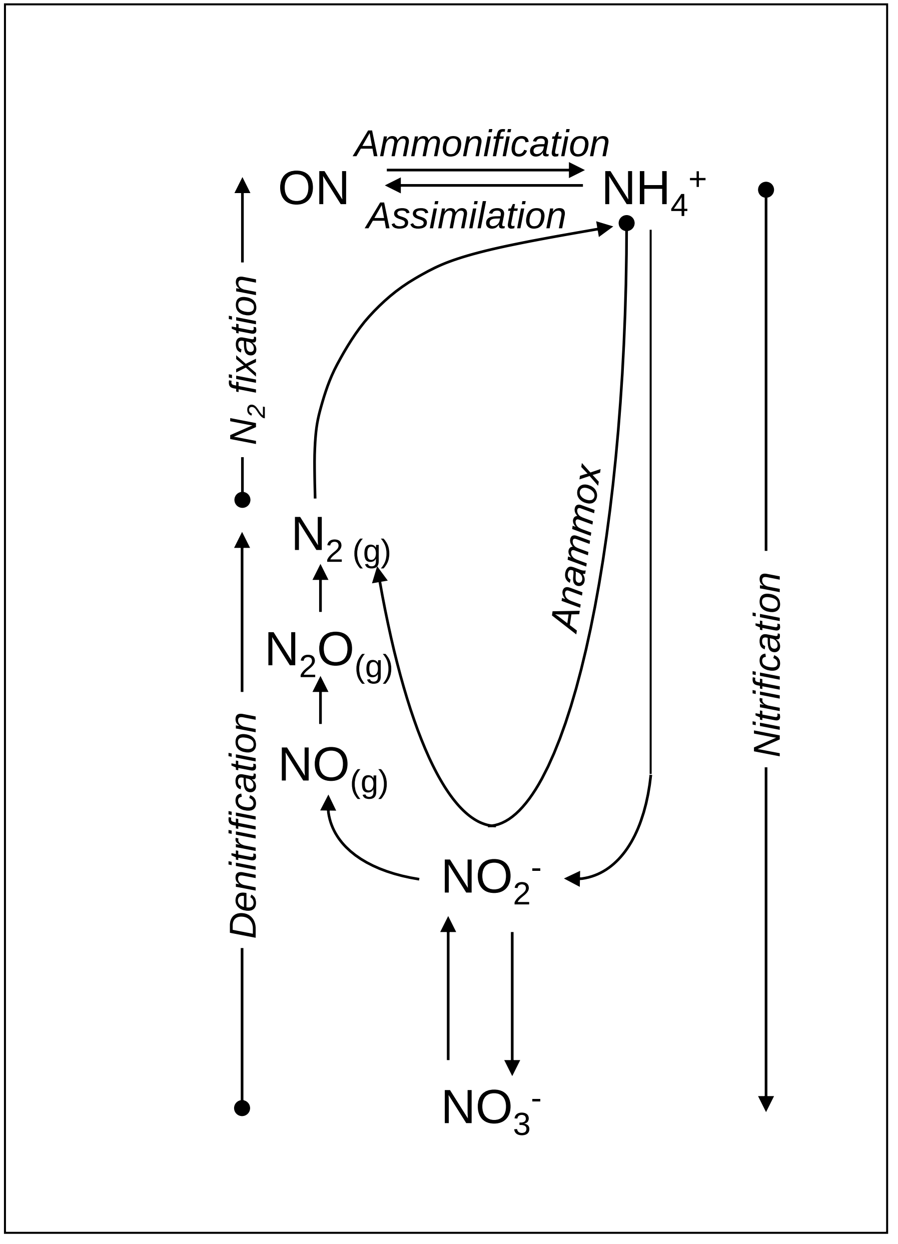
At the Intersection of Nitrogen Transformation and Pharmaceuticals

Nancy G. Love, Ph.D., P.E., BCEE, WEF Fellow
Department of Civil and Environmental Engineering
University of Michigan
nglove@umich.edu

MICHIGAN ENGINEERING
UNIVERSITY of MICHIGAN



NG Love, Univ Michigan

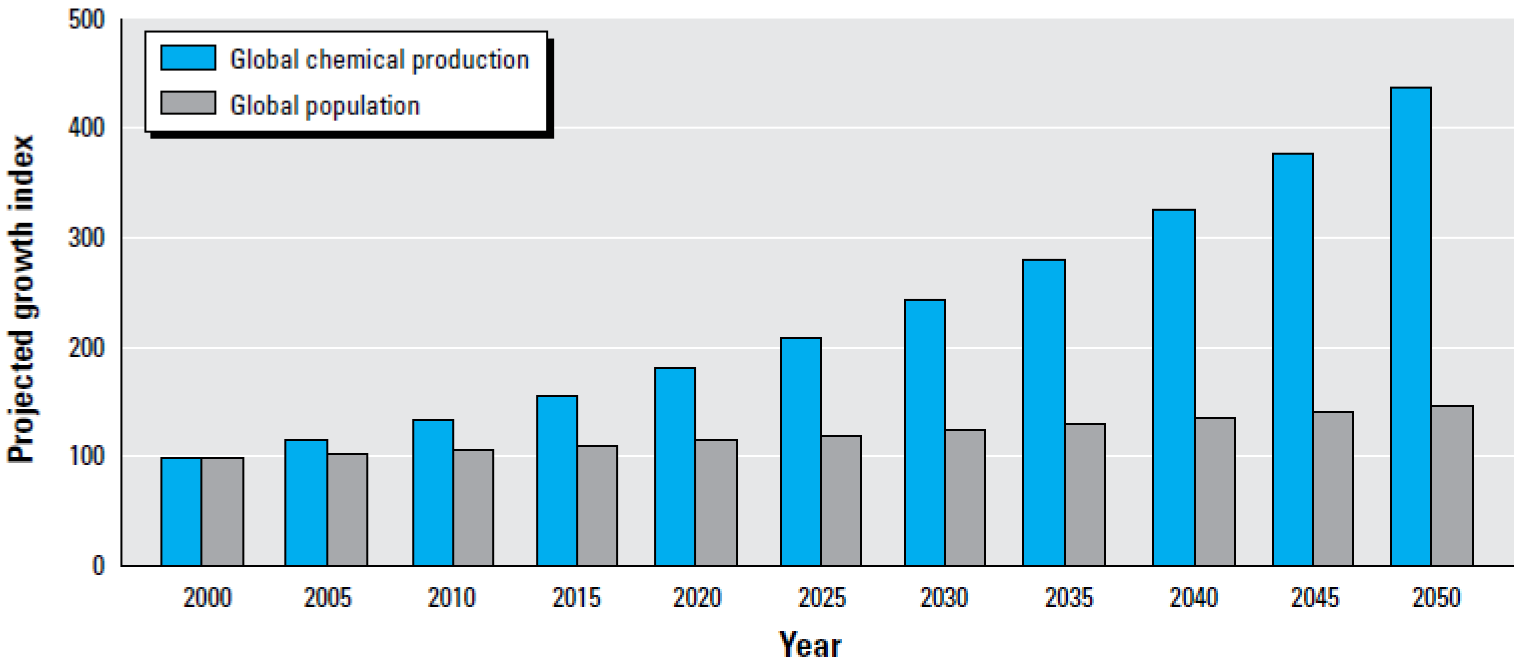
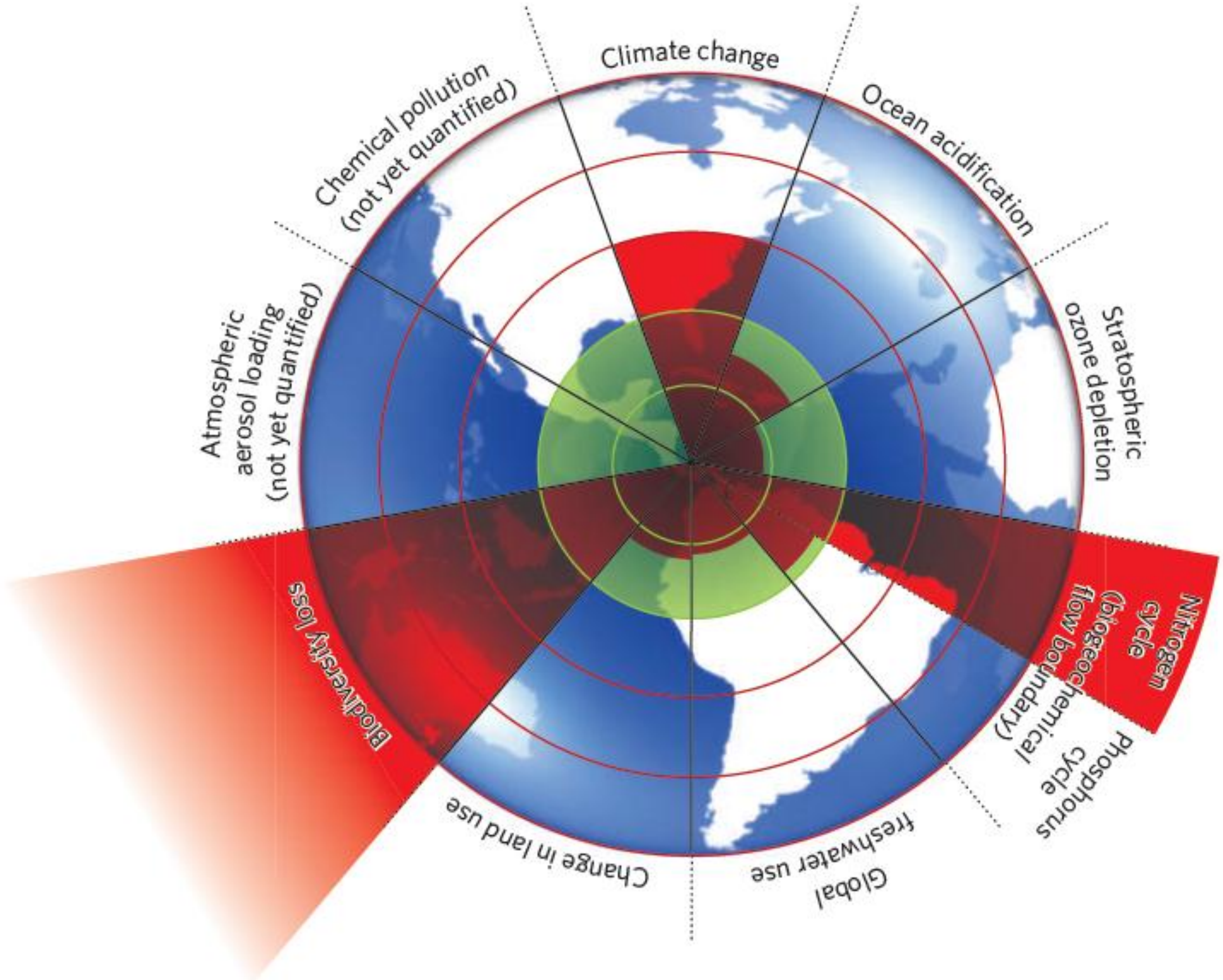


Figure 2. Global chemical production is projected to grow at a rate of 3% per year, rapidly outpacing the rate of global population growth, estimated at 0.77% per year. On this trajectory, chemical production will double by 2024, indexed to 2000 (American Chemistry Council 2003; OECD 2001; United Nations 2004).

Wilson and Schwarzman (2009) Toward a New U.S. Chemicals Policy: Rebuilding the Foundation to Advance New Science, Green Chemistry, and Environmental Health, *Environ. Health Perspect.* **117**:1202-1209.

Chemical Pollution is a planetary boundary that is currently not quantified



Rockström et al. (2009) A safe operating space for humanity, *Nature* **461**: 472-475.

NG Love, Univ Michigan

Life Sciences Vol. 20, pp. 337-342, 1977.
Printed in the U. S. A.
Pergamon Press

DRUGS AND DRUG METABOLITES AS ENVIRONMENTAL CONTAMINANTS: CHLOROPHENOXYISOBUTYRATE AND SALICYLIC ACID IN SEWAGE WATER EFFLUENT

Charles Hignite and Daniel L. Azarnoff

Kansas City Veterans Administration Hospital
Kansas City, Missouri
and
Clinical Pharmacology-Toxicology Center
Departments of Medicine and Pharmacology
University of Kansas Medical Center
College of Health Sciences and Hospital
Kansas City, Kansas

(Received in final form December 6, 1976)

SUMMARY

Chlorophenoxyisobutyrate (CPIB) and salicylic acid, the metabolites of clofibrate and aspirin, were quantitated by gas chromatography-mass spectrometry in the effluent of a sewage disposal plant in Kansas City, Missouri. The average daily output of CPIB was 2.1 (0.76-2.92) kg and salicylic acid 8.64 (0.55-28.69) kg over a 10 month period. Approximately one-half of the clofibrate consumed in this area is discharged into the Missouri River.

Pergamon

Wat. Res. Vol. 32, No. 11, pp. 3245–3260, 1998

Printed in Great Britain
0043-1354/98 $19.00 + 0.00

PII: S0043-1354(98)00099-2

OCCURRENCE OF DRUGS IN GERMAN SEWAGE TREATMENT PLANTS AND RIVERS*

THOMAS A. TERNES†

ESWE-Insitute for Water Research and Water Technology, Söhnleinstrasse 158, D-65201 Wiesbaden, Germany

NG Love, Univ Michigan

Life Sciences Vol. 20, pp. 337-342, 1977. Pergamon Press
Printed in the U. S. A.

DRUGS AND DRUG METABOLITES AS ENVIRONMENTAL CONTAMINANTS: CHLOROPHENOXYISOBUTYRATE AND SALICYLIC ACID IN SEWAGE WATER EFFLUENT

Charles Hignite and Daniel L. Azarnoff

Kansas City Veterans Administration Hospital
Kansas City, Missouri
and
Clinical Pharmacology-Toxicology Center
Departments of Medicine and Pharmacology
University of Kansas Medical Center
College of Health Sciences and Hospital
Kansas City, Kansas

(Received in final form December 6, 1976)

SUMMARY

Chlorophenoxyisobutyrate (CPIB) and salicylic acid, the metabolites of clofibrate and aspirin, were quantitated by gas chromatography-mass spectrometry in the effluent of a sewage disposal plant in Kansas City, Missouri. The average daily output of CPIB was 2.1 (0.76-2.92) kg and salicylic acid 8.64 (0.55-28.69) kg over a 10 month period. Approximately one-half of the clofibrate consumed in this area is discharged into the Missouri River.

Pergamon

Wat. Res. Vol. 32, No. 11, pp. 3245–3260, 1998

Printed in Great Britain
0043-1354/98 $19.00 + 0.00

PII: S0043-1354(98)00099-2

OCCURRENCE OF DRUGS IN GERMAN SEWAGE TREATMENT PLANTS AND RIVERS*

THOMAS A. TERNES†

ESWE-Insitute for Water Research and Water Technology, Söhnleinstrasse 158, D-65201 Wiesbaden, Germany

NG Love, Univ Michigan

Pharmaceuticals, personal care products, trace organic pollutants add a new dimension to the notion of toxicity.

