

# Pharmaceuticals in municipal wastewater

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# Problem statement

Active pharmaceutical ingredients (**APIs**)

frequently reported in water in low parts per billion range

Biologically active at low concentrations

initial concern: effects like therapeutic effects?

blood pressure? sexual development? antibiotic resistance?

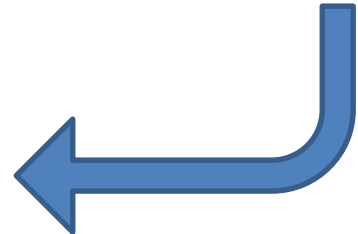
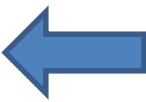
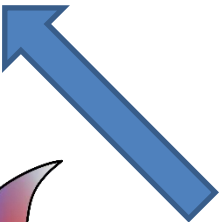
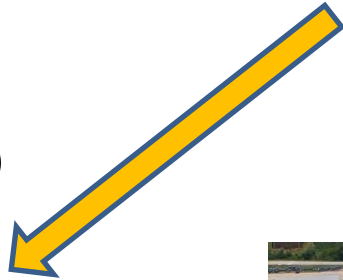
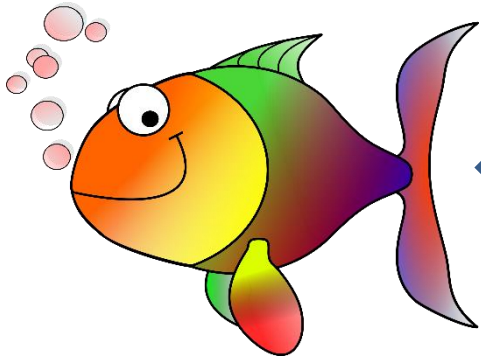
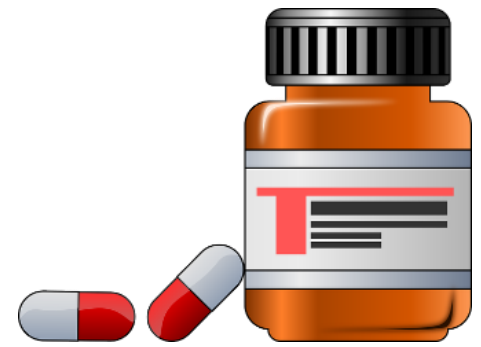
**What are risks to humans and aquatic life?**

Challenges:

**well over 1000 APIs** approved by FDA for use in the US

occurrence **studies limited to several dozen** APIs at a time

aquatic life toxicity studies typically one API at a time



# Project intent

**Inform prioritization of EPA research** related to:

Clean Water Act: discharges into ambient waters

Safe Drinking Water Act: drinking water quality

Provide screening level estimates of risk

for humans and aquatic life

**narrow the scope of concern**

which drugs? effect types? intensity? target populations?

Risk-based prioritization

for potential future occurrence or toxicology studies

**focus on the drugs most likely to present risks**

**identify the critical (for risk estimation) unknowns**

# Conceptual approach

Prioritize based on risk: higher risk = higher priority

Assume risk proportional to:

**concentration / effective dose**

Occurrence data limited; other data more abundant

have marketing data and wastewater production rates

calculate "predicted environmental concentrations" (PECs)

