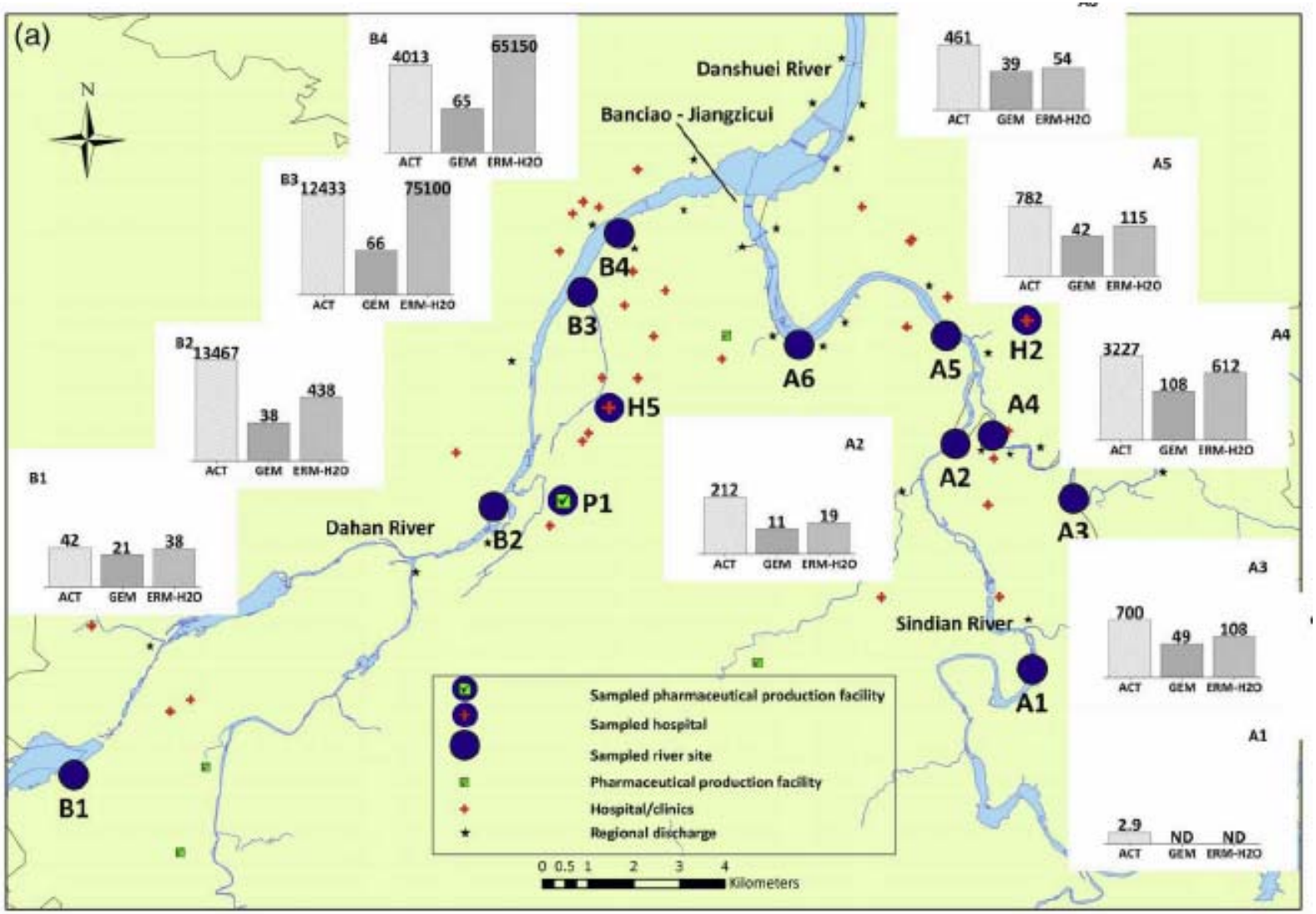


Fig. 1. Sampling sites and the occurrence of controlled substances (ng L^{-1}) in Dahan river and Sindian river in Taipei, Taiwan. Acronyms of four compounds ar methamphetamine: METH; ketamine: KET; codeine: COD; morphine: MOP.