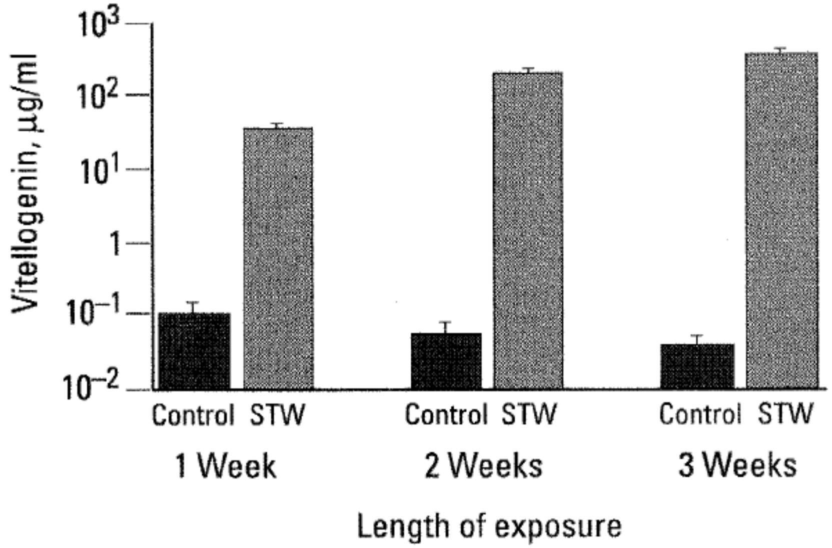
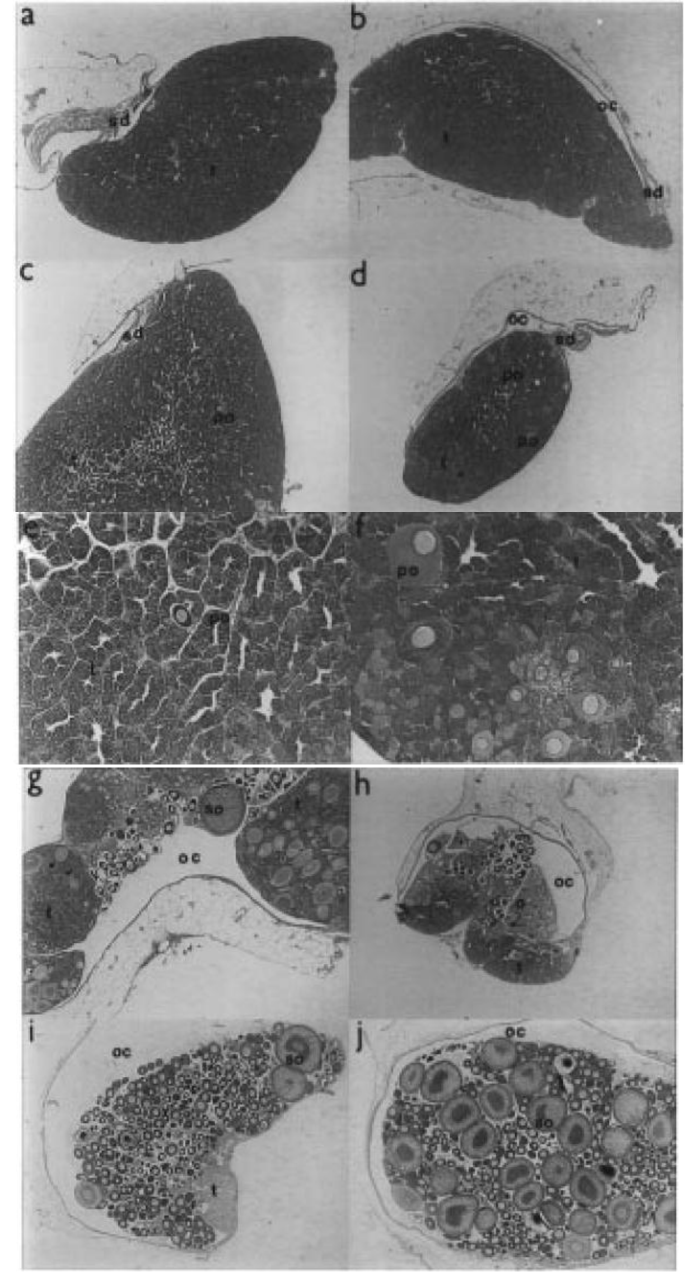


Figure 2. The effect of effluent from a sewage-treatment works on the plasma vitellogenin concentration of male rainbow trout. One cage containing 20 male trout was placed directly in the effluent channel of a sewage-treatment works (STW), and another (control) was maintained in a laboratory supplied with high-quality spring water. Plasma samples were collected after 1, 2, and 3 weeks and assayed for vitellogenin. Exposure to effluent caused a pronounced increase in the plasma vitellogenin concentration ($p < 0.001$ at all times). Results are mean ± SEM ($n = 20$).

Sumpter & Jobling (1995) Vitellogenesis as a biomarker for estrogenic contamination of the aquatic environment. *Environ Health Perspec.* **103**:173-178.

Jobling et al. (1998) Widespread sexual disruption in wild fish. *Environ Sci Technol.* **32**:2498-2506



Feminization of fish downstream of wastewater treatment plants.

NG Love, Univ Michigan

Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999–2000: A National Reconnaissance

DANA W. KOLPIN*
U.S. Geological Survey, 400 S. Clinton Street, Box 1230, Iowa City, Iowa 52244

EDWARD T. FURLONG
U.S. Geological Survey, Box 25046, MS 407, Denver, Colorado 80225-0046

MICHAEL T. MEYER
U.S. Geological Survey, 4500 SW 40th Avenue, Ocala, Florida 34474

E. MICHAEL THURMAN
U.S. Geological Survey, 4821 Quail Crest Place, Lawrence, Kansas 66049

STEVEN D. ZAUGG
U.S. Geological Survey, Box 25046, MS 407, Denver, Colorado 80225-0046

LARRY B. BARBER
U.S. Geological Survey, 3215 Marine Street, Boulder, Colorado 80303

HERBERT T. BUXTON
U.S. Geological Survey, 810 Bear Tavern Road, West Trenton, New Jersey 08628

Environ. Sci. Technol. **2002**, *36*, 1202–1211

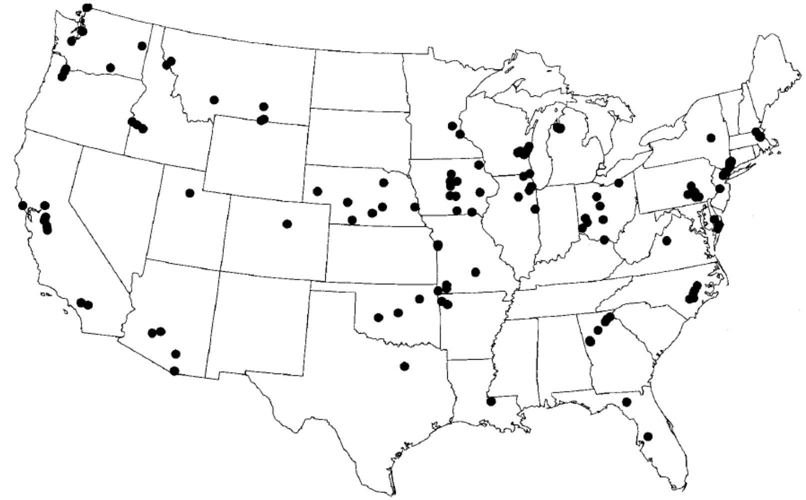


FIGURE 1. Location of 139 stream sampling sites.

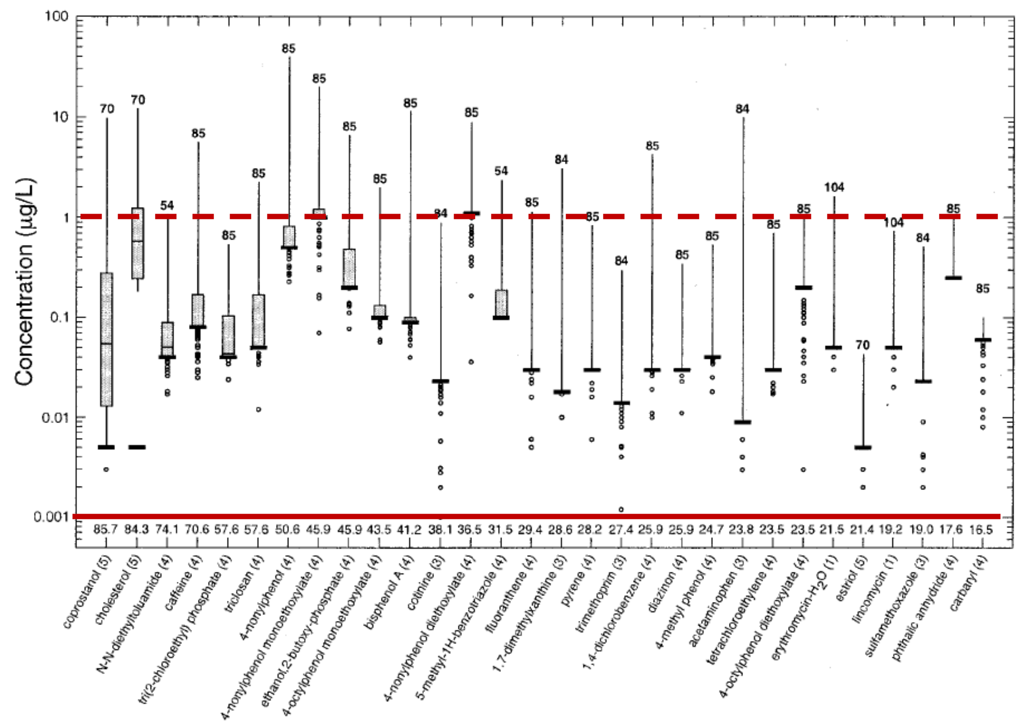
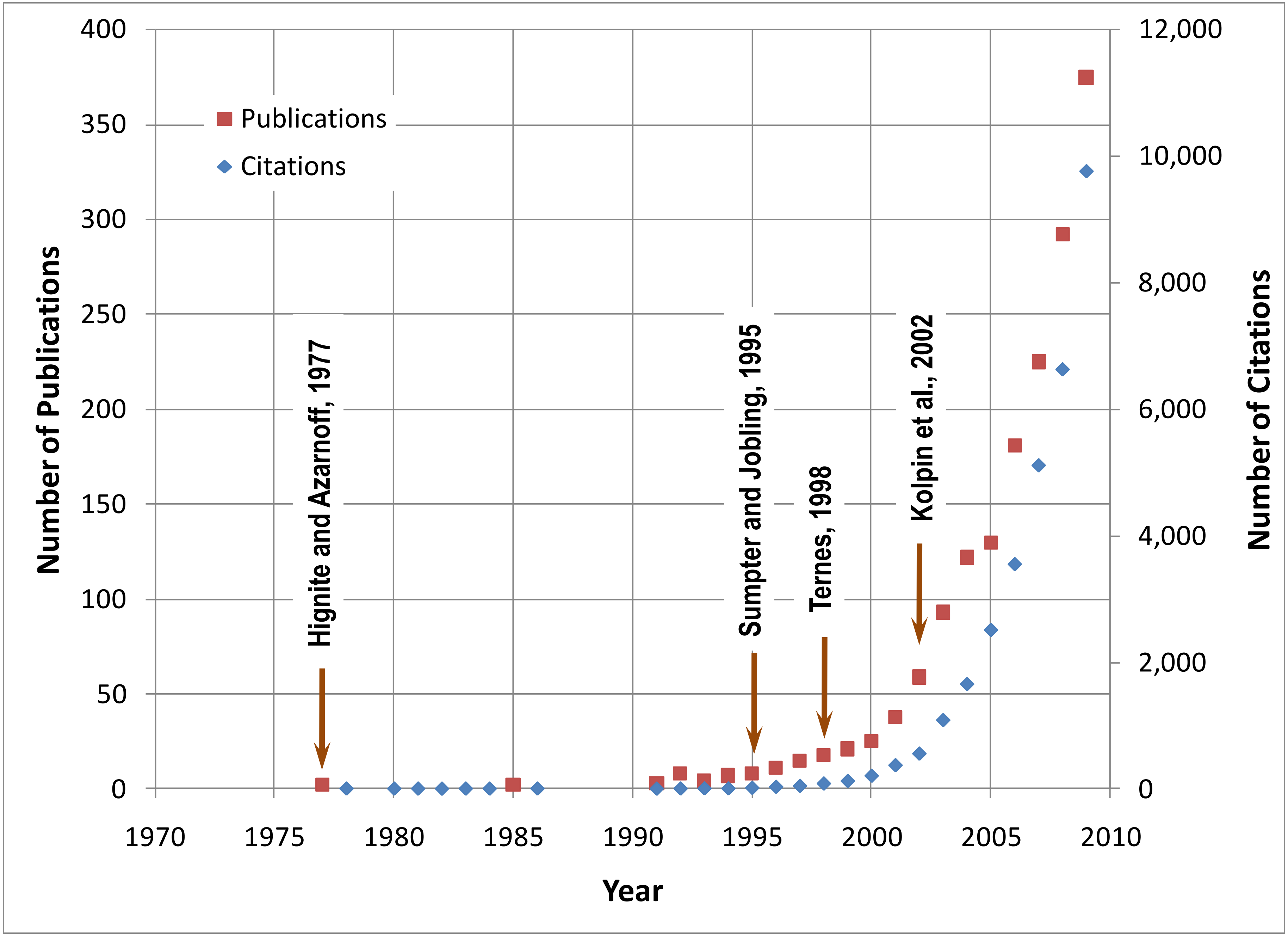


FIGURE 2. Measured concentrations for the 30 most frequently detected organic wastewater contaminants. Boxplots show concentration distribution truncated at the reporting level. Estimated values below the reporting level are shown. Estimated maximum values for coprostanol and cholesterol obtained from Method 5 (Table 1) are not shown. The analytical method number is provided (in parentheses) at the end of each compound name. An explanation of a boxplot is provided in Figure 3.

NG Love, Univ Michigan



NG Love, Univ Michigan

Should We Care?

PNAS | May 22, 2007 | vol. 104 | no. 21 | 8897–8901

Collapse of a fish population after exposure to a synthetic estrogen

Karen A. Kidd*†, Paul J. Blanchfield*, Kenneth H. Mills*, Vince P. Palace*, Robert E. Evans*, James M. Lazorchak‡, and Robert W. Flick‡

*Fisheries and Oceans Canada, Freshwater Institute, 501 University Crescent, Winnipeg, Manitoba, Canada R3T 2N6; and ‡Molecular Indicators Research Branch, United States Environmental Protection Agency, 26 West Martin Luther King Drive, Cincinnati, OH 45268

Should We Care?