Approximate potency with **min therapeutic daily dose**

ignores differences in endpoints

Focus on upper end (~99th percentile) of distributions

more broadly protective -- asks **how bad might it get?**

Employ tiered approach

# Tolerating uncertainty

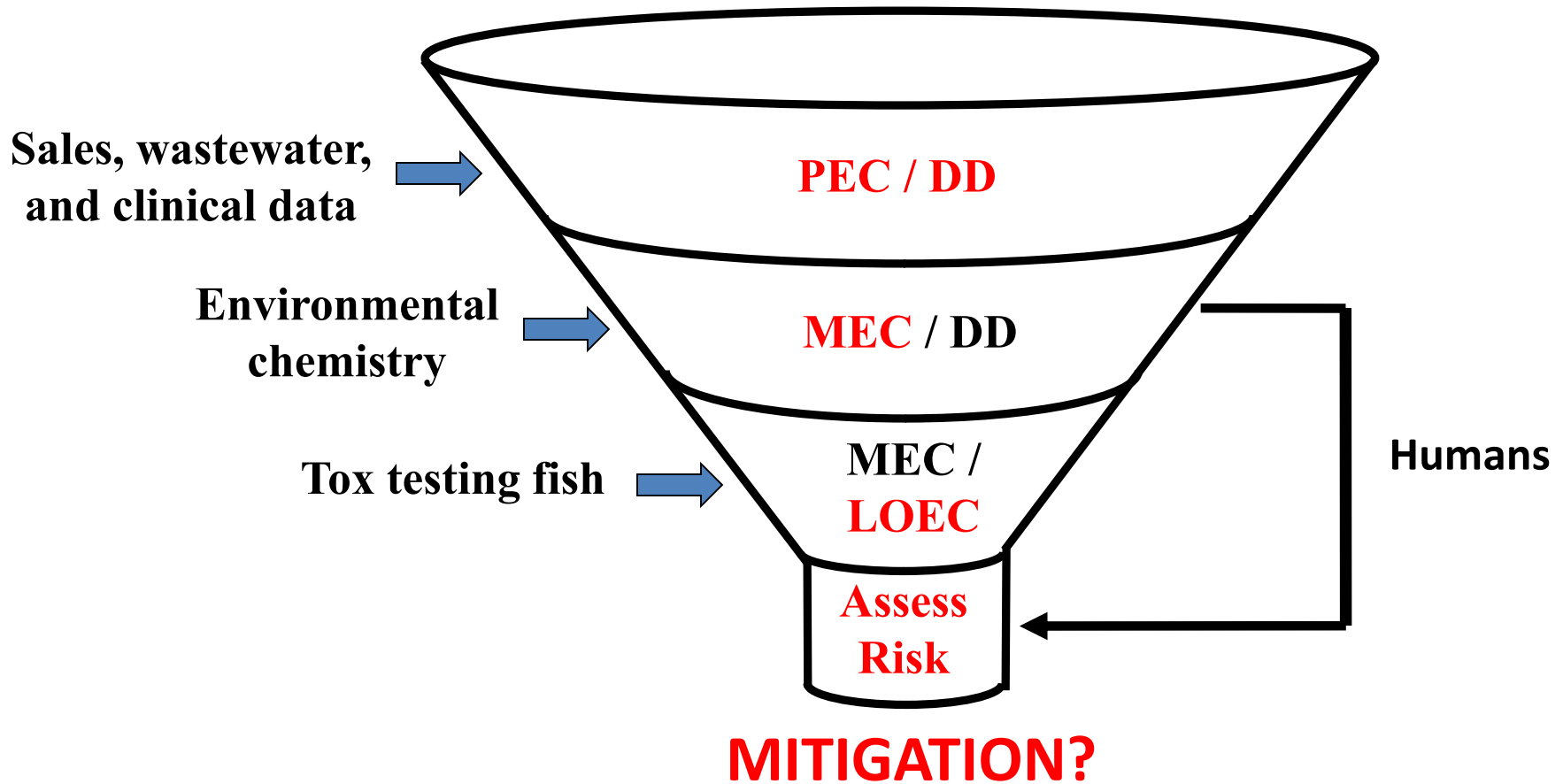
There are a lot of uncertainties in model parameters like:  
physiological degradation, WWTP removal,  
in-stream removal, ecotoxicology, etc.

Replace unknowns with protective defaults:  
translates uncertainty into higher risk quotient  
prioritization highlights critical uncertainties  
false positives much more likely than false negatives

How much uncertainty can we accept?

For example: if 105 PPT is 'safe' level then:  
if PEC is 100 PPT: 0.1-fold (up to 110 PPT) may be problem  
if PEC is 0.01 PPT: 1000-fold (up to 10 PPT) is ok

# Tiered prioritization



**PEC** = Predicted Environmental Concentration from sales / wastewater volume

**DD** = minimum Daily Dose rate from clinical data

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**LOEC** = Lowest Observable Effect Concentration in sensitive aquatic species