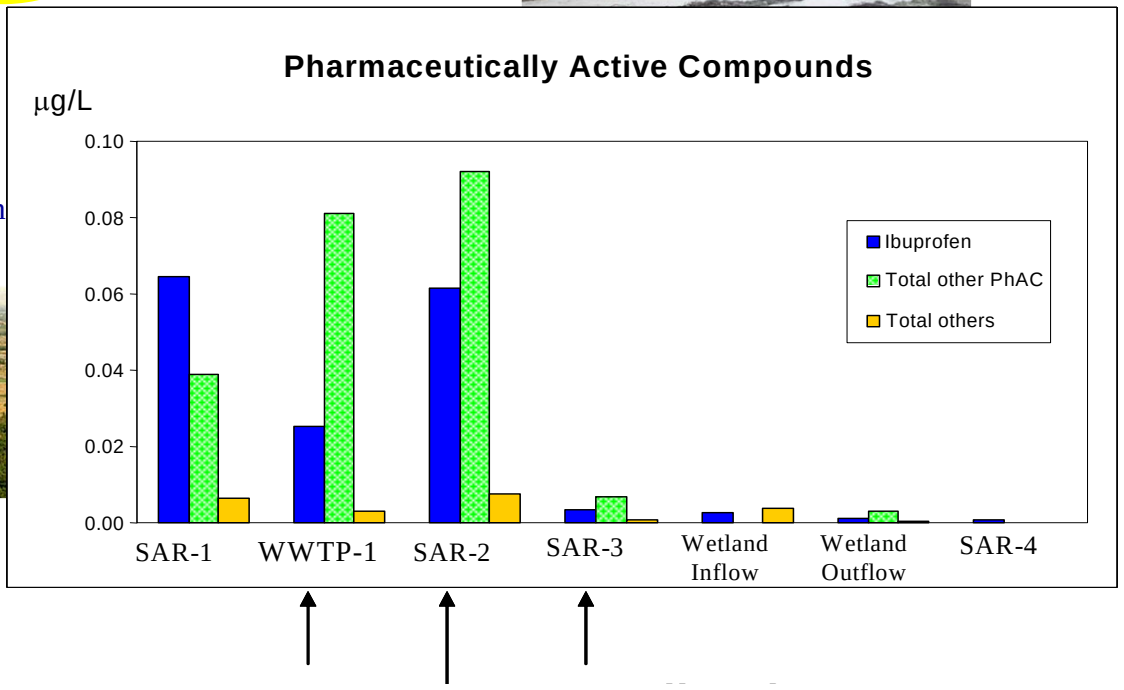
Ref: Lin et al. 2010 Chemosphere



Ref: Lin and Tsai 2009 Sci. Total Environment

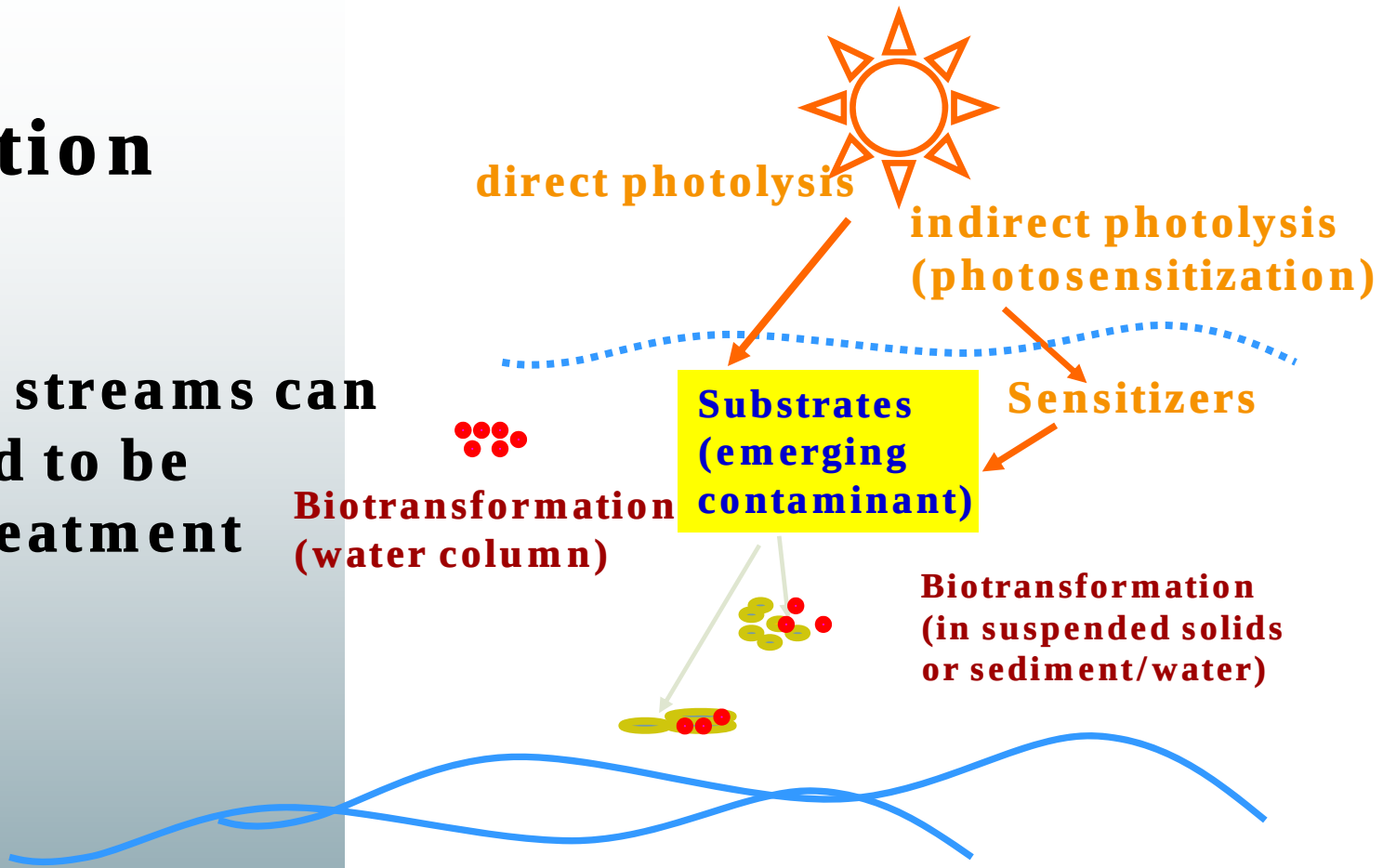
- 2700mi²
- 4million people
- Precipitation: Nov – March

Santa Ana River (SAR)



Natural Attenuation

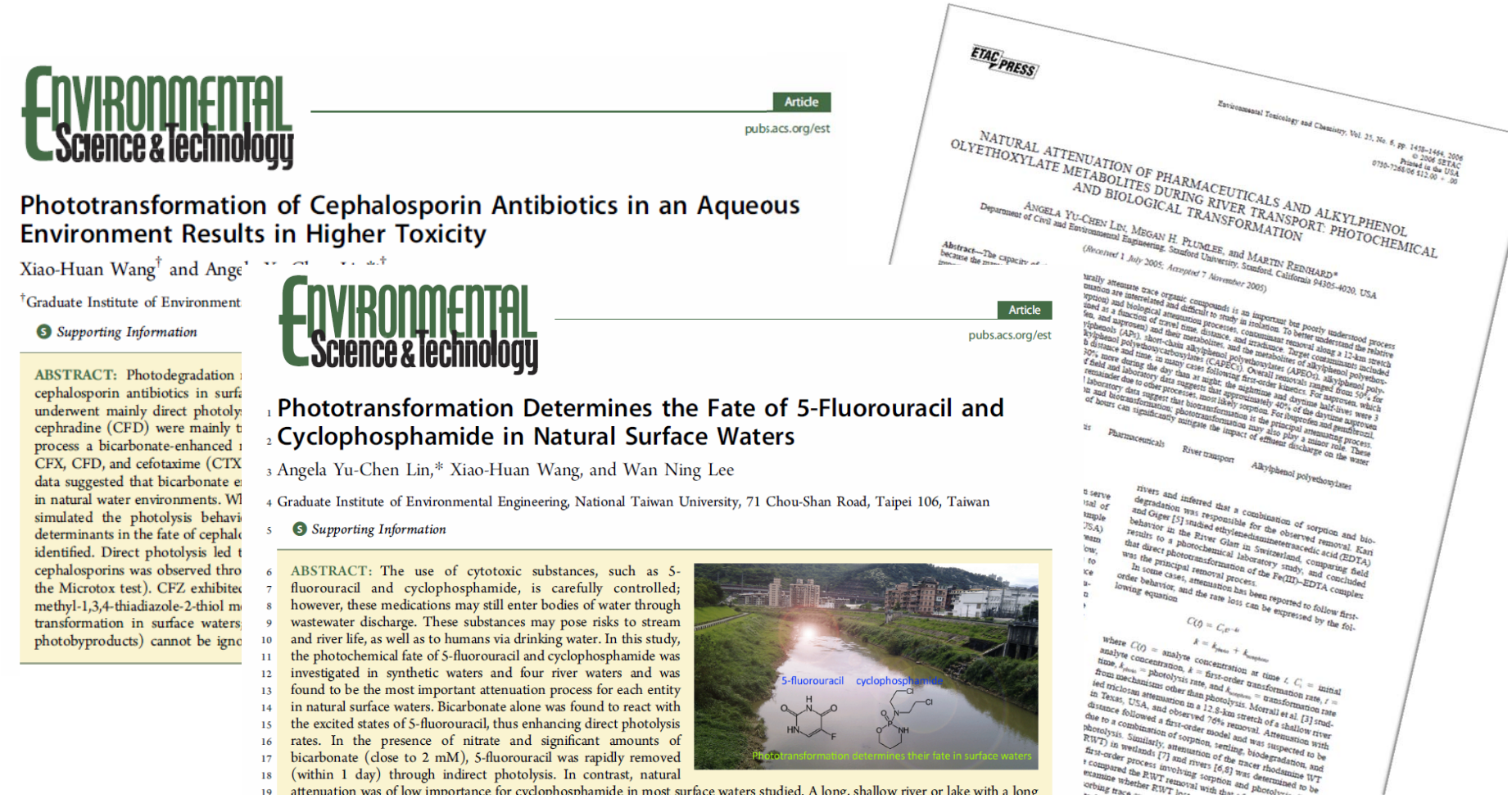
Rivers and streams can be expected to be efficient treatment systems.