PNAS |

Collapse of a ... posure
to a syntheti

Karen A. Kidd*†, Paul J. Blan ... Evans*,
James M. Lazorchak‡, and Rc

*Fisheries and Oceans Canada, Fresh ... 3T 2N6; and ‡Molecular Indicators
Research Branch, United States Envir ... nati, OH 45268

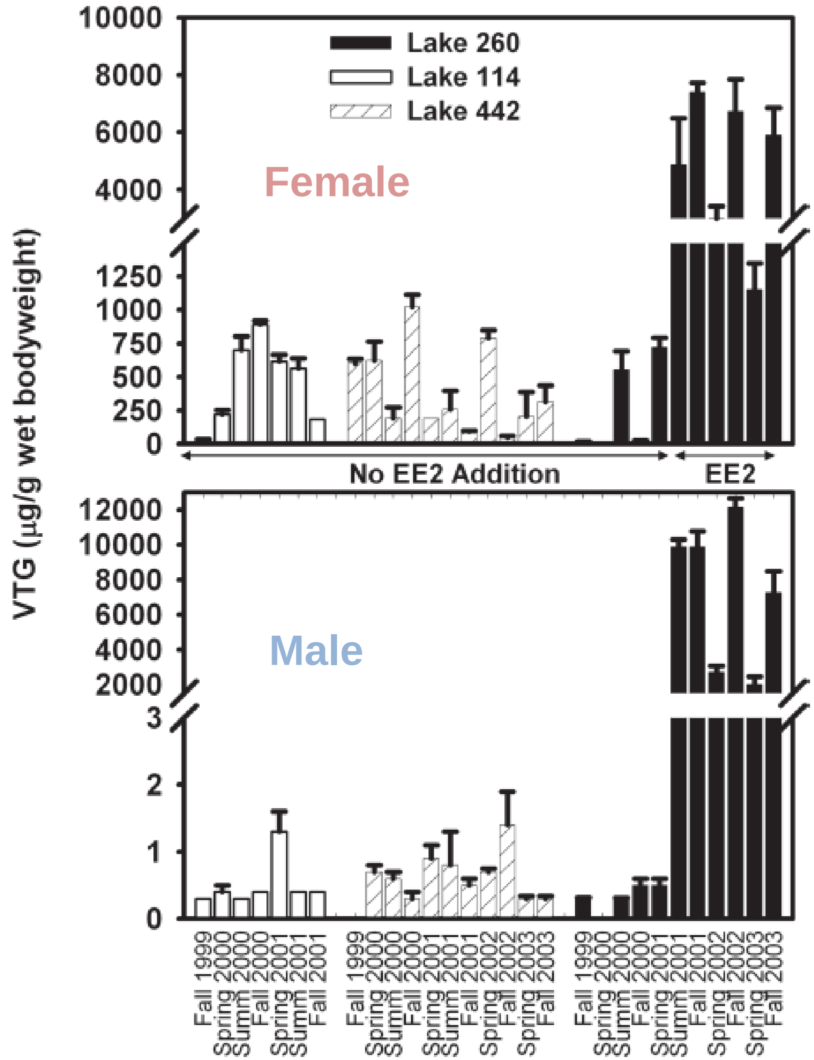


Fig. 1. Mean ± SE (n = 4–7) VTG concentrations in whole-body homogenates of male (*Lower*) and female (*Upper*) fathead minnow captured in 1999–2003 from reference Lakes 114 and 442 and from Lake 260 before and during additions of 5–6 ng·L^{-1} of EE2 (low catches of fish in Lake 260 in 2004 and 2005 did not allow for these analyses in the latter 2 years of the study).

NG Love, Univ Michigan

Should We Care?

PNAS | May 22, 2007 | vol. 104 | no. 21 | 8897–8901

Collapse of a fish population after exposure to a synthetic estrogen

Karen A. Kidd*†, Paul J. Blanchfield*, Kenneth H. Mills*, Vince P. Palace*, Robert E. Evans*, James M. Lazorchak‡, and Robert W. Flick‡

*Fisheries and Oceans Canada, Freshwater Institute, 501 University Crescent, Winnipeg, Manitoba, Canada R3T 2N6; and ‡Molecular Indicators Research Branch, United States Environmental Protection Agency, 26 West Martin Luther King Drive, Cincinnati, OH 45268

Review *Int. J. Environ. Res. Public Health* **2010**, *7*, 3929-3953

Human Health Risk Assessment of Pharmaceuticals in Water: Issues and Challenges Ahead

Arun Kumar [1], Biao Chang [2] and Irene Xagoraraki [3,*]

1 Department of Civil Engineering, Indian Institute of Technology Delhi, Hauz Khas, New Delhi 110016, India; E-Mail: arunku@civil.iitd.ac.in

2 School of Civil and Environmental Engineering, Georgia Institute of Technology, 215 Sustainable Education Building, 788 Atlantic Drive NW, Atlanta, GA 30332, USA; E-Mail: bchang6@gatech.edu

3 Department of Civil and Environmental Engineering, A124 Engineering Research Complex, Michigan State University, East Lansing, MI 48824, USA

Should We Care?

PNAS | May 22, 2007 | vol. 104 | no. 21 | 8897–8901

Collapse of a fish population after exposure to a synthetic estrogen

Karen A. Kidd*†, Paul J. Blanchfield*, Kenneth H. Mills*, Vince P. Palace*, Robert E. Evans*, James M. Lazorchak‡, and Robert W. Flick‡

*Fisheries and Oceans Canada, Freshwater Institute, 501 University Crescent, Winnipeg, Manitoba, Canada R3T 2N6; and ‡Molecular Indicators Research Branch, United States Environmental Protection Agency, 26 West Martin Luther King Drive, Cincinnati, OH 45268

Review

Int. J. Environ. Res. Public Health **2010**, *7*, 3929-3953

Human Health Risk Assessment of Pharmaceuticals in Water: Issues and Challenges Ahead

Arun Kumar [1], Biao Chang [2] and Irene Xagoraraki [3,*]

[1] Department of Civil Engineering, Indian Institute of Technology Delhi, Hauz Khas, New Delhi 110016, India; E-Mail: arunku@civil.iitd.ac.in

[2] School of Civil and Environmental Engineering, Georgia Institute of Technology, 215 Sustainable Education Building, 788 Atlantic Drive NW, Atlanta, GA 30332, USA; E-Mail: bchang6@gatech.edu

[3] Department of Civil and Environmental Engineering, A124 Engineering Research Complex, Michigan State University, East Lansing, MI 48824, USA

Should We Care?

PNAS | May 22, 2007 | vol. 104 | no. 21 | 8897–8901

Collapse of a fish population after exposure to a synthetic estrogen

Karen A. Kidd*†, Paul J. Blanchfield*, Kenneth H. Mills*, Vince P. Palace*, Robert E. Evans*, James M. Lazorchak‡, and Robert W. Flick‡

*Fisheries and Oceans Canada, Freshwater Institute, 501 University Crescent, Winnipeg, Manitoba, Canada R3T 2N6; and ‡Molecular Indicators Research Branch, United States Environmental Protection Agency, 26 West Martin Luther King Drive, Cincinnati, OH 45268

YES

Review

Int. J. Environ. Res. Public Health **2010**, *7*, 3929-3953

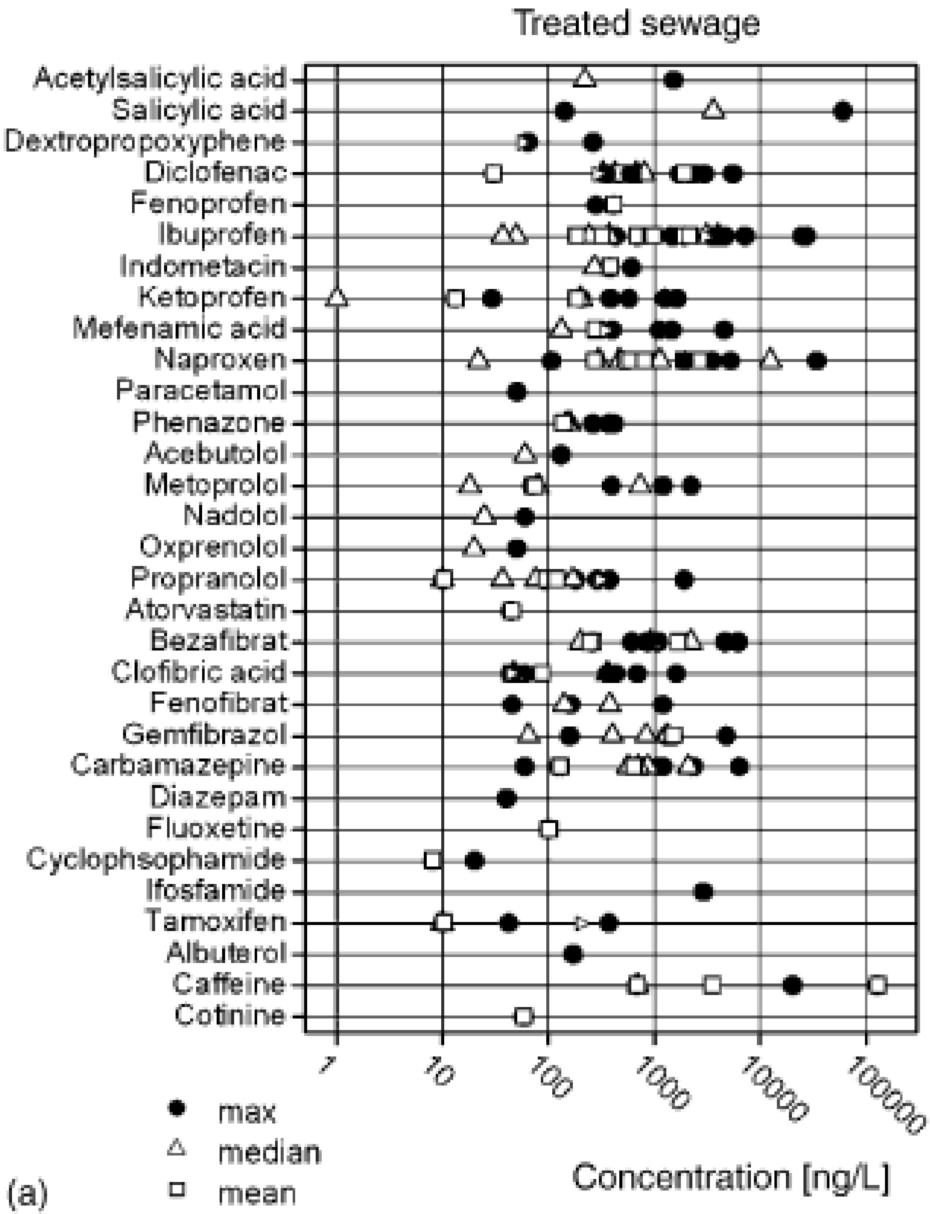
Human Health Risk Assessment of Pharmaceuticals in Water: Issues and Challenges Ahead

Arun Kumar [1], Biao Chang [2] and Irene Xagoraraki [3,*]

[1] Department of Civil Engineering, Indian Institute of Technology Delhi, Hauz Khas, New Delhi 110016, India; E-Mail: arunku@civil.iitd.ac.in

[2] School of Civil and Environmental Engineering, Georgia Institute of Technology, 215 Sustainable Education Building, 788 Atlantic Drive NW, Atlanta, GA 30332, USA; E-Mail: bchang6@gatech.edu

[3] Department of Civil and Environmental Engineering, A124 Engineering Research Complex, Michigan State University, East Lansing, MI 48824, USA



Fent, Weston and Caminada (2006) Ecotoxicology of human pharmaceuticals, *Aquatic Toxicology*, **76**:122-159.

Wide range of variation in treatment efficiencies across studies a result of not understanding treatment conditions that actually influence biotransformation

NG Love, Univ Michigan

Nitrification/nitrogen removal processes, which occur with long solids residence times, are found to have higher removal efficiencies for some pharmaceuticals

ENVIRONMENTAL SCIENCE & TECHNOLOGY / VOL. 37, NO. 18, 2003

Fate of Estrogens in a Municipal Sewage Treatment Plant

HENRIK ANDERSEN,[†]
HANSRUEDI SIEGRIST,[‡]
BENT HALLING-SØRENSEN,[†] AND
THOMAS A. TERNES*,[§]
The Danish University of Pharmaceutical Sciences, Institute of Analytical Chemistry, Universitetsparken 2, DK-2100 Copenhagen, Denmark, EAWAG, Ueberlandstrasse 133, 8600 Duebendorf, Switzerland, Bundesanstalt für Gewässerkunde (BfG), Kaiserin-Augusta-Anlagen 15-17, D-56068 Koblenz, Germany

Water Research 38 (2004) 2323–2330

Biodegradation of natural and synthetic estrogens by nitrifying activated sludge and ammonia-oxidizing bacterium *Nitrosomonas europaea*

Jianghong Shi*, Saori Fujisawa, Satoshi Nakai, Masaaki Hosomi

Department of Applied Chemistry, Graduate School of Technology, Tokyo University of Agriculture and Technology, 2-24-16 Naka, Koganei, Tokyo 184-8588, Japan

Water Research 39 (2005) 97–106

The solids retention time—a suitable design parameter to evaluate the capacity of wastewater treatment plants to remove micropollutants