# DPD = Daily Doses Per Decade

Assumes drinking 2 L **wastewater influent** per day

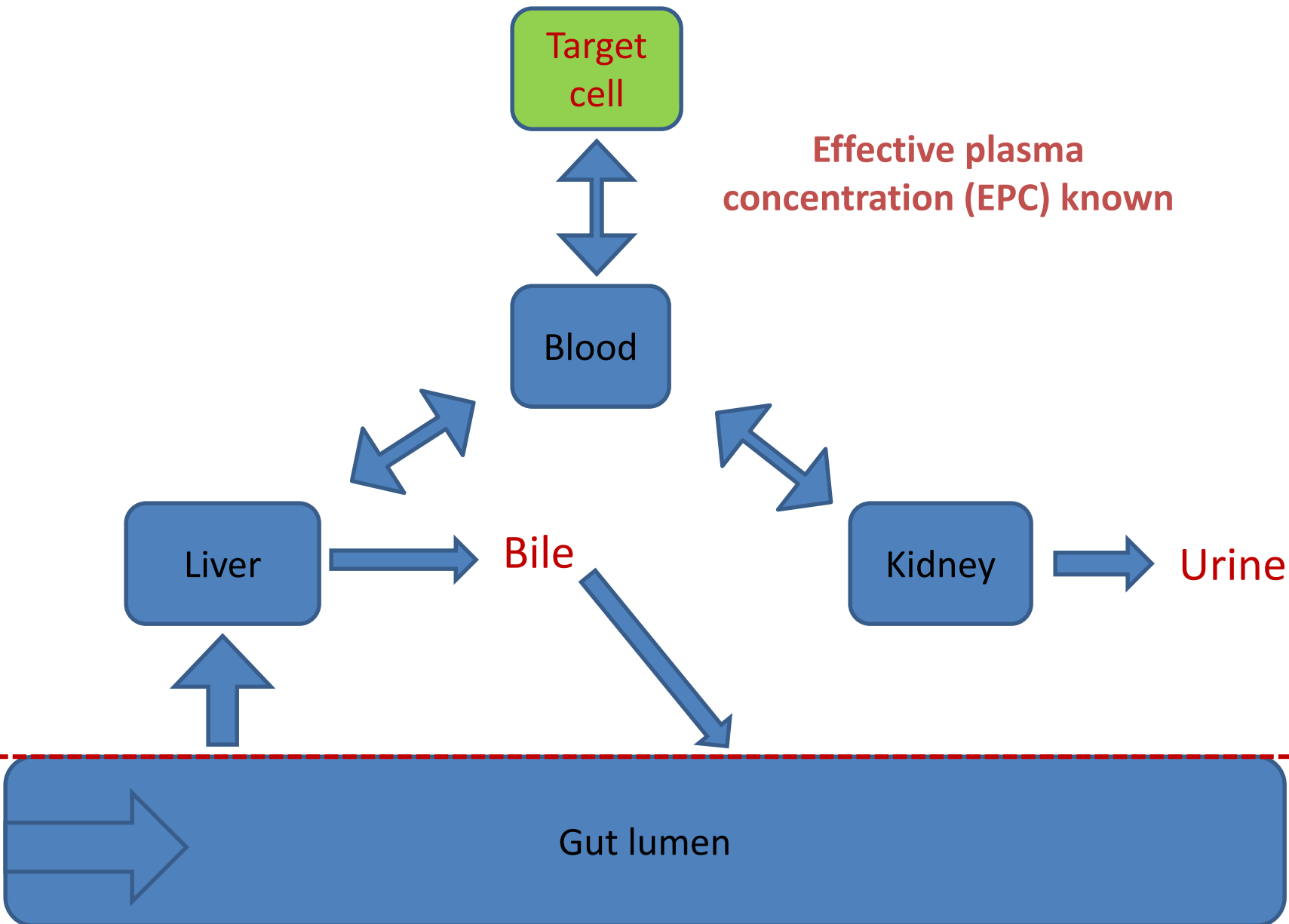
Rank	API	PEC (PPT)	DPD
1	levothyroxine	19	<b>14</b>
2	estradiol	617	9
3	hydrochlorothiazide	13947	8.2
4	hydrocodone	2561	3.7
5	prednisone	2194	3.2
6	betamethasone	93	2.7
7	furosemide	7283	2.7
...	...	...	...
<b>50</b>	nitroglycerin	2.9	<b>0.07</b>