Sorption onto sediments or suspended solids

Phototransformation

- Phototransformation determines the fate of many recalcitrant pharmaceuticals in natural surface waters



ENVIRONMENTAL Science & Technology

Article

pubs.acs.org/est

Phototransformation of Cephalosporin Antibiotics in an Aqueous Environment Results in Higher Toxicity

Xiao-Huan Wang† and Ange

†Graduate Institute of Environment

Supporting Information

ABSTRACT: Photodegradation
cephalosporin antibiotics in surfa
underwent mainly direct photoly
cephradine (CFD) were mainly t
process a bicarbonate-enhanced
CFX, CFD, and cefotaxime (CTX
data suggested that bicarbonate e
in natural water environments. W
simulated the photolysis behavi
determinants in the fate of cephal
identified. Direct photolysis led t
cephalosporins was observed thro
the Microtox test). CFZ exhibite
methyl-1,3,4-thiadiazole-2-thiol m
transformation in surface waters
photobyproducts) cannot be igno

ENVIRONMENTAL Science & Technology

Article

pubs.acs.org/est

Phototransformation Determines the Fate of 5-Fluorouracil and Cyclophosphamide in Natural Surface Waters

Angela Yu-Chen Lin,* Xiao-Huan Wang, and Wan Ning Lee

Graduate Institute of Environmental Engineering, National Taiwan University, 71 Chou-Shan Road, Taipei 106, Taiwan

Supporting Information

ABSTRACT: The use of cytotoxic substances, such as 5-fluorouracil and cyclophosphamide, is carefully controlled; however, these medications may still enter bodies of water through wastewater discharge. These substances may pose risks to stream and river life, as well as to humans via drinking water. In this study, the photochemical fate of 5-fluorouracil and cyclophosphamide was investigated in synthetic waters and four river waters and was found to be the most important attenuation process for each entity in natural surface waters. Bicarbonate alone was found to react with the excited states of 5-fluorouracil, thus enhancing direct photolysis rates. In the presence of nitrate and significant amounts of bicarbonate (close to 2 mM), 5-fluorouracil was rapidly removed (within 1 day) through indirect photolysis. In contrast, natural attenuation was of low importance for cyclophosphamide in most surface waters studied. A long, shallow river or lake with a long

5-fluorouracil cyclophosphamide

Phototransformation determines their fate in surface waters

ETAC PRESS

Environmental Toxicology and Chemistry, Vol. 25, No. 6, pp. 1458–1464, 2006

© 2006 SETAC

Printed in the USA

0730-7268/06 $12.00 + .00

NATURAL ATTENUATION OF PHARMACEUTICALS AND ALKYLPHENOL OLYETHOXYLATE METABOLITES DURING RIVER TRANSPORT: PHOTOCHEMICAL AND BIOLOGICAL TRANSFORMATION

ANGELA YU-CHEN LIN, MEGAN H. PLUMLEE, and MARTIN REINHARD*

Department of Civil and Environmental Engineering, Stanford University, Stanford, California 94305-4020, USA

(Received 1 July 2005; Accepted 7 November 2005)

Abstract—The capacity

urally attenuate trace organic compounds is an important but poorly understood process
ansion are interrelated and difficult to study in isolation. To better understand the relative
sorption) and biological attenuation processes, contaminant removal along a 12-km stretch
lon, and naproxen) and their metabolites, and irradiance. Target contaminants included
ylphenols (APs), short-chain alkylphenol polyethoxylates of alkylphenol polyethox-
alkylphenol polyethoxycarboxylates (CAPECs). Overall removals ranged from 50% for
30% more during the day than at night; the nighttime and daytime half-lives were 3
h distance and time, as many cases following first-order kinetics. For naproxen, which
of field and laboratory data suggest that approximately 40% of the daytime naproxen
remainder due to other processes; most likely sorption. For ibuprofen and gemfibrozil,
laboratory data suggest that biotransformation may also play a minor role. These
on and biotransformation; phototransformation is the principal attenuating process.
of hours can significantly mitigate the impact of effluent discharge on the water

Pharmaceuticals River transport Alkylphenol polyethoxylates

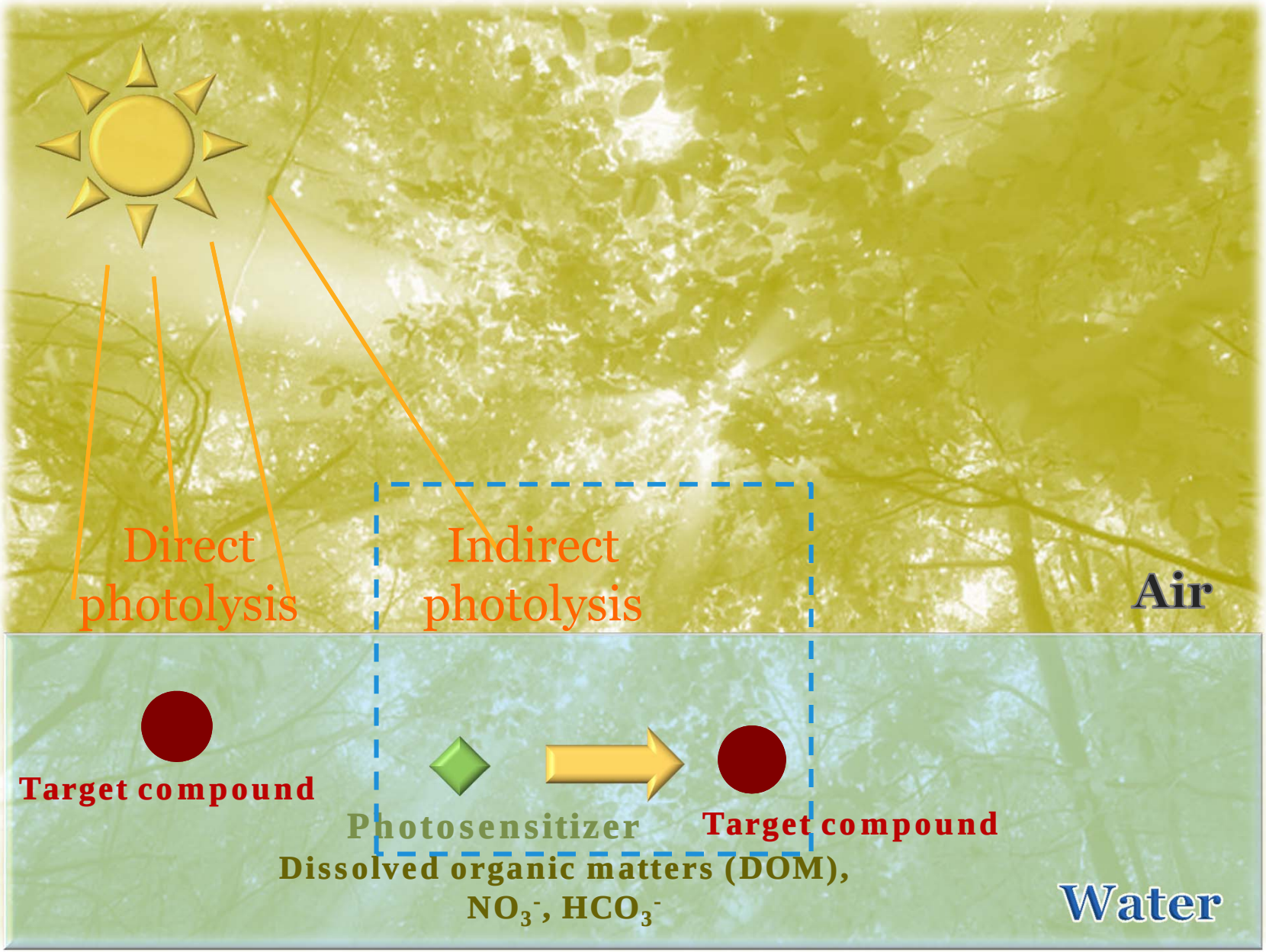
rivers and inferred that a combination of sorption and bio-
degradation was responsible for the observed removal. Kari
and Giger [5] studied ethylenediaminetetraacetic acid (EDTA)
behavior in the River Glatt in Switzerland, comparing field
results to a photochemical laboratory study, and concluded
that direct phototransformation of the Fe(III)–EDTA complex
was the principal removal process.
In some cases, attenuation has been reported to follow first-
order behavior, and the rate loss can be expressed by the fol-
lowing equation