M. Clara[a,*], N. Kreuzinger[a], B. Strenn[a], O. Gans[b], H. Kroiss[a]

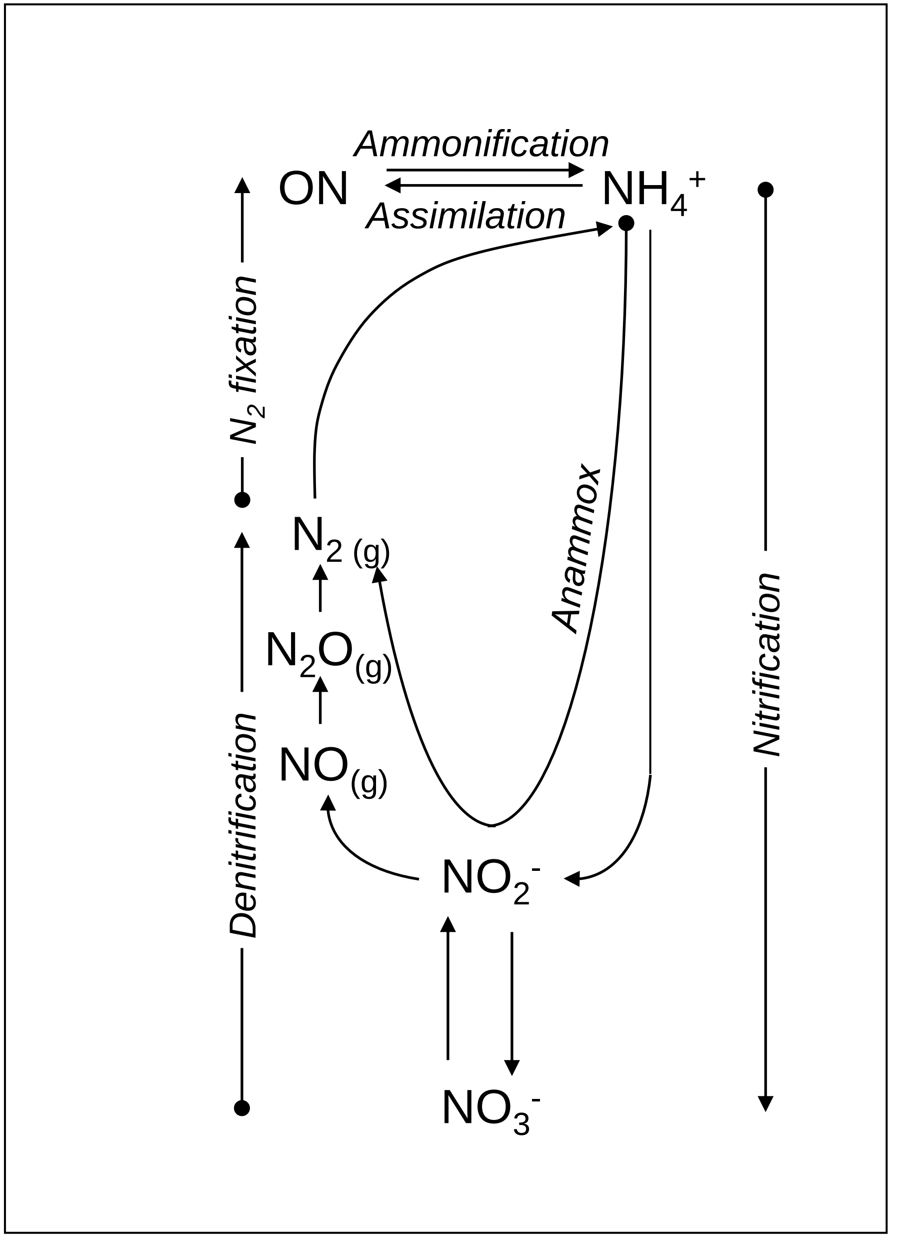
[a] *Institute for Water Quality and Waste Management, Vienna University of Technology, A-1040 Vienna, Karlsplatz 13/226, Austria*
[b] *Umweltbundesamt GmbH, Spittelauer Lände 5, 1090 Vienna, Austria*

Environ. Sci. Technol. **2006**, *40*, 7367–7373

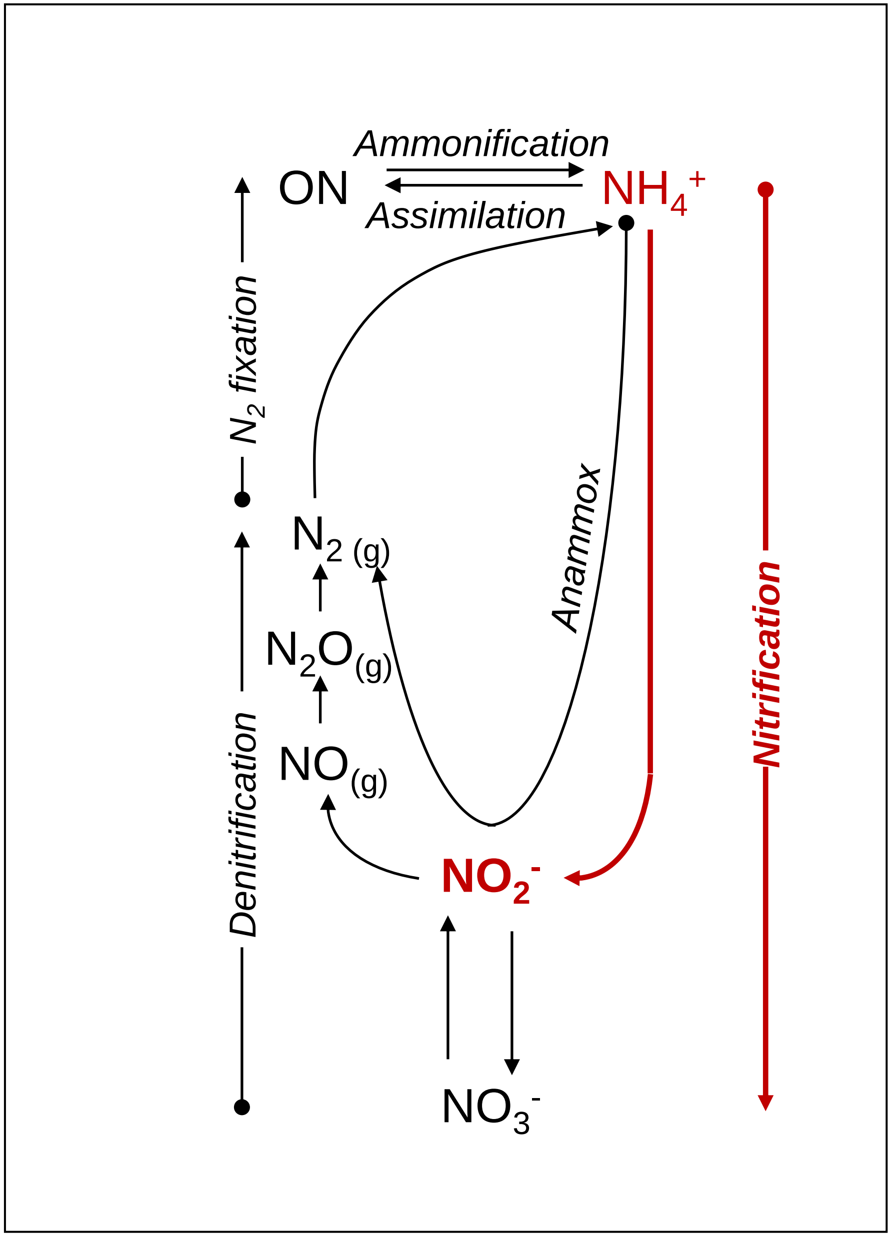
Enhanced Biodegradation of Iopromide and Trimethoprim in Nitrifying Activated Sludge[†]

ANGELA L. BATT, SUNGPYO KIM, AND
DIANA S. AGA*
Department of Chemistry, The State University of New York at Buffalo, 608 Natural Sciences Complex, Buffalo, New York 14260-3000

NG Love, Univ Michigan

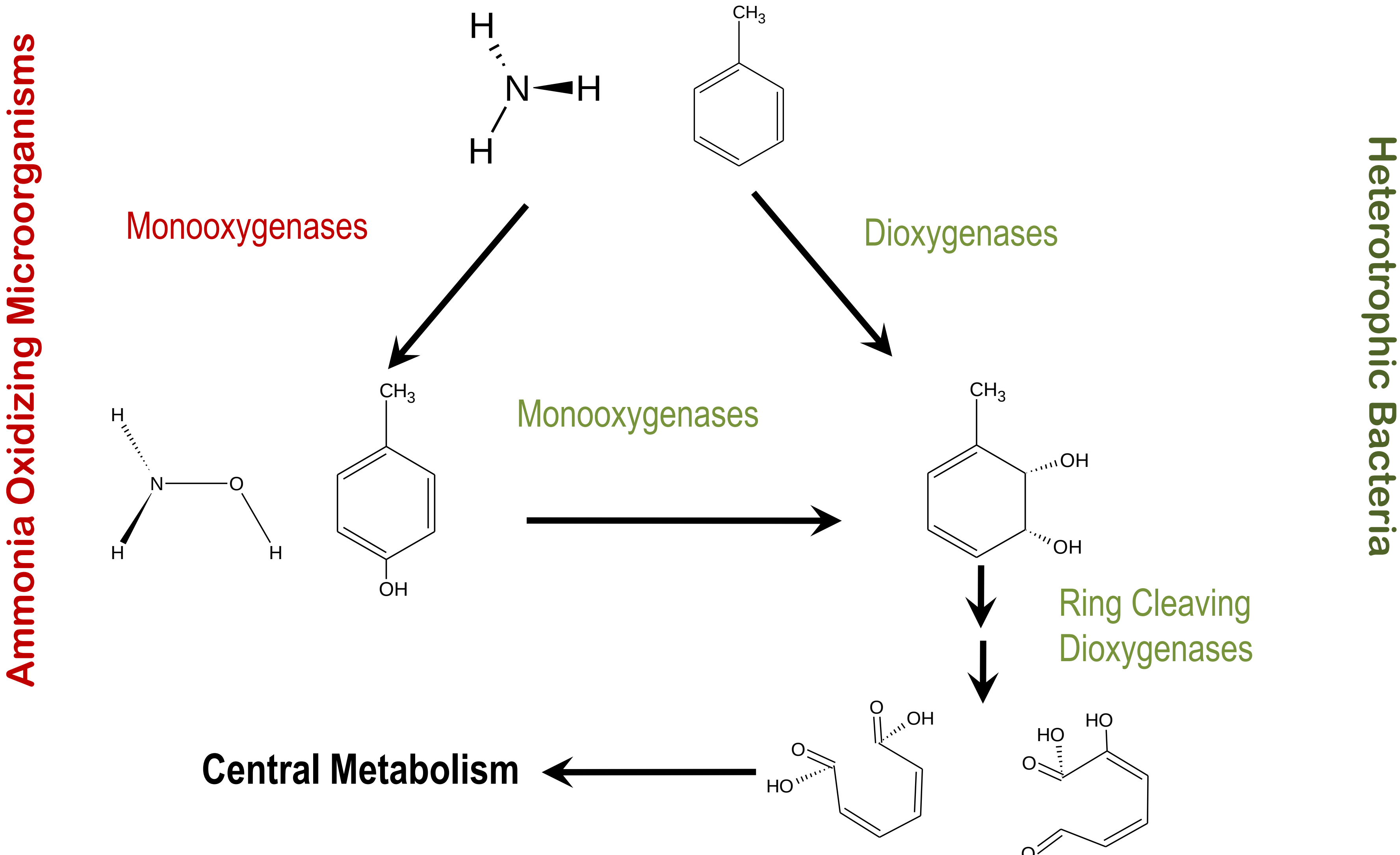


NG Love, Univ Michigan



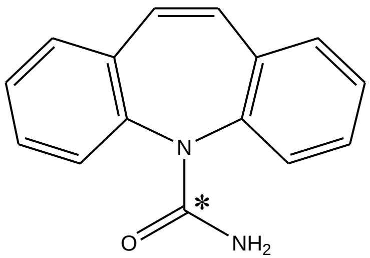
NG Love, Univ Michigan

We hypothesized that biotransformation of aromatic pharmaceuticals depend on the activity of nonspecific oxygenase enzymes.

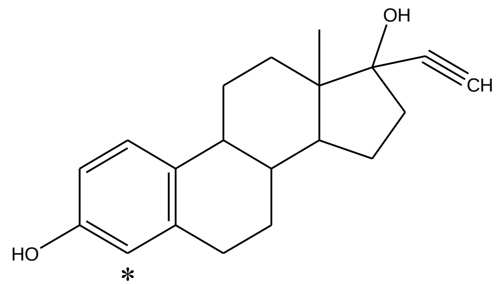


NG Love, Univ Michigan

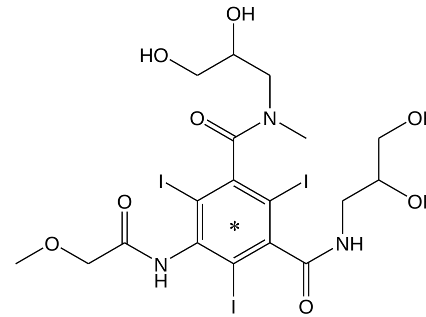
Aromatic rings are common in many pharmaceuticals



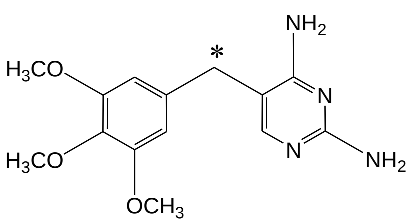
carbamazepine



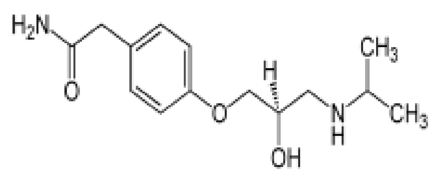
17α-ethinylestradiol



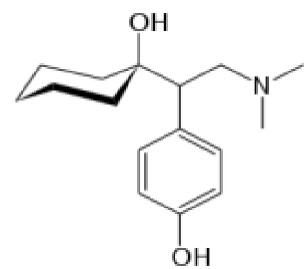
iopromide



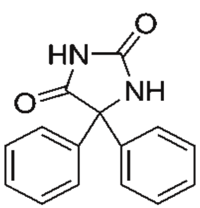
trimethoprim



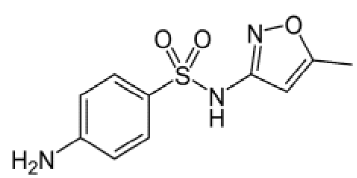
atenolol



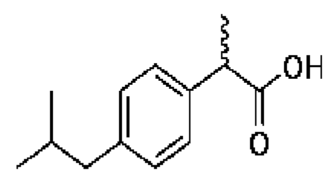
Desvenlafaxine



Phenytoin (Dilantin)