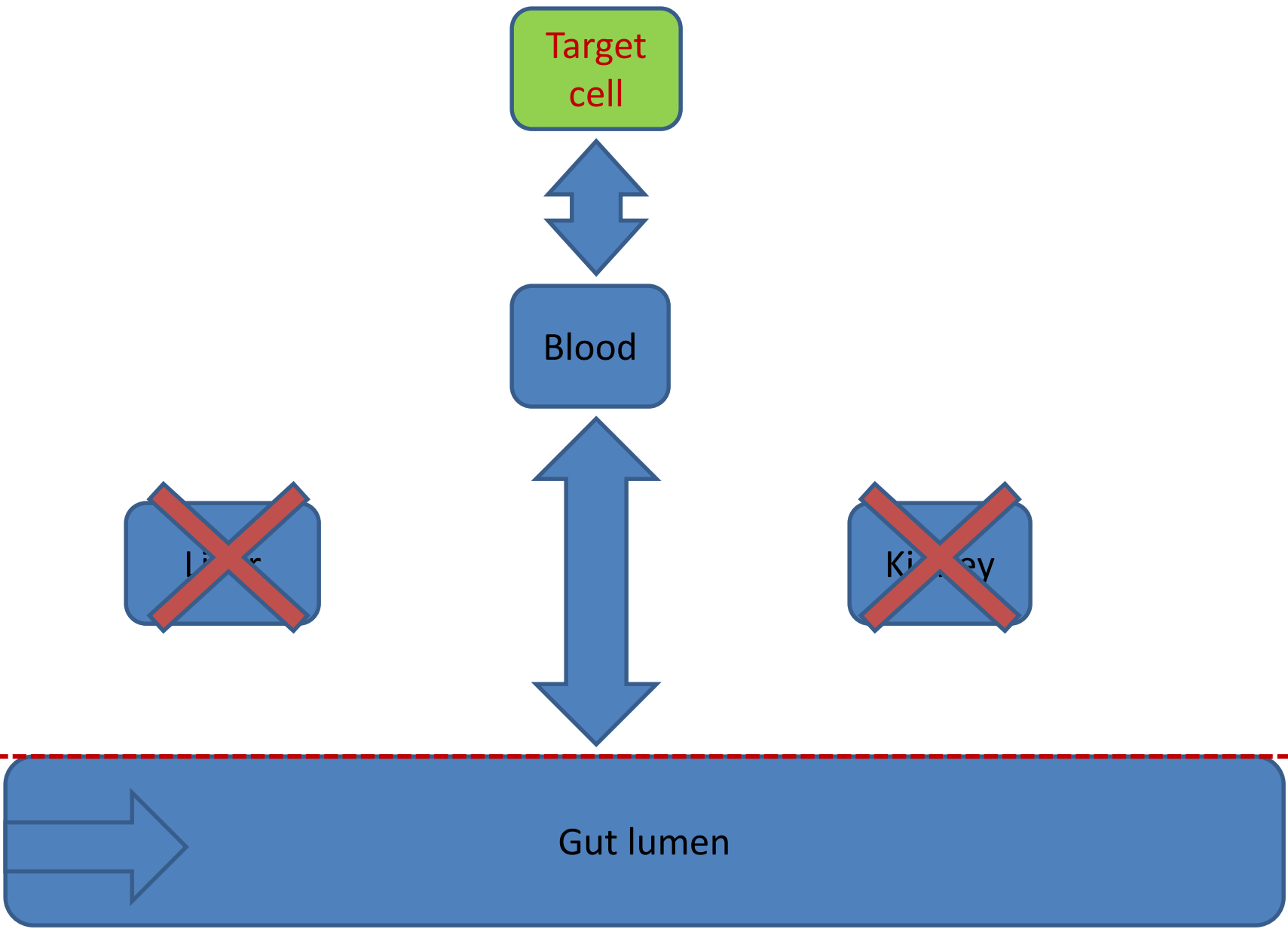


# What about mixtures?

Mode of action	API / Mode	DPD
thyroid hormone modulator	3	<b>30.7</b>
neurotransmitter modulator	105	28.1
anti-inflammatory	32	26.5
anti-hypertensive	36	22.4
reproductive modulator	26	22
anti-hyperglycemic	7	6.6
lipid modifier	9	5.4
h1 anti-histamine	11	1.9
antibacterial	32	1.9
gastric antacid	9	1.2

A few APIs dominate each mode of action (MOA)





**100% bioavailability, no systemic detoxification**



Target  
cell

Wastewater influent

**Compare effective  
plasma concentration (EPC)  
directly to PEC**

# PEC / EPC

EPC = effective plasma concentration

Rank	API	PEC (PPT)	PEC / EPC
1	estradiol	617	<b>2056</b>
2	atorvastatin	2906	45
3	promethazine	1668	6
4	simvastatin	548	6
5	ethinyl estradiol	5.4	5
6	sertraline	615	4
7	hydrocortisone	2368	3
...	...	...	...
<b>50</b>	isosorbide mononitrate	250	<b>0.0012</b>

# Conclusions: modeling PECs

For healthy adults, **AVERAGE exposure rates low**  
relative to therapeutic dose rate, **margin of exposure > 100**

True for single APIs and their mixtures

For top 50 APIs, harder to model  
sensitive human sub-populations, or aquatic life

**After top 50, risks appear low for aquatic life**

Risk estimates vary by >6 orders of magnitude:  
differentiates APIs strongly even relative to likely errors.