$$C(t) = C_0 e^{-kt}$$

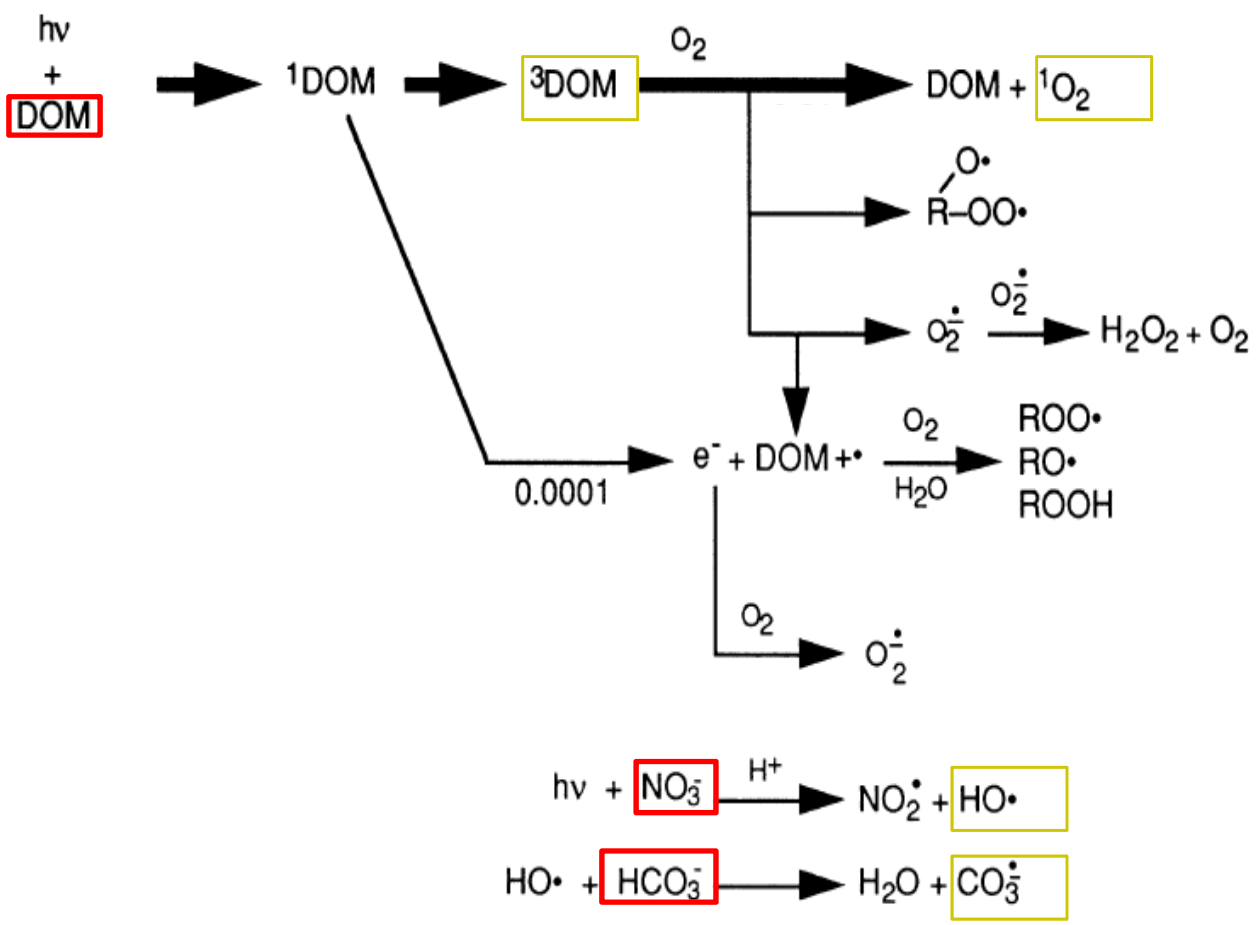
$$k = k_{photo} + k_{biotic}$$

where $C(t)$ = analyte concentration at time t, C_0 = initial analyte concentration, k = first-order transformation rate, t = time, k_{photo} = photolysis rate, and k_{biotic} = transformation rate from mechanisms other than photolysis. Morrall et al. [3] studied triclosan attenuation in a 12.8-km stretch of a shallow river in Texas, USA, and observed 76% removal. Attenuation with distance followed a first-order model and was suspected to be due to a combination of sorption, sorbing biodegradation, and photolysis. Similarly, attenuation of the tracer rhodamine WT (RWT) in wetlands [7] and rivers [6,8] was determined to be first-order process involving sorption and photolysis. We compared the RWT removal with that of examine whether RWT loss

Photochemical Reaction



Photochemical Reaction



Target compo

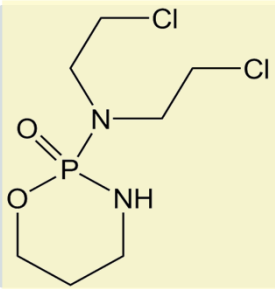
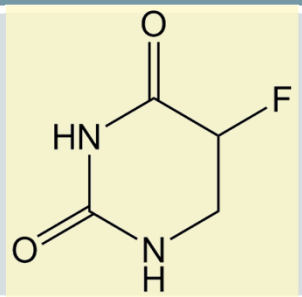
Reference: Haag, W.R. and T. Mill., 1989.