Sulfamethoxazole



Ibuprofen

NG Love, Univ Michigan

Environmental Science & Technology

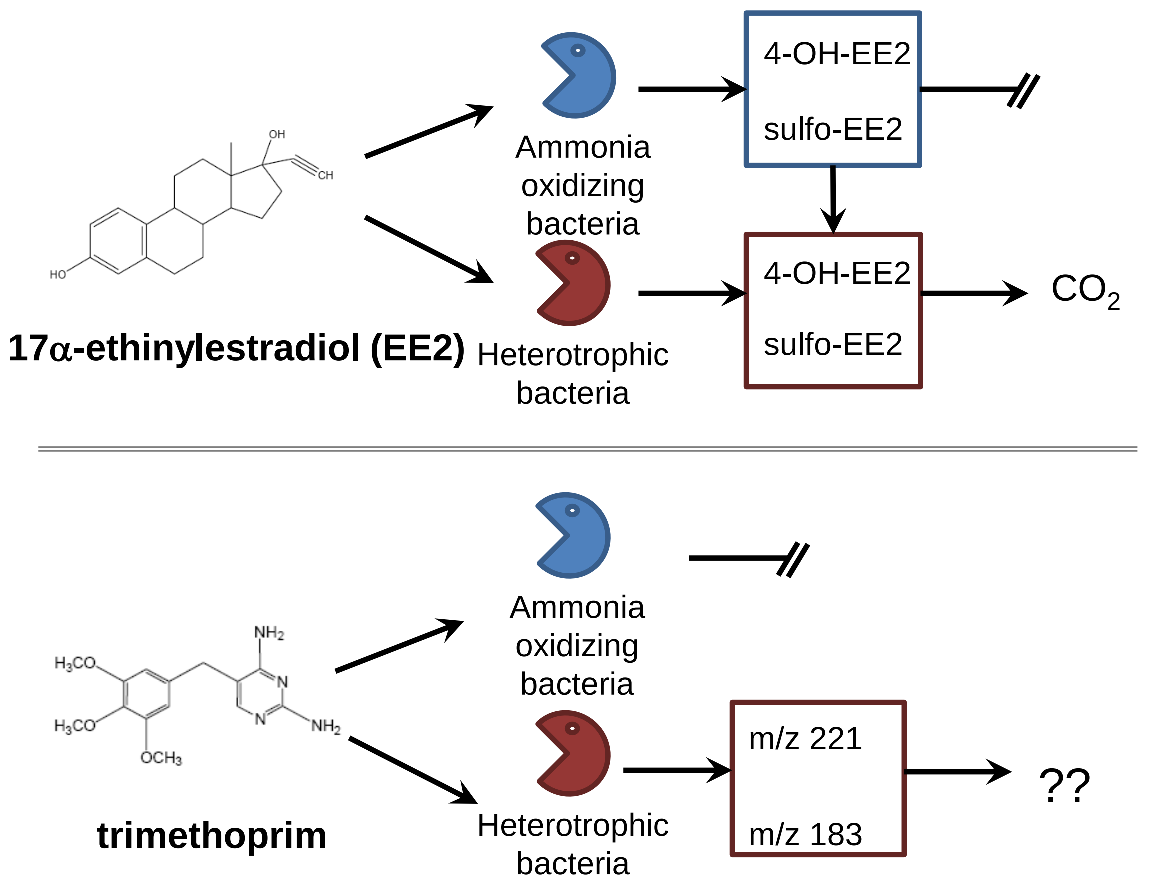
ARTICLE

45(8):3605-3612 (2011)

pubs.acs.org/est

Elucidating the Relative Roles of Ammonia Oxidizing and Heterotrophic Bacteria during the Biotransformation of 17α-Ethinylestradiol and Trimethoprim

W. O. Khunjar,[†,‡] S. A. Mackintosh,[‖] J. Skotnicka-Pitak,[‖] S. Baik,[‖] D. S. Aga,[‖] and N. G. Love*

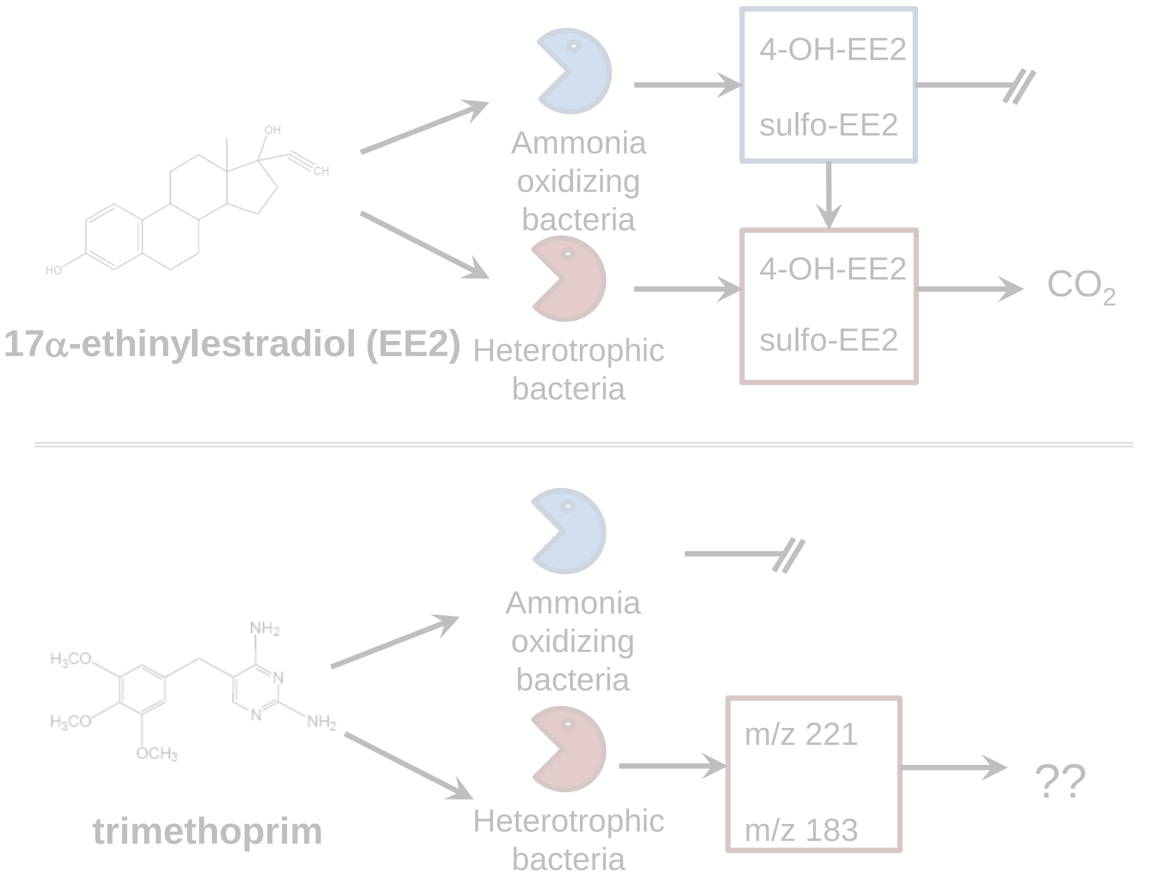


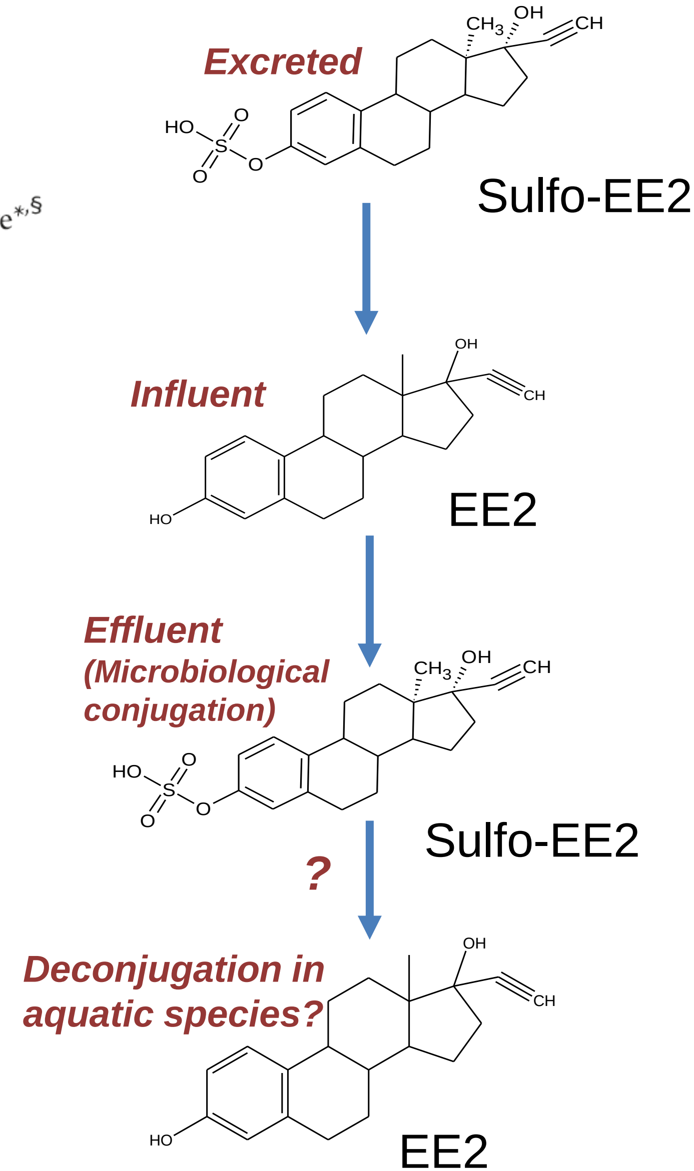
NG Love, Univ Michigan

Environmental Science & Technology
ARTICLE
45(8):3605-3612
pubs.acs.org/est

Elucidating the Relative Roles of Ammonia Oxidizing and Heterotrophic Bacteria during the Biotransformation of 17α-Ethinylestradiol and Trimethoprim

W. O. Khunjar,[†,‡] S. A. Mackintosh,[||] J. Skotnicka-Pitak,[||] S. Baik,[||] D. S. Aga,[||] and N. G. Love*[,§]





NG Love, Univ Michigan

Clarifying the relevancy of ammonia oxidizing bacteria in estrogen biotransformation

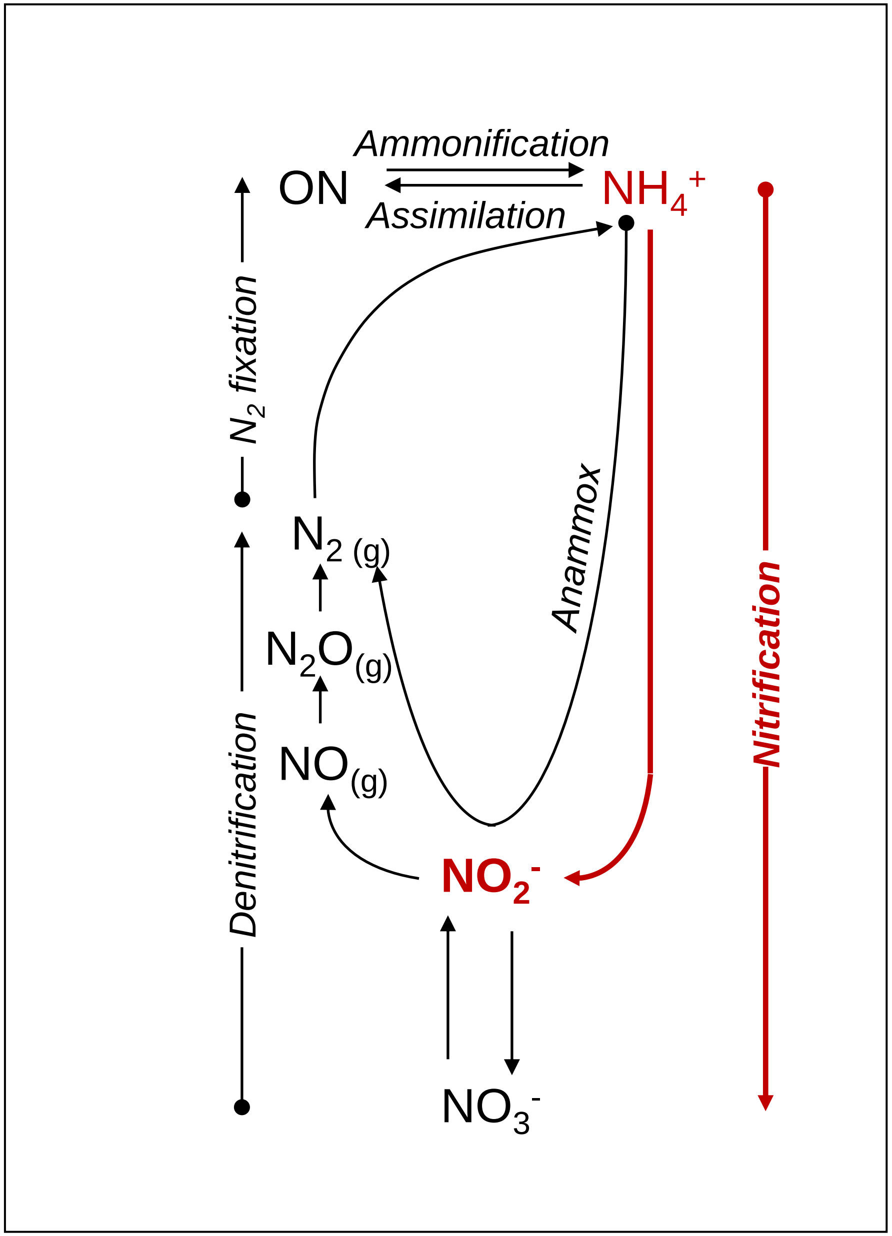
Ammonia-limited conditions

Estrogens are biotransformed

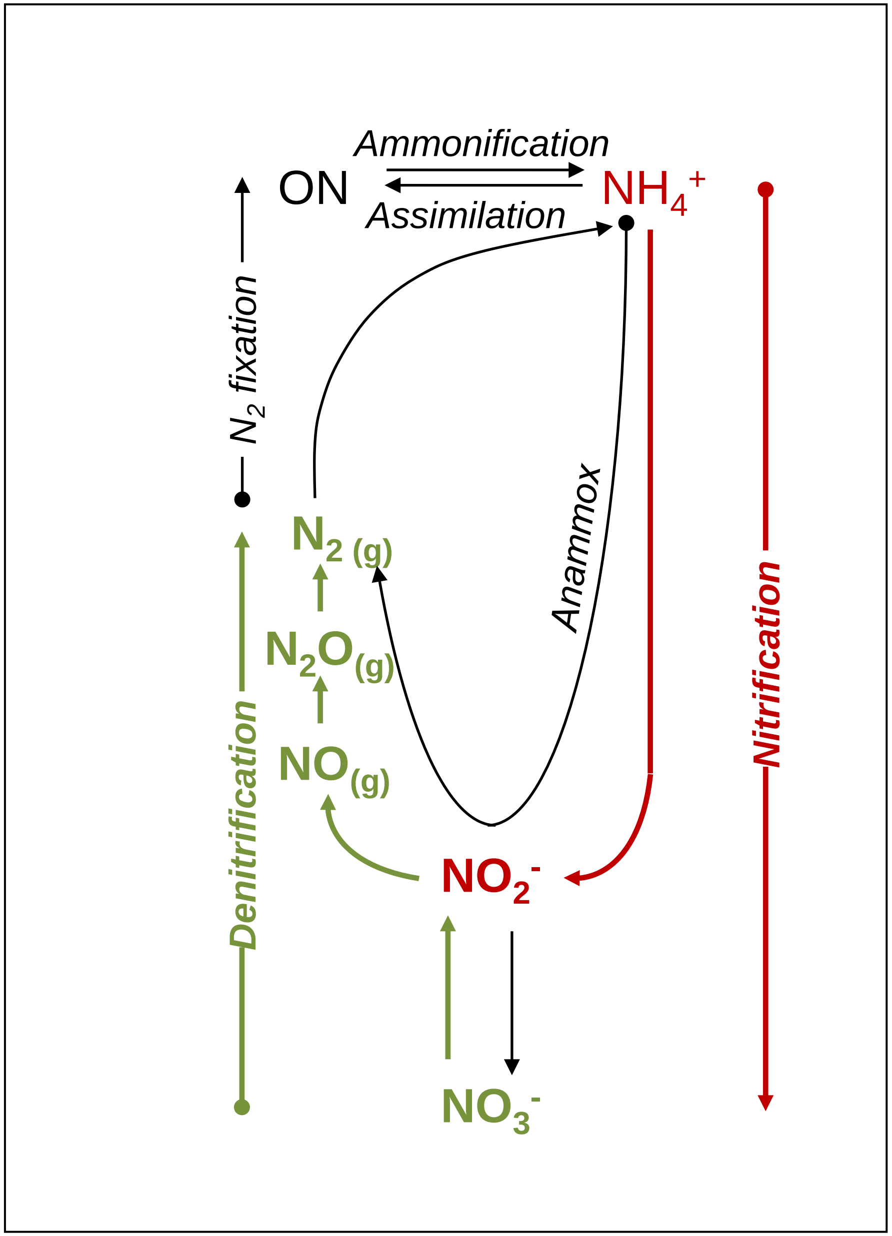
Ammonia-sufficient conditions

Estrogens are not biotransformed

Suggests competition for active site on AMO between estrogen and ammonia



NG Love, Univ Michigan



NG Love, Univ Michigan

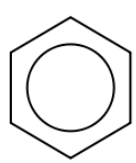
Do microaerobic environments enhance pharmaceutical removal through high affinity oxygenase activity?