Model parameterized with **NATIONAL AVERAGES**

*Kostich and Lazorchak, 2008. STOTEN, 389:320*

# DEA data (controlled APIs)

ZIP CODE	1ST QUARTER	2ND QUARTER
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DRUG CODE: 1100B DRUG NAME: DL-AMPHETAMINE BASE

995	879.09	798.34
996	186.81	196.00
997	143.80	143.08
998	103.86	117.41
999	37.28	26.51

Amount dispensed within 3-digit zip code from DEA  
for 9 controlled APIs

Population size within 3-digit zip code from US Census

Calculate average per capita consumption within area

# Wastewater Plant Data

Plant ID	Zip Code	Total Flow MGD	Population
08209000098	81301	0.3	4350
13000211002	31601	1.21	10900
22000980001	71247	0.05	475
42006166001	15767	1.48	10243
39008371001	45619	0.77	10203

10,631 more wastewater plant records.

From US EPA

**Clean Watersheds Needs Survey**



# Distribution of local PECs

	50%	75%	90%	95%	99%	Avg PPT
Amphetamine	0.9	1.5	2.2	2.7	5.5	95
Methylphenidate	0.9	1.5	2.2	3.0	4.7	207
Codeine	1.3	2.1	3.4	4.7	7.0	298
Oxycodone	1.0	1.6	2.6	4.0	5.8	429
Hydromorphone	1.0	1.7	3.0	4.2	6.9	10
Hydrocodone	1.0	1.6	2.4	2.9	7.6	354
Methadone	0.9	1.7	3.2	4.8	6.4	70
Morphine	1.1	1.7	3.0	4.3	8.6	211
Fentanyl	1.0	1.6	2.4	3.1	<b>10.4</b>	5
People/Flow	1.1	1.4	1.8	1.9	2.7	511

Results suggests use of 10x assessment factor  
for extrapolating from national to local estimates

# Comparing MECs to PECs

From 62 US studies with 111 APIs,  
up to 1237 measurements per API, up to 542 sites per API.

	MEC (PPT)	MEC / PEC	MEC (DPD)	Samples
Ethinyl estradiol	273 (14)	41 (2.1)	100 (5.3)	314 (241)
Ofloxacin	23,500	9.4	1.4	124
Azithromycin	14,900	9.1	0.44	101
Norethindrone	872	7	6.4	78
Trimethoprim	37,000	4.1	1.7	995
Atenolol	14,200	3.3	2.1	386
Ciprofloxacin	5600	2.9	0.082	538
Warfarin	330	2	1.2	381

# Conclusions: MECs vs PECs

Probably some *artifacts* in measurement data  
or perhaps another route into environment?