Experimental Approach

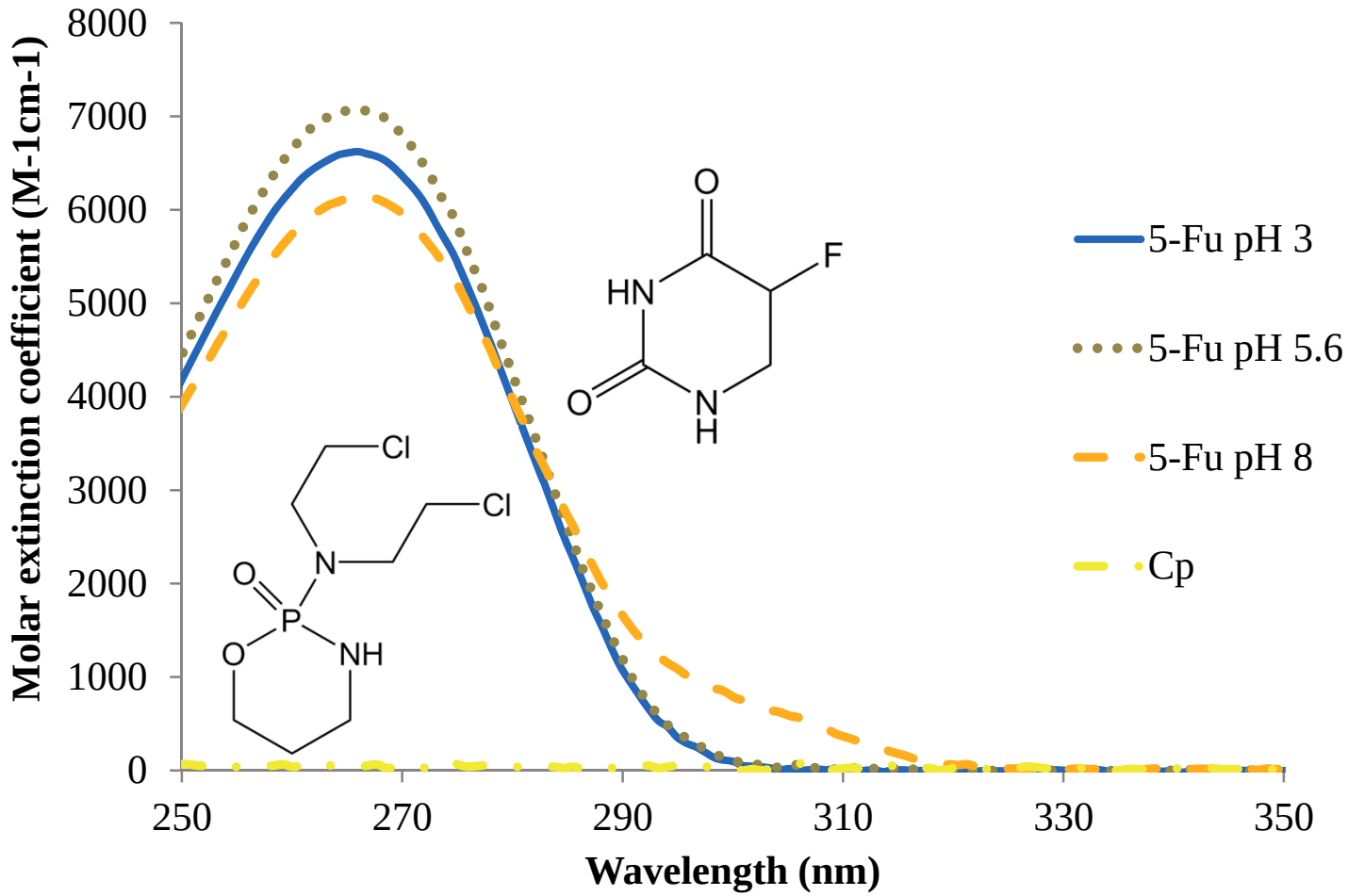
Sunlight Simulator CPS+

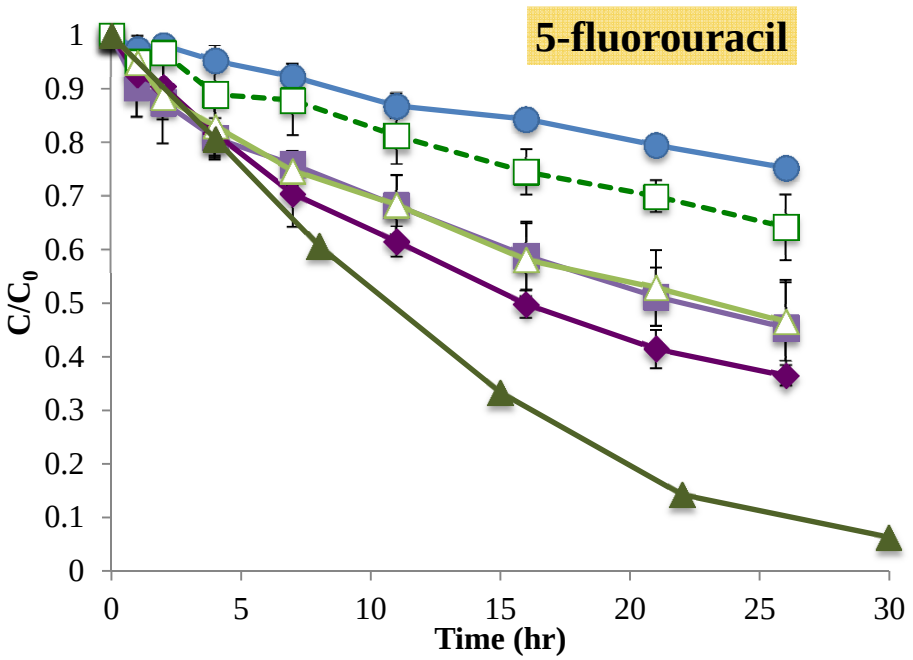
λ: 290-700nm
765 W/m²

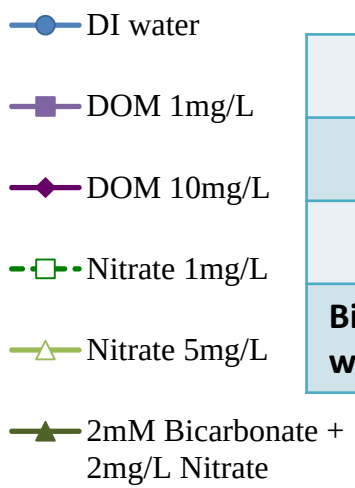
Compounds	National Health Institute 2005 usage data	
	Doses	**Amount in each dose**
Cyclophasphamide	543,316	50mg, 200mg, 500mg
5-fluorouracil	296,940	250mg, 500mg, 1000mg

	(Cyclophosphamide, CP)	(5-fluorouracil, 5-FU)
Structure		
Function	Cytotoxic agent Treatment of lymphomas, brain cancer, leukemia and some solid tumors Treatment of autoimmune diseases	Cytotoxic agents Treatment of solid tumors, i.e colorectal and breast cancer
Adverse effects	nausea, vomiting, bone marrow suppression, stomach ache, diarrhea, darkening of the skin/nails, hair loss, lethargy	myelosuppression, mucositis, diarrhea, dermititis