TABLE 1. Biodegradation Rates for Benzene, *o*-, and *p*-Xylene under Aerobic and Microaerobic Conditions

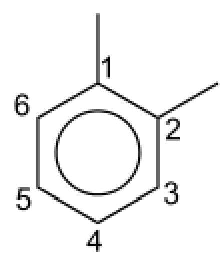
	Biodegradation Rate[a] (mg/g MLVSS/h)			
Compound	Aerobic	Microaerobic with NO_2^--N	Microaerobic without NO_x-N	Microaerobic with NO_3^--N
Benzene	0.229 ± 0.045	0.211 ± 0.013	0.112 ± 0.010	0.291 ± 0.039
o-Xylene	0.251 ± 0.049	0.238 ± 0.006	0.128 ± 0.0071	0.303 ± 0.056
p-Xylene	0.258 ± 0.031	0.250 ± 0.030	0.145 ± 0.037	0.247 ± 0.008

[a]Coefficients for all regressions were between 0.85 and 0.99.

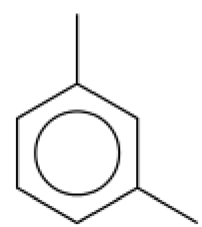
Ma and Love, 2001. J. Env. Eng.



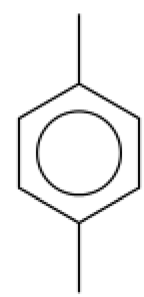
Benzene



1,2-dimethylbenzene (*ortho*-xylene)



1,3-dimethylbenzene (*meta*-xylene)



1,4-dimethylbenzene (*para*-xylene)

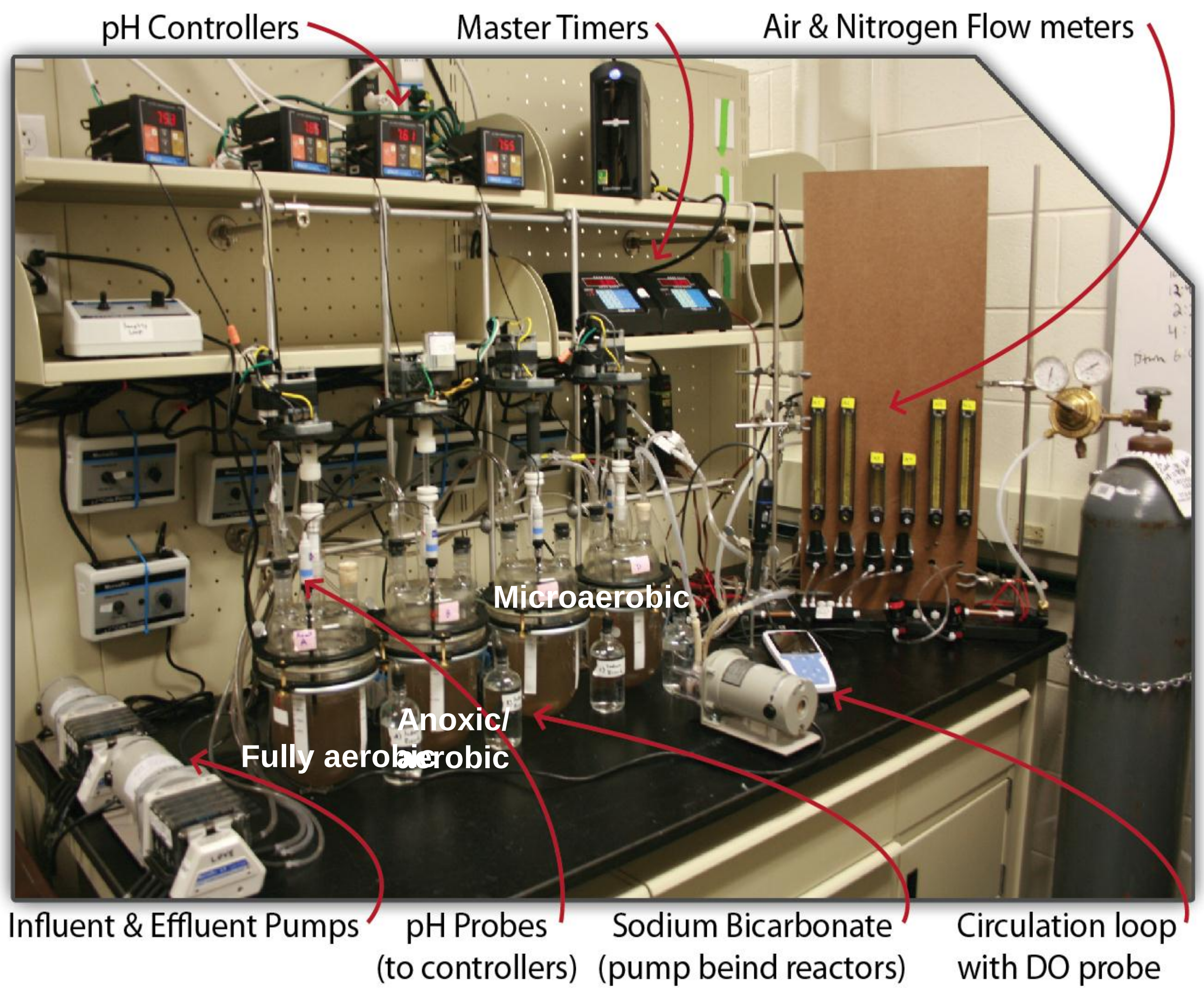
NG Love, Univ Michigan

How does redox environment influence pharmaceutical removal?

Aerobic

Anoxic/Aerobic

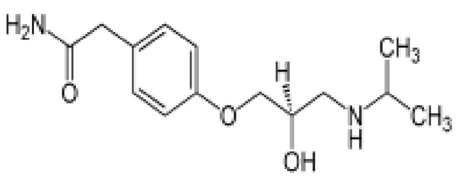
Microaerobic



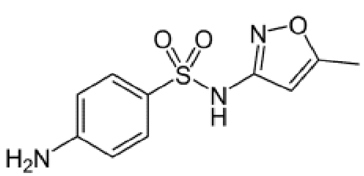
NG Love, Univ Michigan

Modes of transformation varies between pharmaceuticals

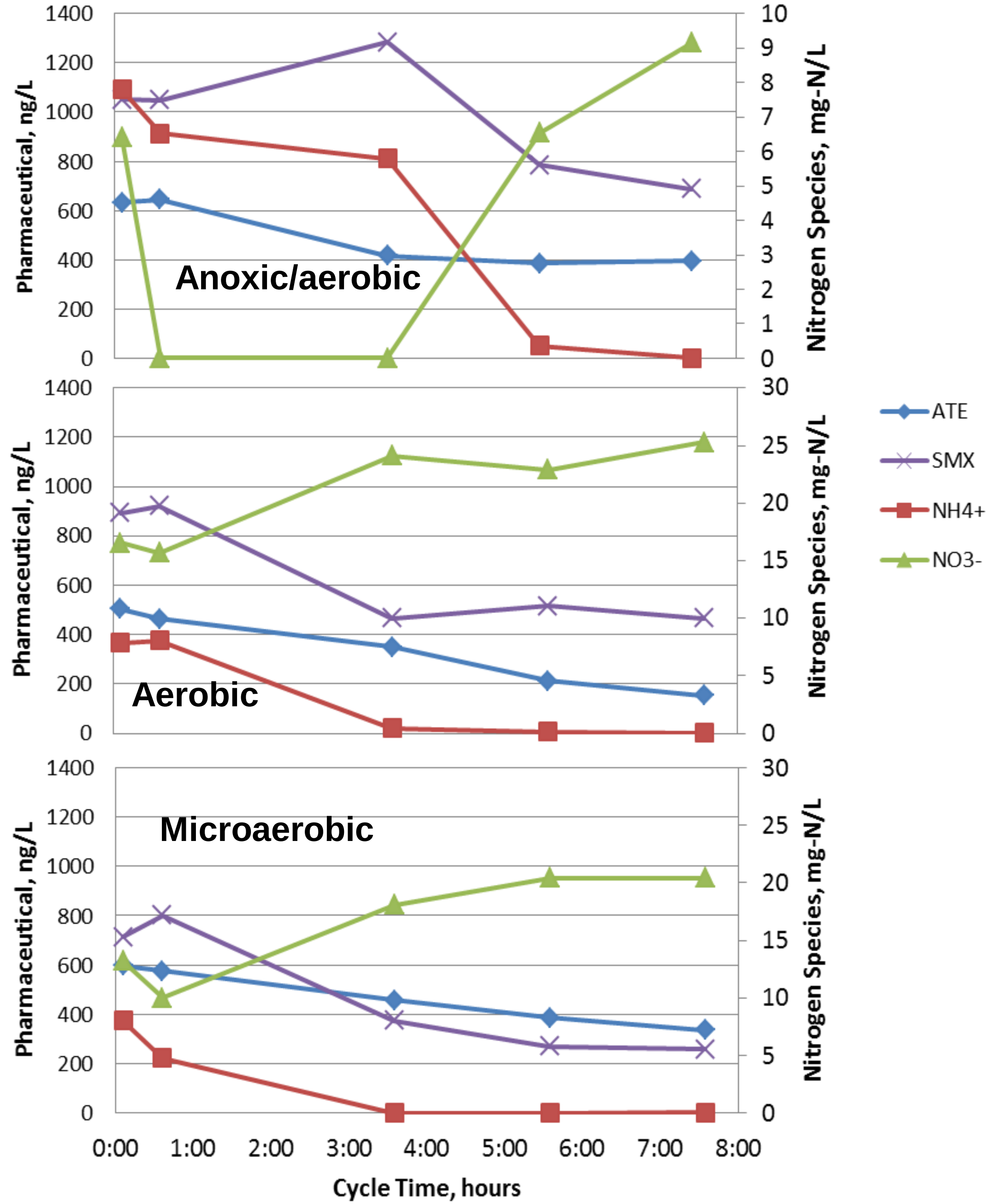
- **SMX response relative to ammonia is the opposite of EE2**
- **ATE biotransforms independent of ammonia concentration, but rate slows as DO decreases**