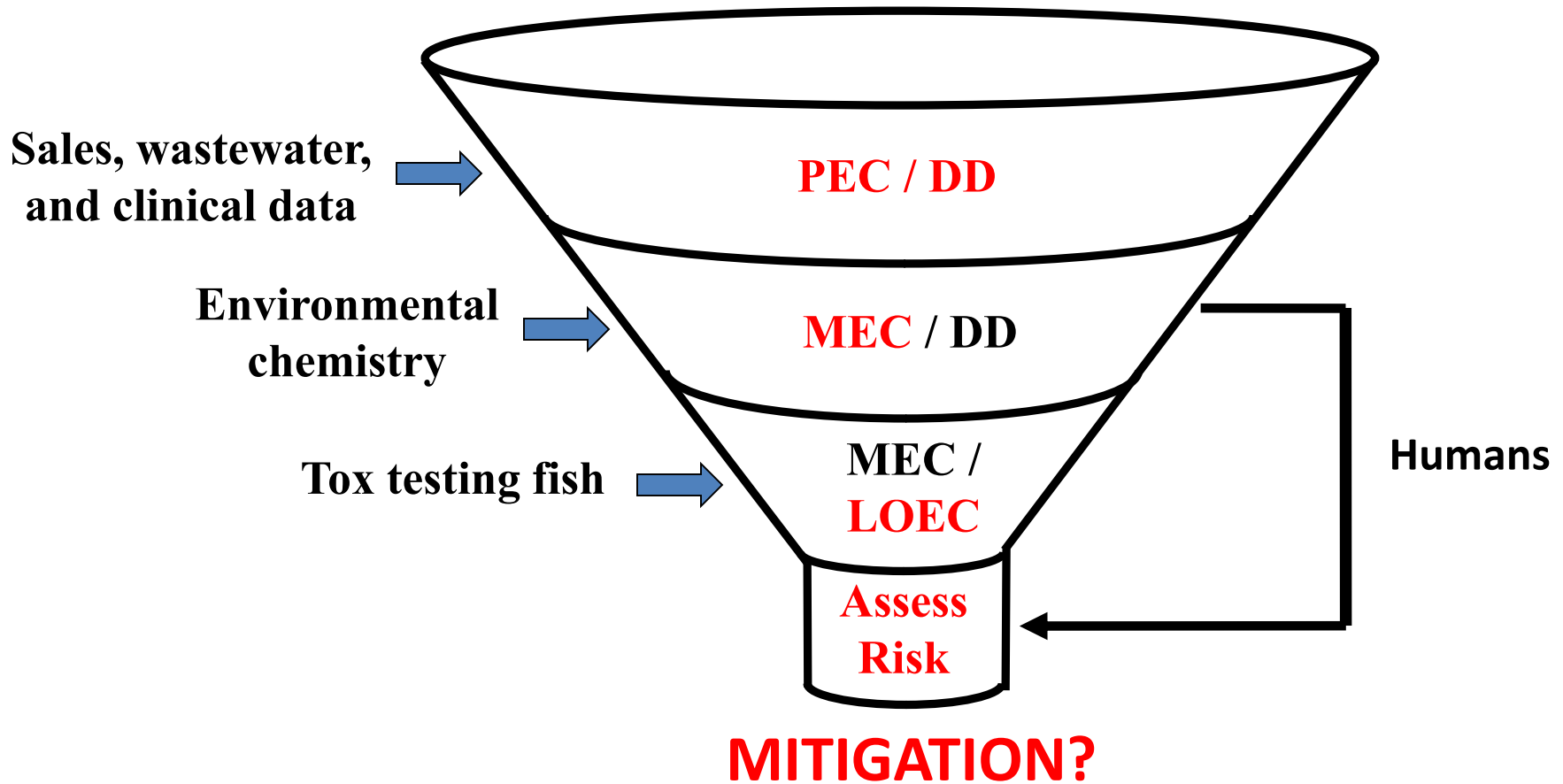
**'Assessment factor' of 10x** on national PECs  
to account for spatial + temporal variability

**Suggests potential exposure rates for healthy adults low**  
relative to therapeutic levels (**margin of exposure >300**)

True for single APIs and their mixtures

*Kostich, Batt, Glassmeyer, & Lazorchak, 2010. STOTEN, 408:4504.*

# Tiered prioritization



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# Municipal Effluent Study

24-hour composite samples

from 50 very large WWTPs (15 to >500 MGD)

Assume effluent is worst case water concentration relevant to humans and aquatic life

**These 50 WWTPs serve 46M people,**

produce ~17% of all municipal WWTP effluent

**Analytes selected using PEC-based DPD estimates**

steroidal estrogens, androgens, and other emerging contaminants will be reported elsewhere.

LC-MS/MS with isotopically labeled standards.

*Kostich, Batt, and Lazorchak, 2014. Env Pol, 184:354.*

# Top number of detections

	RL	N	Detects	Mean PPT	Max PPT
hydrochlorothiazide	10.0	50	<b>50</b>	1100	2800
metoprolol	14.0	50	49	410	660
atenolol	6.0	50	48	940	3000
carbamazepine	4.4	50	48	97	240
furosemide	38.0	50	45	280	810
ofloxacin	10.0	49	44	160	660
propranolol	4.4	50	44	33	260
sulfamethoxazole	1.0	49	44	330	1000

**Hydrochlorothiazide (blood pressure med)  
in every sample**

**RL** = reporting limit (in PPT = ng/L)

**N** = number of samples passing QA

# Top maximum concentrations

	RL	N	Detects	Mean PPT	Max PPT
valsartan	11.0	41	40	1600	<b>5300</b>
ibuprofen	12.0	50	23	460	4200
lisinopril	45.0	49	23	180	3300
atenolol	6.0	50	48	940	3000
sulfamethoxazole	1.6	50	40	910	2900
hydrochlorothiazide	10.0	50	50	1100	2800
gemfibrozil	10.0	50	38	420	2300
acetaminophen	5.0	50	7	79	1500

**Valsartan (blood pressure med) up to 5300 PPT**

in 24-hour composite effluent samples

Somewhat lower than highest reported elsewhere

maybe composite vs. grab sample? big WWTP vs. little?