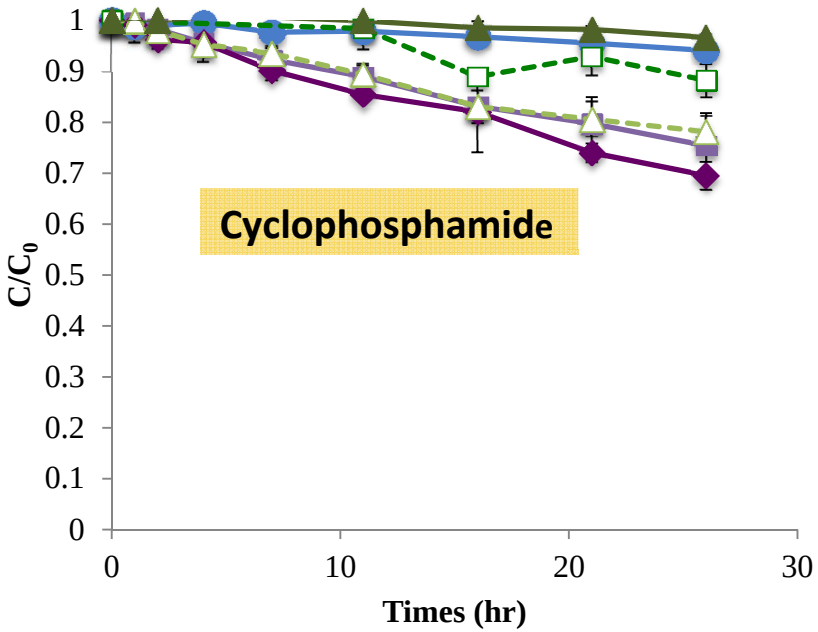
UV-Vis adsorption spectrum



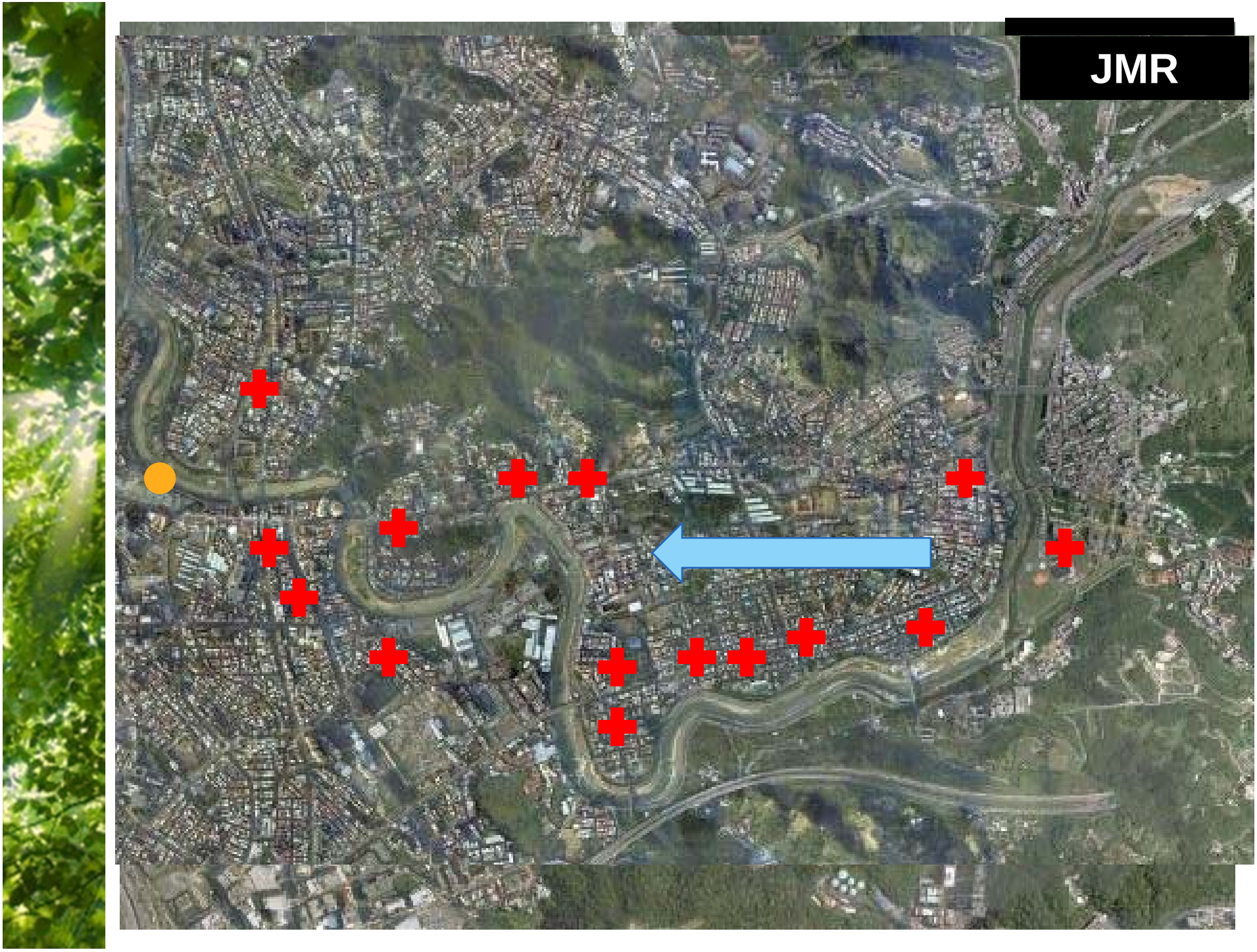




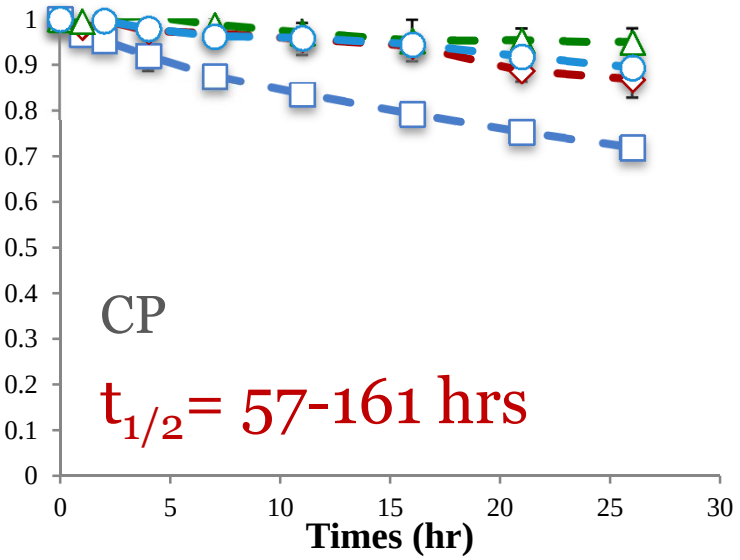
Direct	43 hrs
DOM	16.0~28.2 hrs
Nitrate	18.2~40.5 hrs
Bicarbonate with Nitrate	8.0 hrs

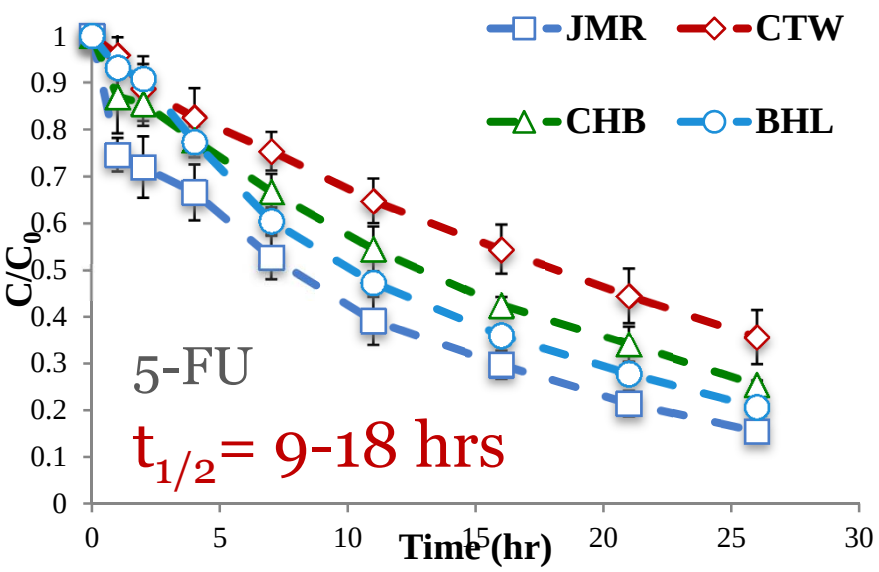


Direct	No degradation
DOM	48.5~86.6 hrs
Nitrate	58.7~112 hrs
Bicarbonate with Nitrate	No degradation