Atenolol, beta-blocker

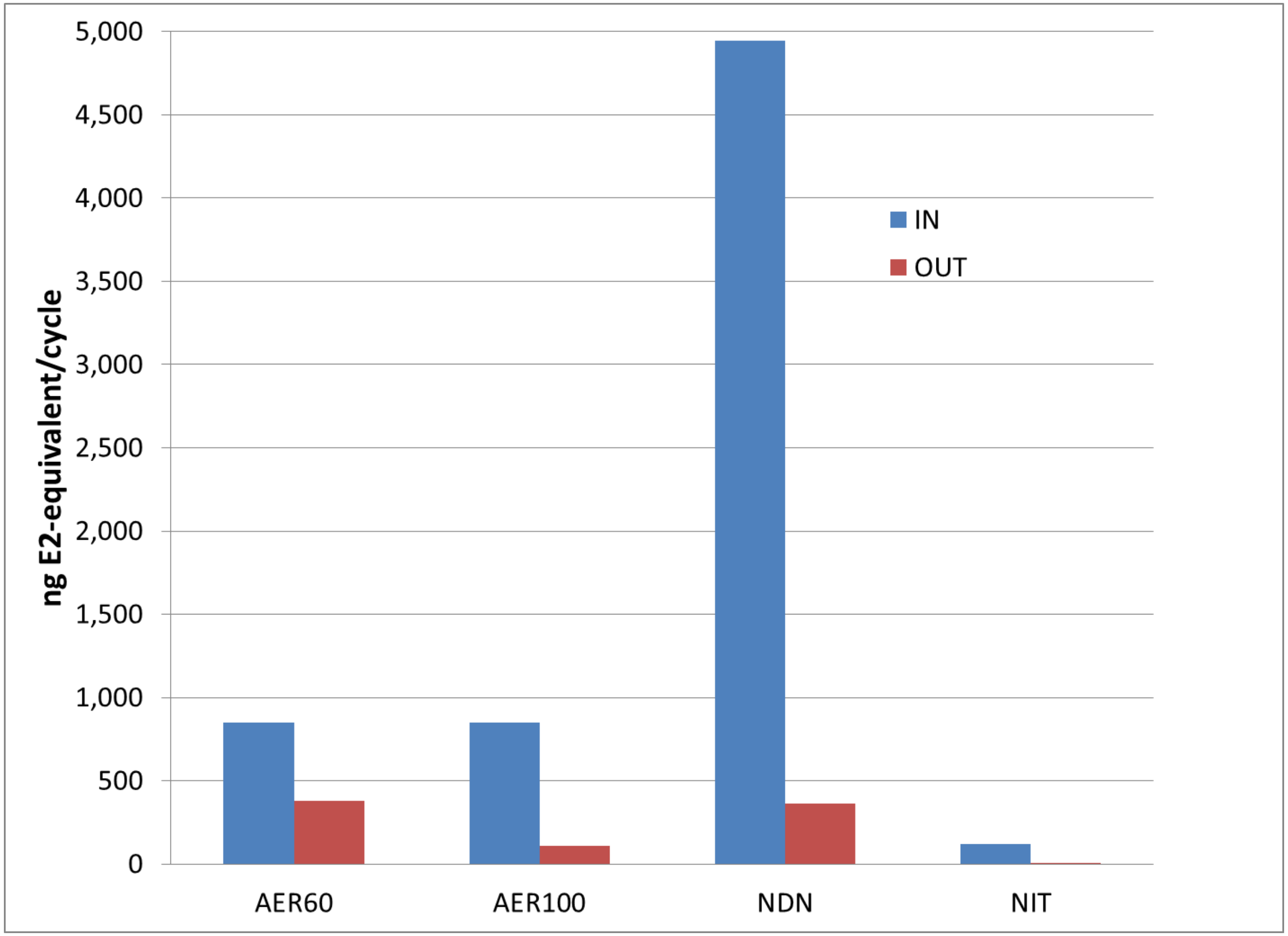


Sulfamethoxazole, antibiotic



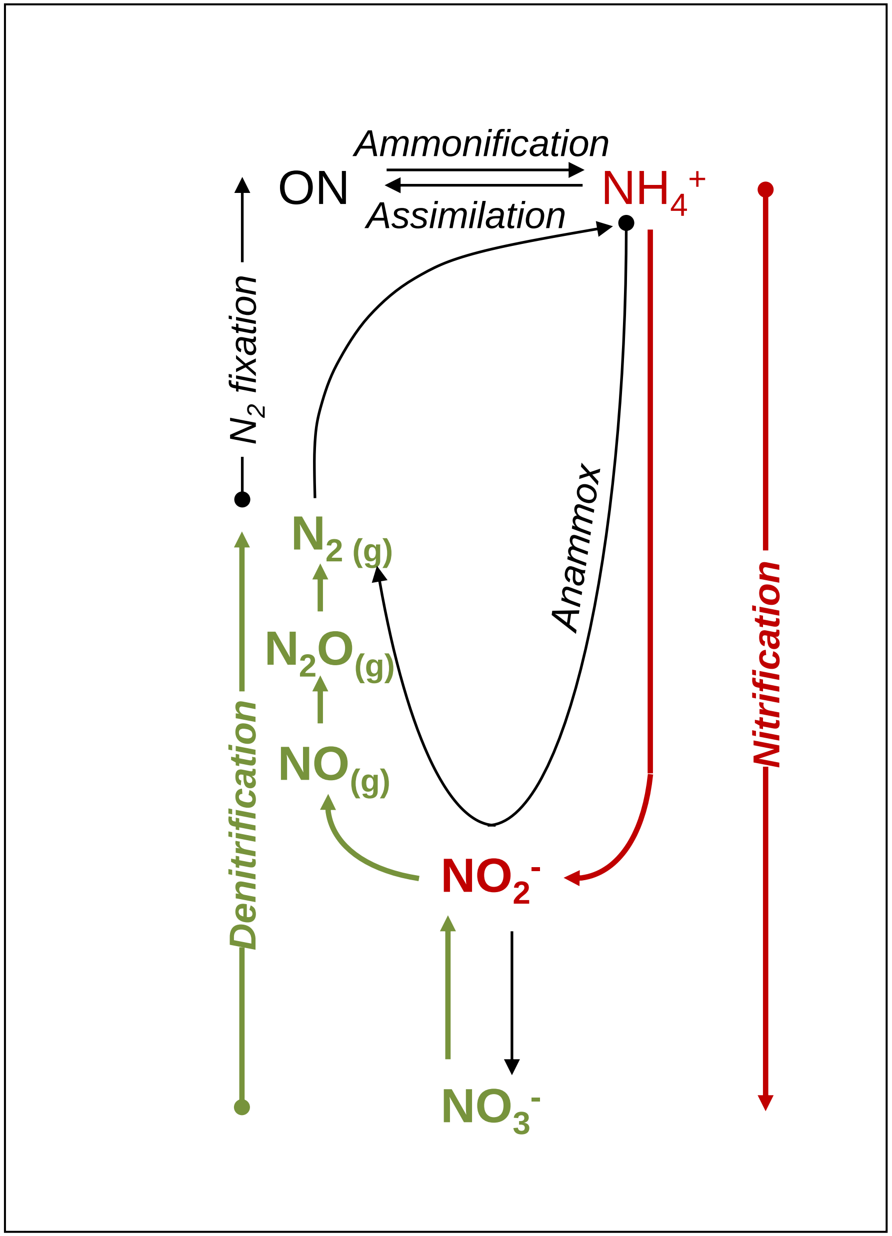
NG Love, Univ Michigan

Nitrogen and Estrogen Transformation/Removal in Managed Dairy Manure is Enhanced by Aeration

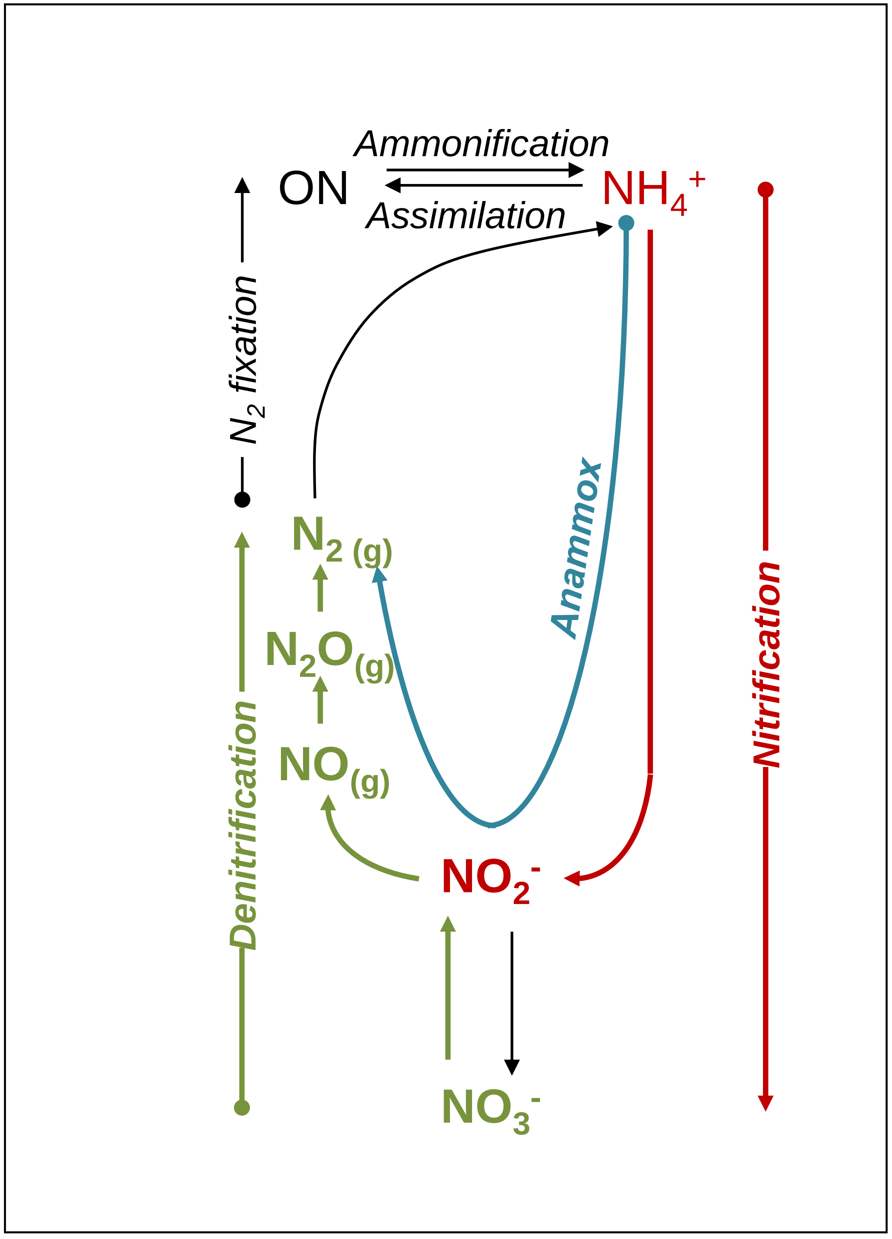


Zhao, Z., K. F. Knowlton, N. G. Love, and J. A. Ogejo. 2011. Estrogen removal from dairy manure by pilot-scale treatment reactors. *Transactions of the American Society of Agricultural and Biological Engineers (ASABE)*. 53(4):1295-1301.

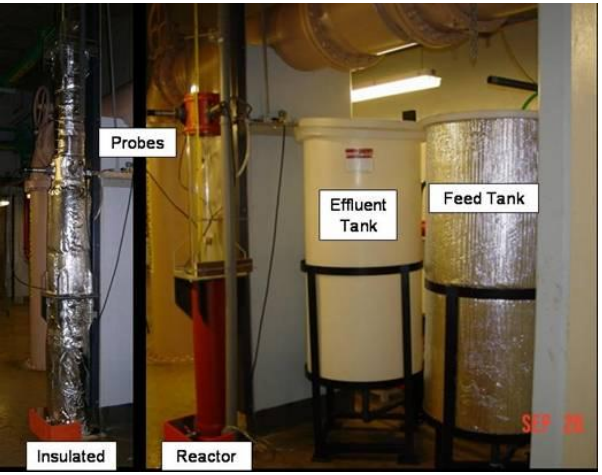
NG Love, Univ Michigan



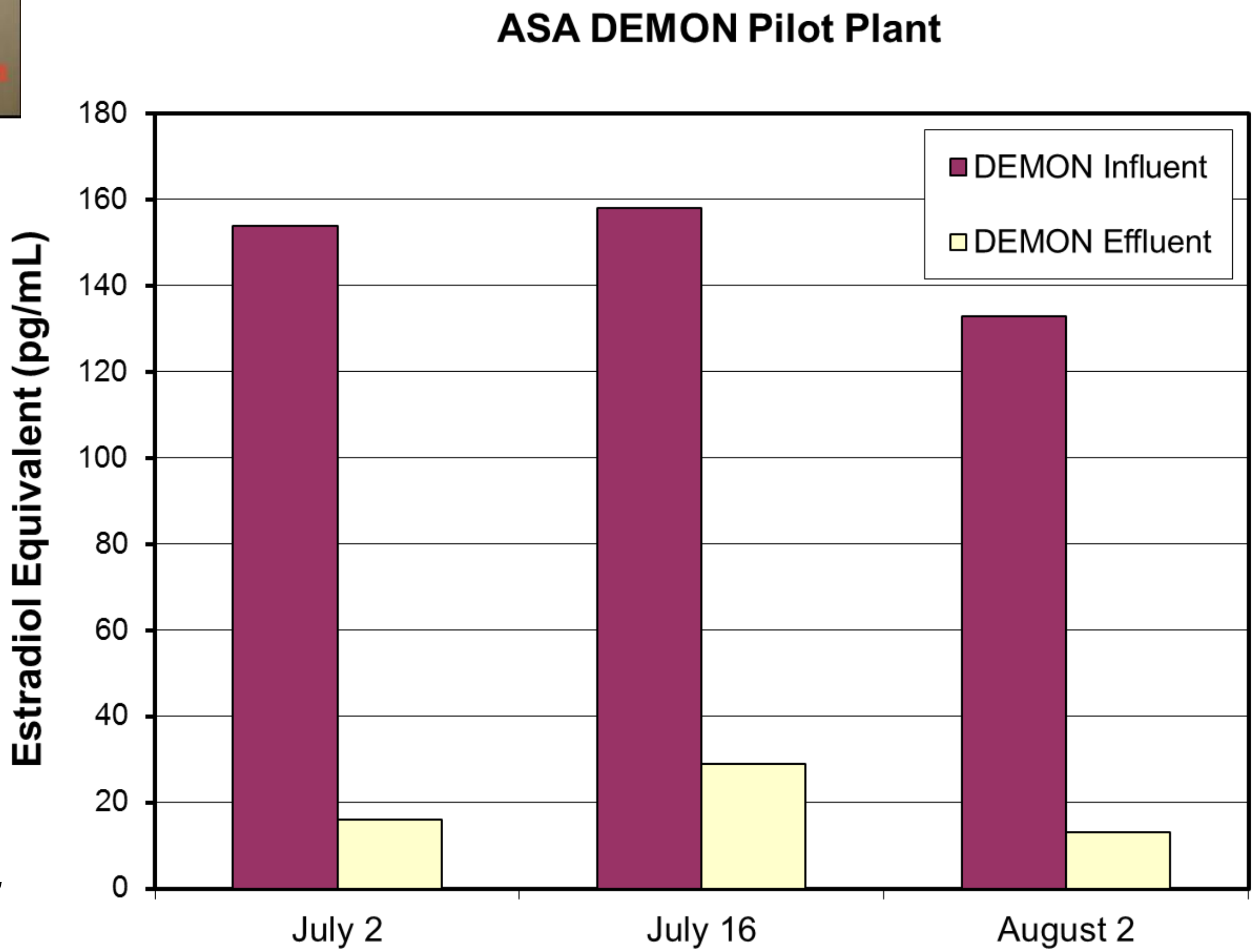
NG Love, Univ Michigan



NG Love, Univ Michigan



DEMON (microaerobic nitritation plus anammox) achieved very good estrogenicity removal



Musabyimana, Khunjar and Love, unpublished data
2007 ASA pilot plant

NG Love, Univ Michigan

Fate of hormones and pharmaceuticals during combined anaerobic treatment and nitrogen removal by partial nitritation-anammox in vacuum collected black water