# Top doses per decade (DPD)

	RL	N	Detects	Max PPT	DPD
lisinopril	45.0	49	23	3300	9.70
hydrochlorothiazide	10.0	50	50	2800	1.60
valsartan	11.0	41	40	5300	0.96
atenolol	6.0	50	48	3000	0.45
enalaprilat	9.0	49	5	150	0.42
metoprolol	14.0	50	49	660	0.38
alprazolam	9.1	50	15	31	0.30
furosemide	38.0	50	45	810	0.30

**One dose per year for lisinopril (blood pressure med)**

but for most APIs, less than 1 dose / lifetime

**Additive mixtures w/i MOA: similar picture**

a few analytes dominate each MOA



# Top ( MEC / EPC )

	RL	N	Detects	Max PPT	PPT / EPC
sertraline	5.0	50	32	71	<b>0.71</b>
propranolol	4.4	50	44	260	0.65
desmethylsertraline	9.4	50	9	24	0.24
valsartan	11.0	41	40	5300	0.18
furosemide	38.0	50	45	810	0.08
lisinopril	45.0	49	23	3300	0.07

**Below 1 for all, but four APIs a bit close for comfort**  
for rest: less than 10% of EPC (effective plasma conc)

**For a few APIs: Potential risks to aquatic life?**  
**suggests study of concentration-response across taxa**

# Top ( MEC / Breakpoint )

	RL	N	Detects	Max PPT	PPT / BP
ofloxacin	10.0	49	44	660	<b>0.0003</b>
ciprofloxacin	10.0	49	30	260	0.0003
trimethoprim	2.5	43	37	370	0.00009
sulfamethoxazole	1.6	50	40	2900	0.00004
sulfamethazine	10.0	49	1	87	0.000002

**All below 0.1% of clinical resistance breakpoint (BP)**

**Unlikely to directly select for clinical resistance**

MEC << tolerable concentration for patients

# Top ( MEC / MIC )

	RL	N	Detects	Max PPT	PPT / MIC
ofloxacin	10.0	49	44	660	<b>0.66</b>
ciprofloxacin	10.0	49	30	260	0.26
trimethoprim	2.5	43	37	370	0.03
sulfamethoxazole	1.6	50	40	2900	0.02
sulfamethazine	10.0	49	1	87	5.5e-06

**Well below MIC (of most sensitive microbe) for most**  
ofloxacin and ciprofloxacin close to 1  
**additive model very close to 1**

**Potential inhibition of 'good' microbes?**

**Potential selection for low-level resistance?**

# Max ( MEC / PEC )

	RL	N	Detects	Max PPT	MEC / PEC
lisinopril	45.0	49	23	3308	<b>4.06</b>
valsartan	11.0	41	40	5263	2.00
atenolol	6.0	50	48	3046	0.74
metoprolol	14.0	50	49	656	0.45
enalaprilat	9.0	49	5	145	0.39
alprazolam	9.1	50	15	31	0.30
propranolol	4.4	50	44	260	0.26