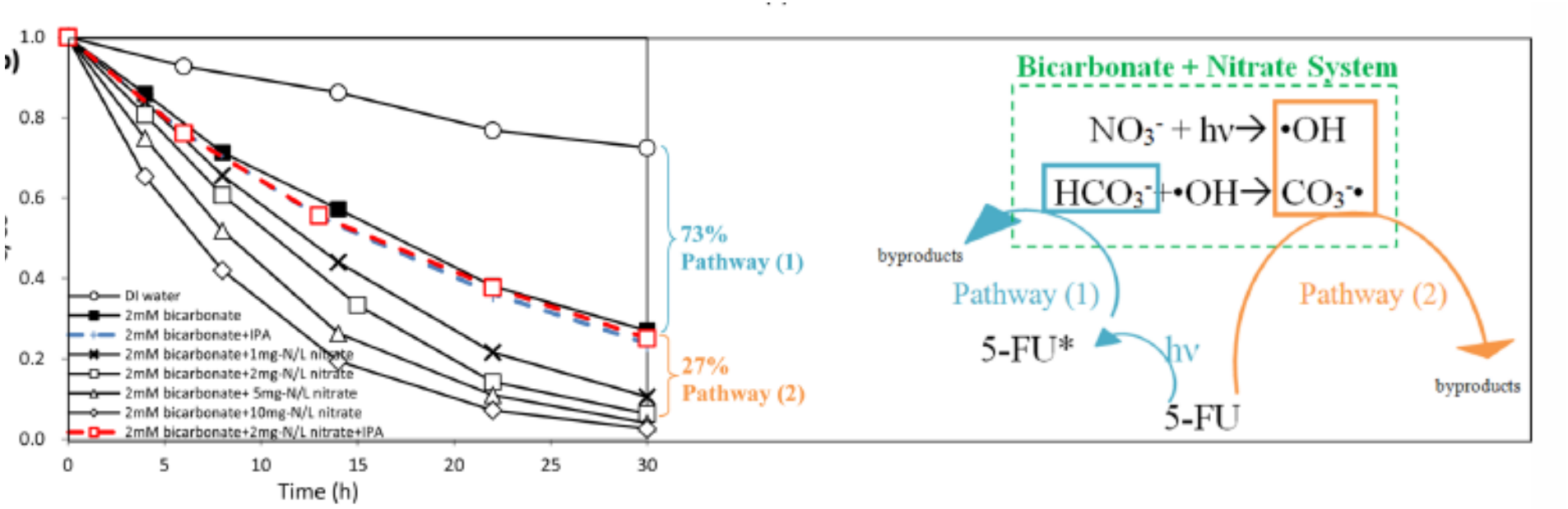

JMR

Photolysis in Surface Waters





Sampling site	Type	pH	DOC (mg/L)	NO_3-N (mg/L)	Alkalinity (mg/L as $CaCO_3$)
JingMei River (JMR)	river	7.5 – 7.7	2.0 – 4.0	2.0 – 2.2	85.0 (1.7 mM HCO3-)
ChingTan Weir (CTW)	river	7.6 – 7.9	0.6 – 1.0	0.2 – 0.4	25.0 (0.5 mM HCO3-)
ChungHsing Bridge (CHB)	river	7.5 – 7.8	2.4 – 6.3	0.2	137.5 (2.75 mM HCO3-)
BiHu Lake (BHL)	lake	8.0 – 9.2	4.1 – 5.5	0.1	61.3 (1.2 mM HCO3-)



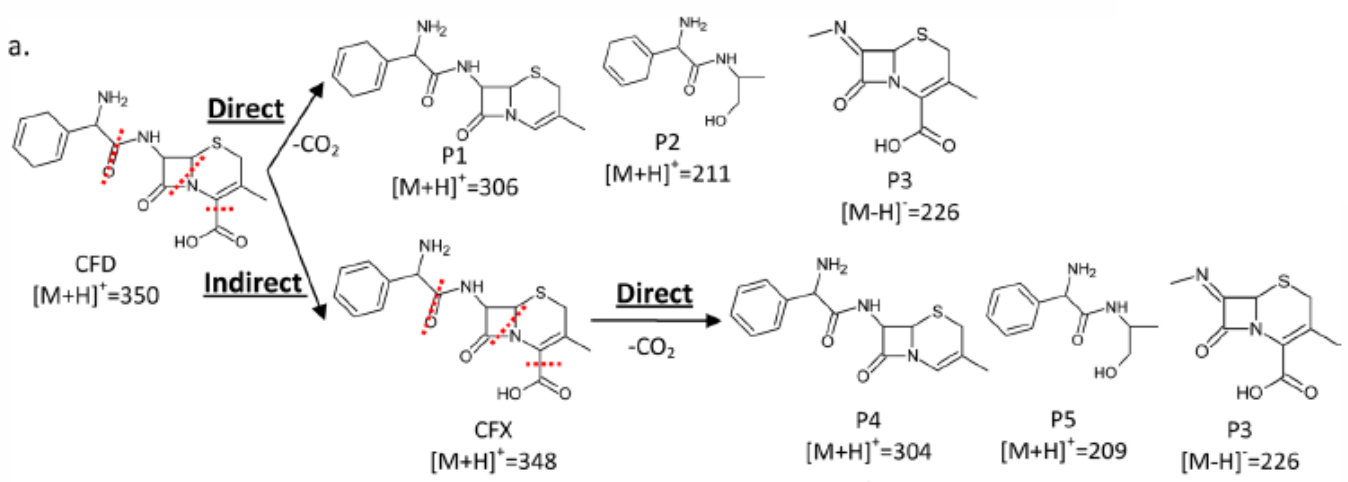
Ref: Lin et al. 2013, Environmental Science &Technology