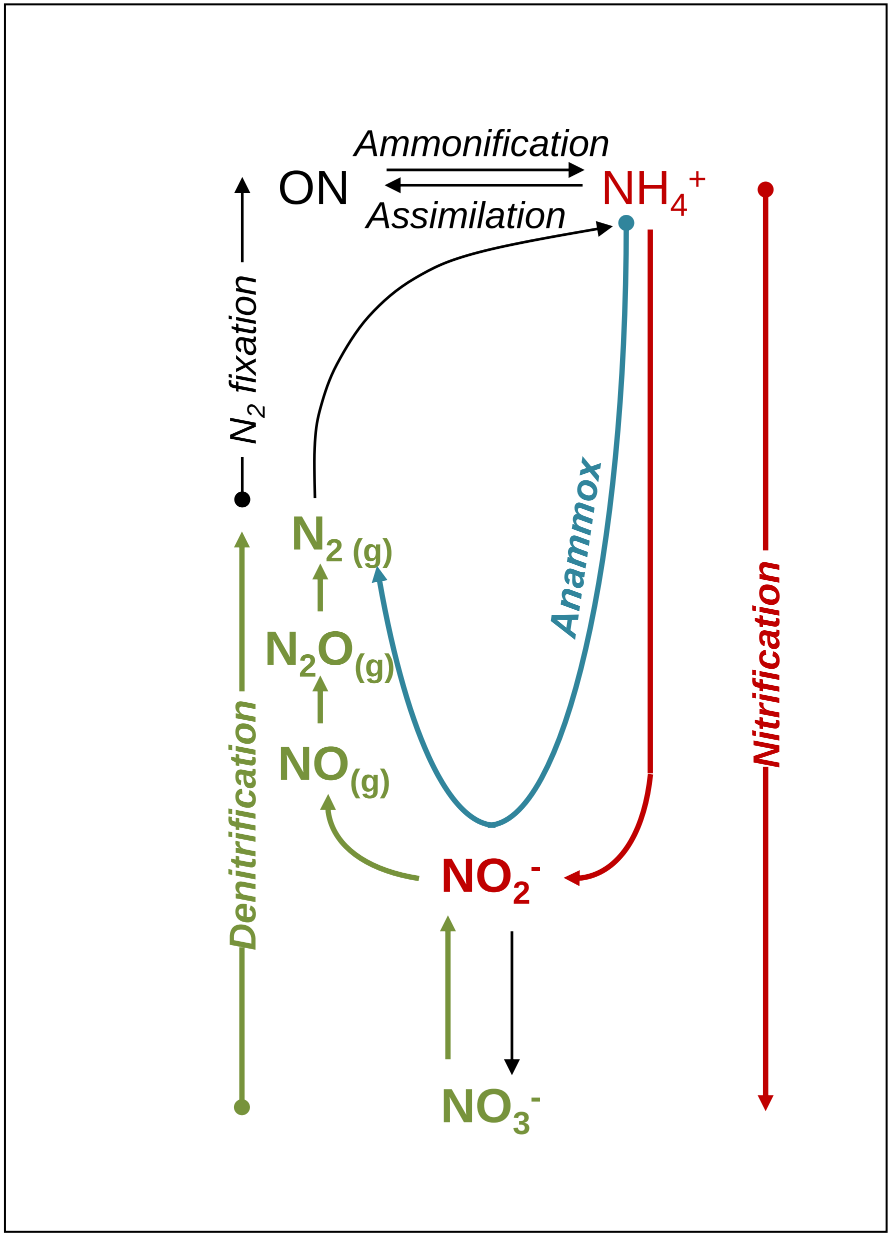
M.S. de Graaff[a,b,*], N.M. Vieno[a,1], K. Kujawa-Roeleveld[b], G. Zeeman[b], H. Temmink[a,b], C.J.N. Buisman[a,b]

Table 2 – Removal efficiencies during anaerobic treatment (UASB), aerobic treatment (PN) and anoxic treatment (AMX); literature information about the biodegradability under different redox conditions and the tendency to adsorb to sludge.

Compound	UASB	PN	AMX	Overall	Anaerobic/ Anoxic biodegradable?	Aerobic readily biodegradable?	Likely to adsorb to sludge?
Paracetamol	>90%[a]	x	x	>90%[a]	n.f.	Yes[b]	No[c]
Trimethoprim	–	–	–	–	n.f.	No[d,e]	No[f]
Tetracycline	–	–	–	–	n.f.	No[d]	Yes[f,g]
Metoprolol	−7%	67%	−23%	56%	No/No[h]	No[i]	No[i]
Doxycycline	0%	69%	–	69%	n.f.	No[d]	Yes[g]
Propranolol	–	–	–	–	n.f.	No[i]	No[i]
Carbamazepine	–	–	–	–	No[h,j]/No[h]	No[l]	No[k]
Cetirizine	−20%	−23%	52%	29%	n.f.	No[m]	No[m]
Ibuprofen	−23%	16%	77%	76%	Yes, but limited[h,j]/Yes[h]	Yes[h,n]	No[k]
Diclofenac	22%	x	−75%	−37%	Yes, but limited[h,j]/No[h]	No[o]	No[k,o]

WATER RESEARCH 45 (2011) 375–383

UASB = upflow anaerobic sludge blanket effluent
PN = partial nitritation effluent
AMX = anammox effluent



NG Love, Univ Michigan

Polychromatic UV-irradiated nitrified effluents are subject to advanced oxidation of trace organic chemicals.

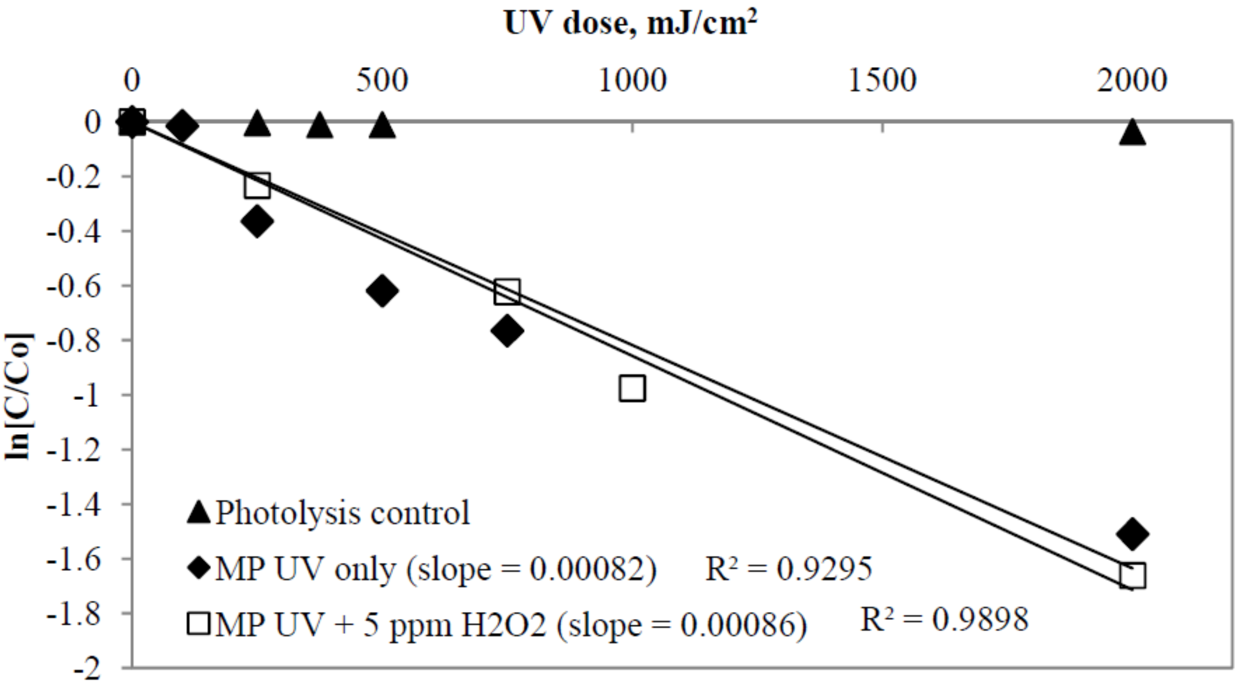
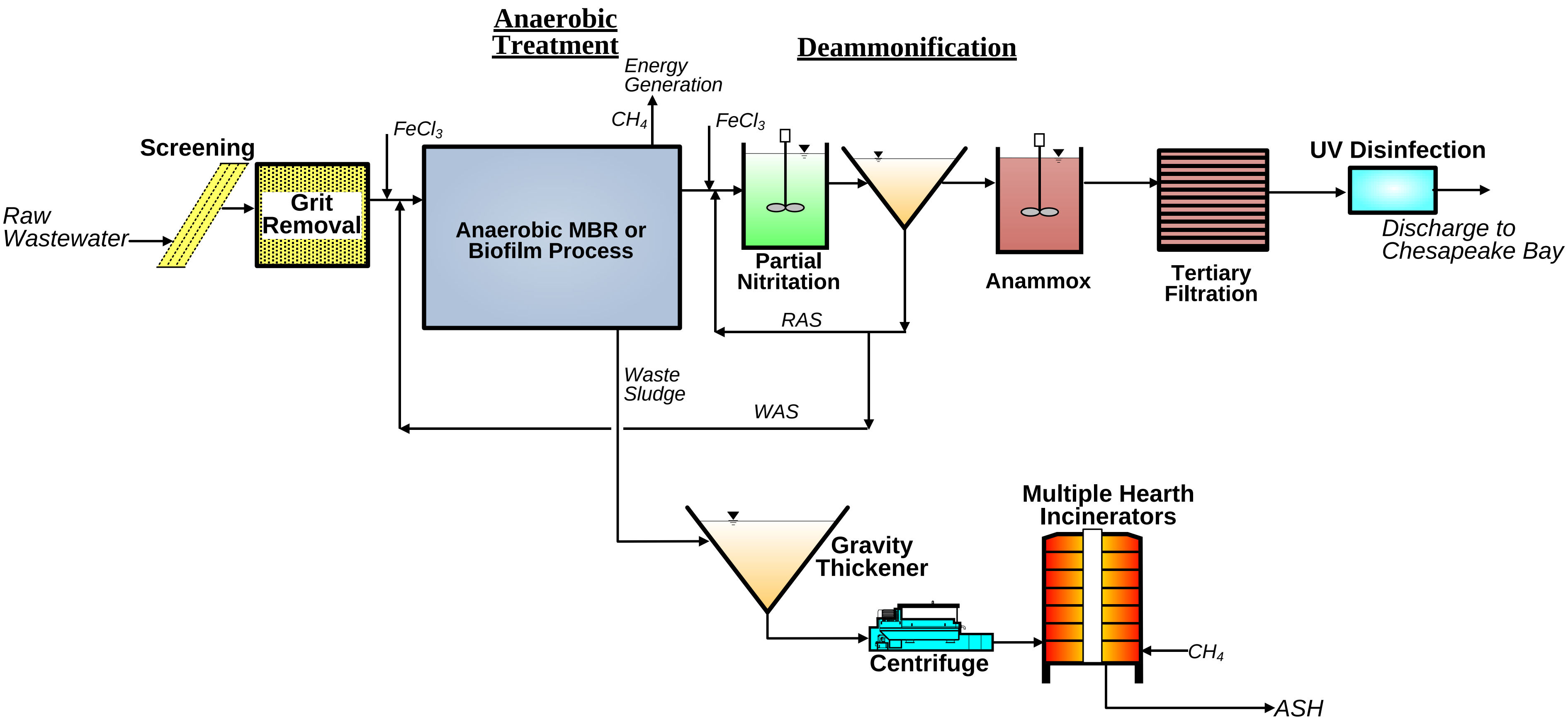


Figure 2: Degradation of carbamazepine in wastewater effluent containing 16.2 mg-N/L of nitrate with and without 5 mg/L of H_2O_2 (adapted from Linden et al. 2011)

Nitrifying wastewater treatment plants utilizing polychromatic UV systems at disinfection dose levels can be expected to achieve up to 30% degradation of some micropollutants by hydroxyl radical oxidation. Increasing UV fluence to levels used during advanced oxidation could achieve over 95% degradation of some compounds.

Keen, Love and Linden. Accepted pending minor changes. The role of effluent nitrate in contaminant oxidation during UV disinfection. *Water Research*.

Possible "Treatment Plant of the Future"



From Charles Bott, HRSD

Source Separation as a Sustainable Waste Management Solution for the Future

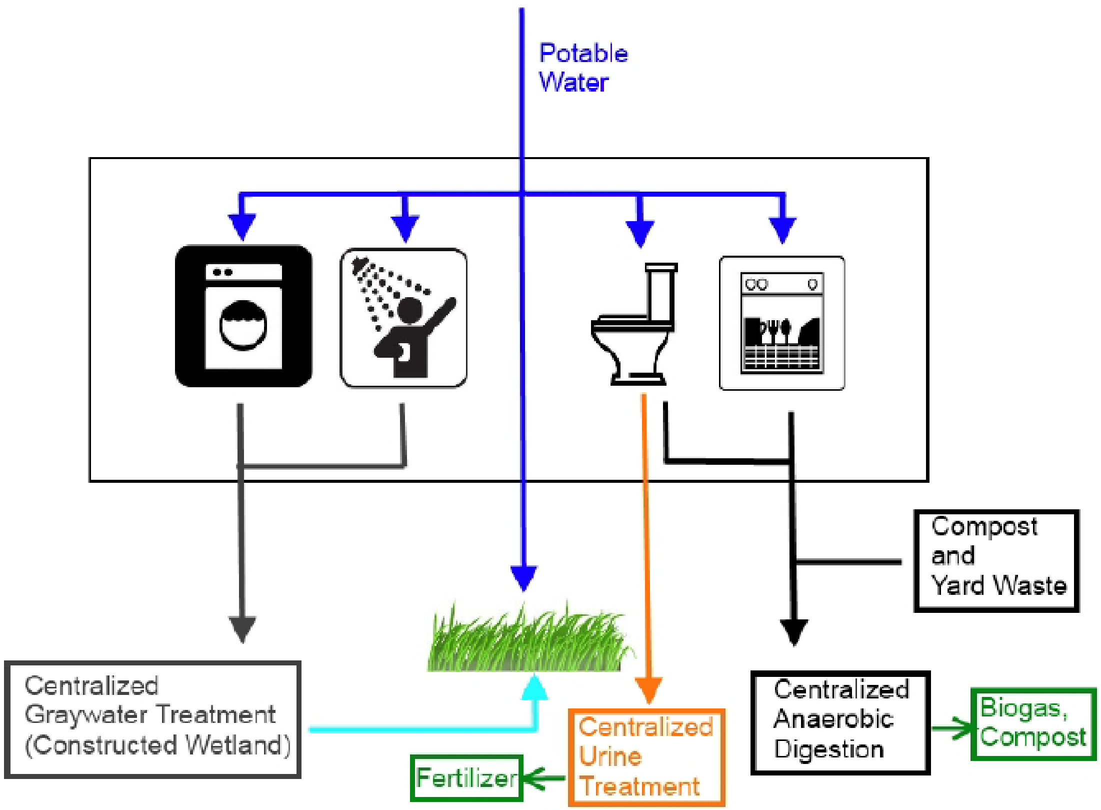


Figure 1-1. Potential Decentralized Wastewater Treatment Scenario.

WERF Report No. INFR4SG09b-Source Separation and Treatment of Anthropogenic Urine

[Larsen et al. *Environ. Sci. Technol.* 2009]

Black Water	Yellow Water
Majority of COD	~75% N ~55% P

About 65% of pharmaceuticals end up in urine and 35% in feces.
Lienert et al. (2007) *Water Sci. Technol.* **56**:87-96

The ecotoxicological risk of pharmaceuticals and metabolites in urine and feces are equal.
Lienert et al. (2007) Environ Sci Technol. **41**:4471-4478.

NG Love, Univ Michigan

<u>Utility Collaborators</u>: Ann Arbor WWTP; ASA-Alexandria; Blacksburg VPI WWTP; Boulder CO WWTP; DC Water; HRSD; Loudoun County VA

MichiganEngineering

NSF

WERF

At the Intersection of Nitrogen Removal and Trace Organic Chemicals

Nancy G. Love, Ph.D., P.E., BCEE, WEF Fellow
Department of Civil and Environmental Engineering
University of Michigan
nglove@umich.edu

MICHIGAN ENGINEERING
UNIVERSITY of MICHIGAN