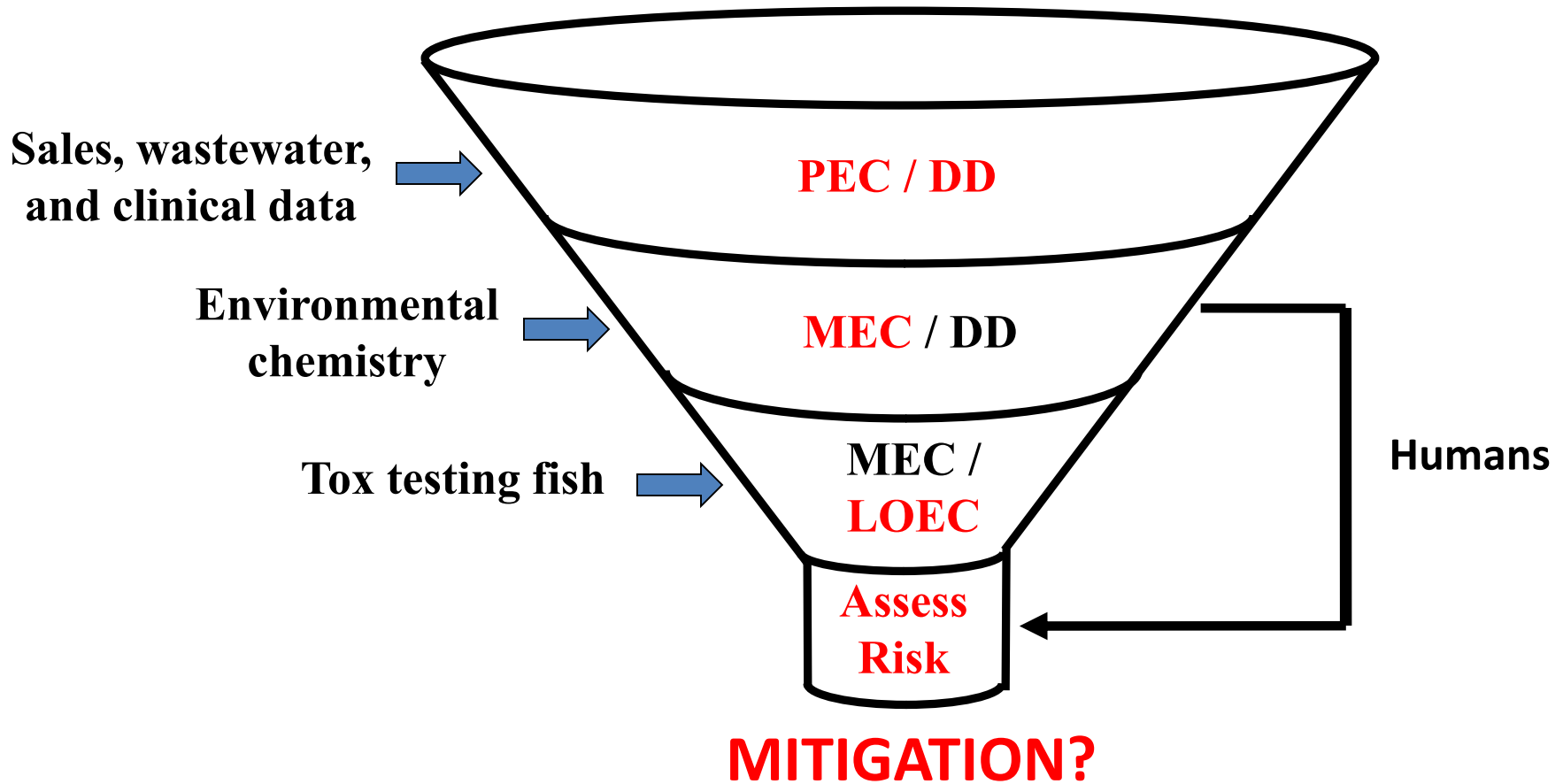
**Well within 10-fold 'assessment factor'**

accounts for spatio-temporal variability

**Suggests reliability of model estimates**

and **very low risks for lower priority, unmeasured APIs**  
based on applying assessment factor to PECs

# Tiered prioritization



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# Conclusions from this work

Risks to healthy adults low: therapeutic effects unlikely  
harder to assess risks to sensitive human sub-populations  
pregnant, children, liver or kidney impairment, allergic  
how to ethically/practically characterize this dose-response?

Potential risks to aquatic life for a few?

anti-hypertensive & psychiatric meds (& estrogens)

Potential risks of microbial effects + selection for a few?

**Narrows down >1000 APIs to about 10 for future study**

ecological dose response measurements

physiological modeling?

Does not address risks from other routes and sources

biosolids, agriculture, manufacturing, small WWTPs

# Acknowledgements

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**50 WWTPs whose voluntary participation made this study possible**

## ACRONYMS

API: active pharmaceutical ingredient

BP: breakpoint (concentration defining antibiotic resistance)

DD: minimum therapeutic daily dose (for otherwise healthy adult patient)

DPD: DD per decade of consuming 2 liters per day at the PEC or MEC

EPC: effective plasma concentration (freely dissolved fraction) in patients receiving the DD

LC-MS/MS: liquid chromatography-tandem mass spectrometry

LOEC: lowest observable effect concentration (in aquatic life)

MEC: measured environmental concentration

MIC: minimum inhibitory concentration (concentration inhibiting sensitive microbes)

MGD: millions of gallons per day (of wastewater flow)

MOA: (physiological) mechanism of action

N: number of samples passing quality control

PEC: predicted environmental concentration

PPT: parts per trillion (concentration unit equivalent to nanograms per liter)

RL: reporting limit (lowest concentration that can be reliably measured)

WWTP: municipal waste water treatment plant



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