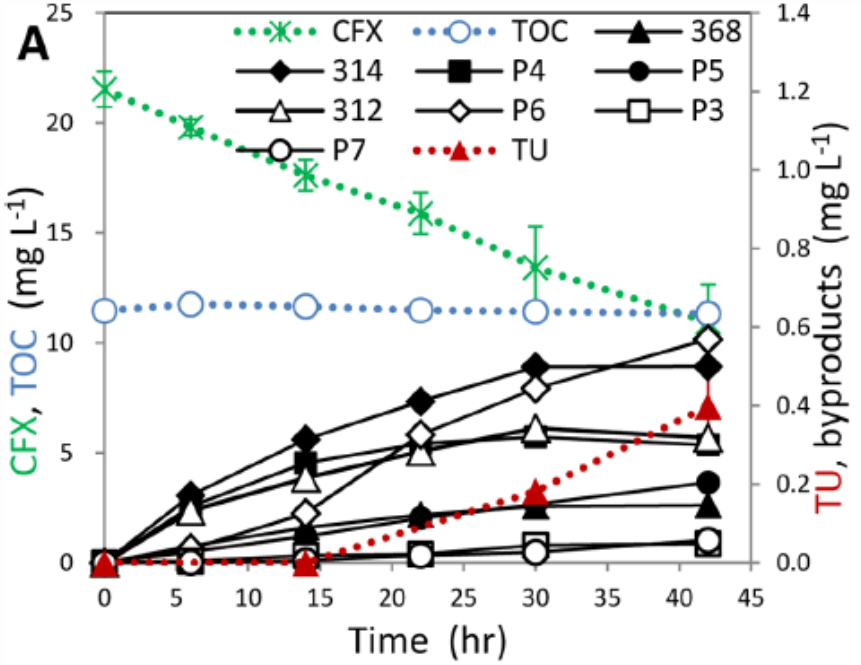
Natural Attenuation Processes

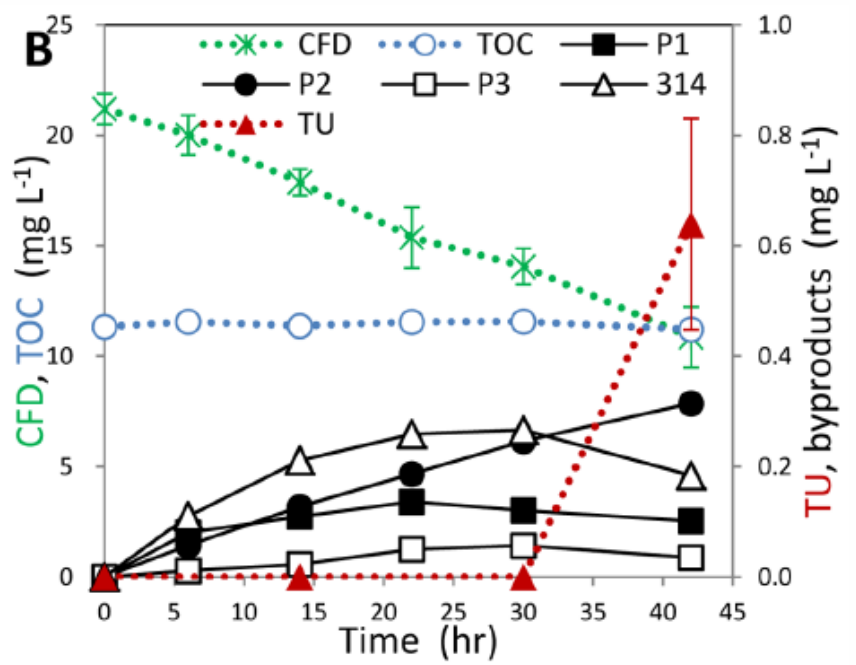
Attenuation Processes	Cyclophosphamide Persistent in surface water	5-Fluouracil Absent in surface water
Hydrolysis	No degradation in 30 days	No degradation in 30 days
Biodegradation	No degradation[a]	No degradation in river water in 40 days[b] Less than 60% removal after 50 days of incubation[c]
Volatilization	Not likely (Henry's law constant: 6.9 x 10^{-11}atm L/mol)[d]	Not likely (Henry's law constant: 1.66 x 10^{-10} atm m^3/mol)[e]
Sorption	Not likely (log K_{ow}=0.63)[f]	Not likely (log K_{ow}= -0.89)[e] No adsorption due to the suspended solids and materials in raw wastewater over 24hr[g]
Photolysis	$t_{1/2}$= 57-161 hrs (surface waters) Indirect phototransformation is the main degradation pathway (DOM, NO_3^-)	$t_{1/2}$= 9-18 hrs (surface waters) - Undergo both direct and indirect phototrasformation (CO_3^- radical) - No mineralization

Is the photolysis of pharmaceuticals a natural purification process that decreases ecological and human health risks?

Photolysis Byproduct

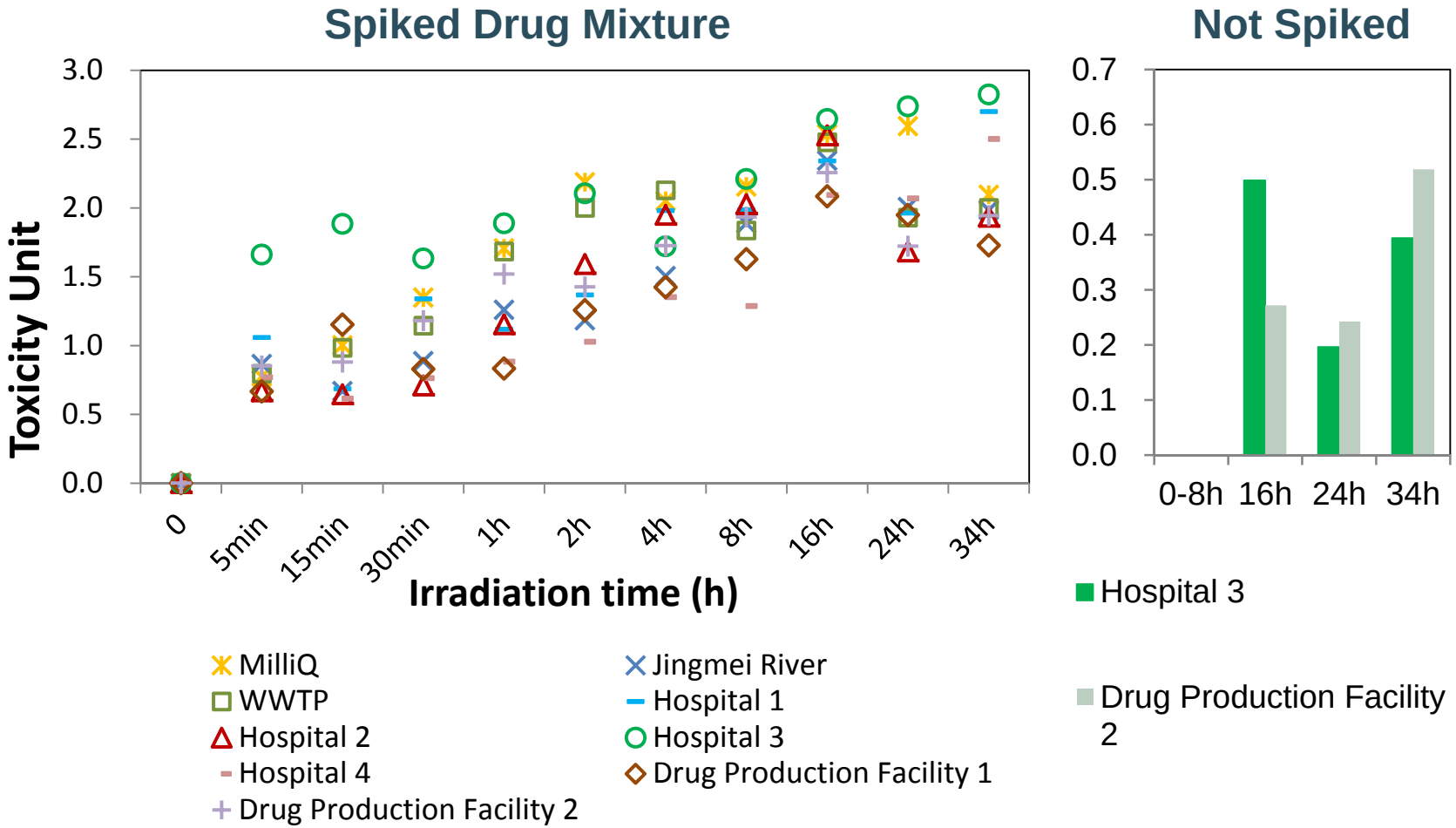






Ref: Wang and Lin 2012, Environmental Science &Technology

Increased toxicity from photobyproducts associated with the pharmaceutical mixture



Ref: Wang and Lin 2014, Environmental Pollution

Are we at risk of drinking our waters?

Perspectives:
National Resources Defense Council

"Although the levels reported to contaminate our waterways are much lower than therapeutic doses, **it would be naïve to think of this as 'safe**', knowing that the agents are chemically reactive in our bodies, and that we are exposed daily over a life-time to multiple compounds in unknown combinations."

Acknowledgement

Ministry of Science and Technology

National Health Research Institute

Taiwan Environmental Protection Agency

- To next lecture