Health Risk-Based Screening Levels for Pharmaceuticals and EDCs in Drinking and Reuse Water

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Do Pharmaceuticals and Personal Care Products (PPCPs) & Endocrine Disrupting Compounds (EDCs) in drinking water pose a human health risk?

Risk Assessment of PPCPs and EDCs

Projects and Funding:

- **AwwaRF/ Water Research Foundation** and **WateReuse Foundation**
  - **AwwaRF/WRF 3085/04-003**: Toxicological Relevance of Endocrine Disruptors and Pharmaceuticals in Drinking Water (2004-2008); with SNWA (Shane Snyder, PI)
  - **AwwaRF 3033**: Comprehensive Utility Guide for Endocrine Disrupting Chemicals, Pharmaceuticals, and Personal Care Products in Drinking Water (2005-2007); with SNWA (Shane Snyder, PI)
  - **WRF-06-018**: Tools to Assess and Understand the Relative Risks of Indirect Potable Reuse and Aquifer Storage and Recovery Projects (2006-present) (*In press*); with Nellor Environmental Associates, Inc. and Soller Environmental, LLC (Margie Nellor and Jeff Soller, PIs)
  - **WRF-05-005**: Identifying Hormonally Active Compounds, Pharmaceutical Ingredients, and Personal Care Product Ingredients of Most Health Concern from Their Potential Presence in Water Intended for Indirect Potable Reuse (2006-present) (*In press*); with SNWA (Shane Snyder, PI)

Acknowledgements

- This work was conducted in collaboration with a number of other organizations:
  - Southern Nevada Water Authority (SNWA)
  - California Urban Water Agencies (CUWA)
  - Nellor Environmental Associates, Inc.
  - Soller Environmental, LLC
  - Inland Empire Utilities Agency
  - Water Replenishment District of Southern California
  - County Sanitation Districts of Los Angeles County
  - Orange County Water District
  - West Basin Municipal Water District
  - City of Los Angeles Department of Water and Power
  - City of Phoenix Water Services
  - Fairfax Water

Outline

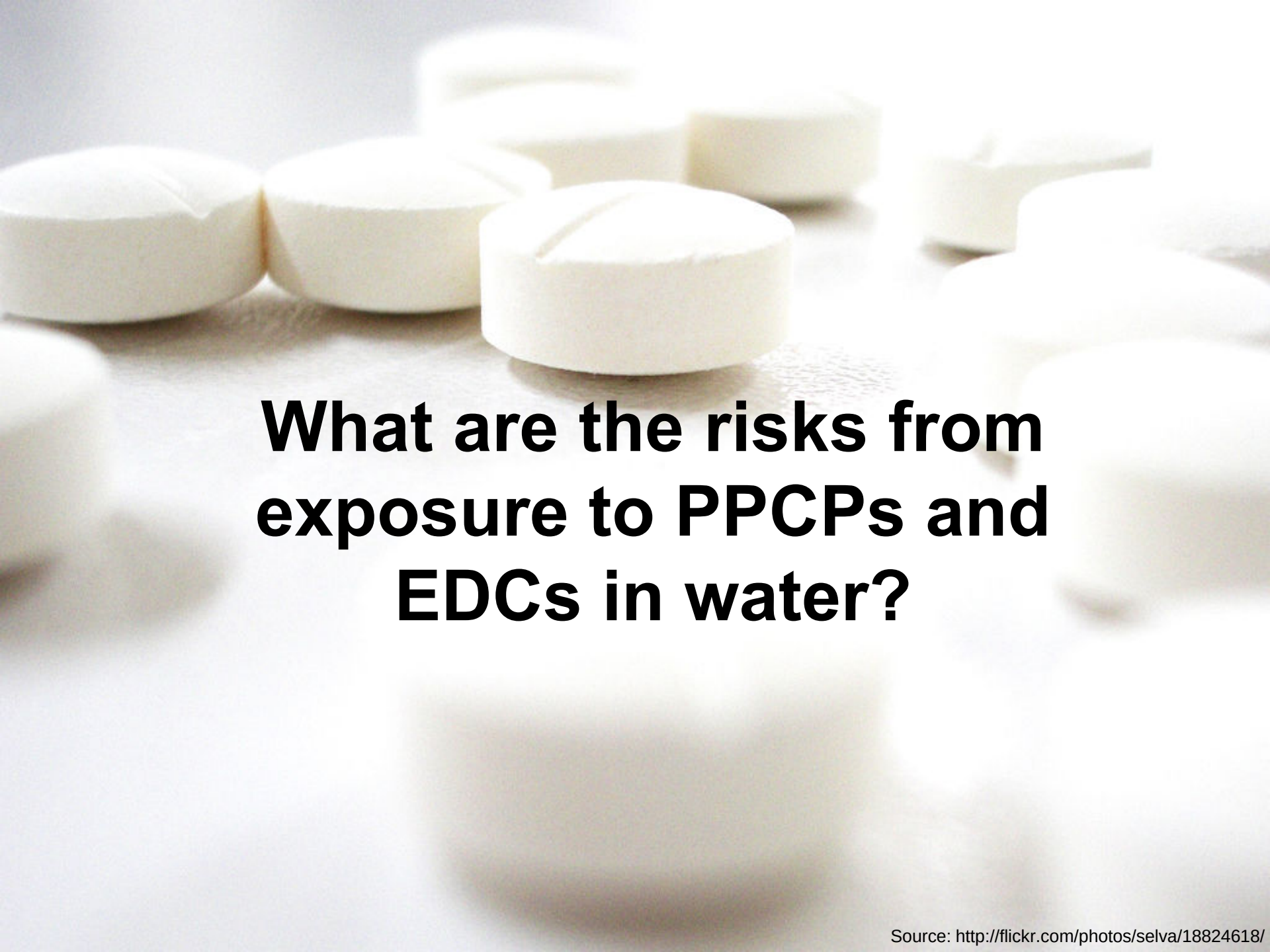
- Regulatory requirements for monitoring PPCPs and EDCs in water
- Risk assessment of PPCPs and EDCs in drinking and reuse water
  - Development of human health risk-based **Acceptable Daily Intakes (ADIs)**
  - Comparison to **drinking water concentrations** measured at utilities nationwide
- Challenges and uncertainties

Regulatory/Stake Holder Activities

Agencies are beginning to consider/recommend monitoring:

- EPA third Contaminant Candidate List (CCL3): listed several pharmaceutical ingredients, including estrogenic hormones and erythromycin
- California Department of Health Services (DHS): specified that PPCPs, EDCs, hormones, and other indicator compounds should be monitored in recycled water used to recharge groundwater basins designated as domestic water supplies
- Center for Biological Diversity: petitioned EPA (1/11/10) to develop water quality criteria under the Clean Water Act for numerous compounds including PPCPs and EDCs

Source: http://media.photobucket.com/image/water%20sample%20jars/baybeeDESIGN/baybeePRELOVED/Samples/SampleJar.jpg



What are the risks from exposure to PPCPs and EDCs in water?

Source: http://flickr.com/photos/selva/18824618/

Risk Assessment of PPCPs and EDCs

Develop Acceptable Daily Intakes (ADIs):

A level of a chemical "*to which a person, including members of sensitive subpopulations, can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect*" (U.S. EPA, 1993).

Reference dose (RfD)

Public health goal (PHG)

Tolerable daily intake (TDI)

Minimal risk level (MRL)

Maximum residue level (MRL)

Pharmaceuticals and Personal Care Products for which we developed ADIs

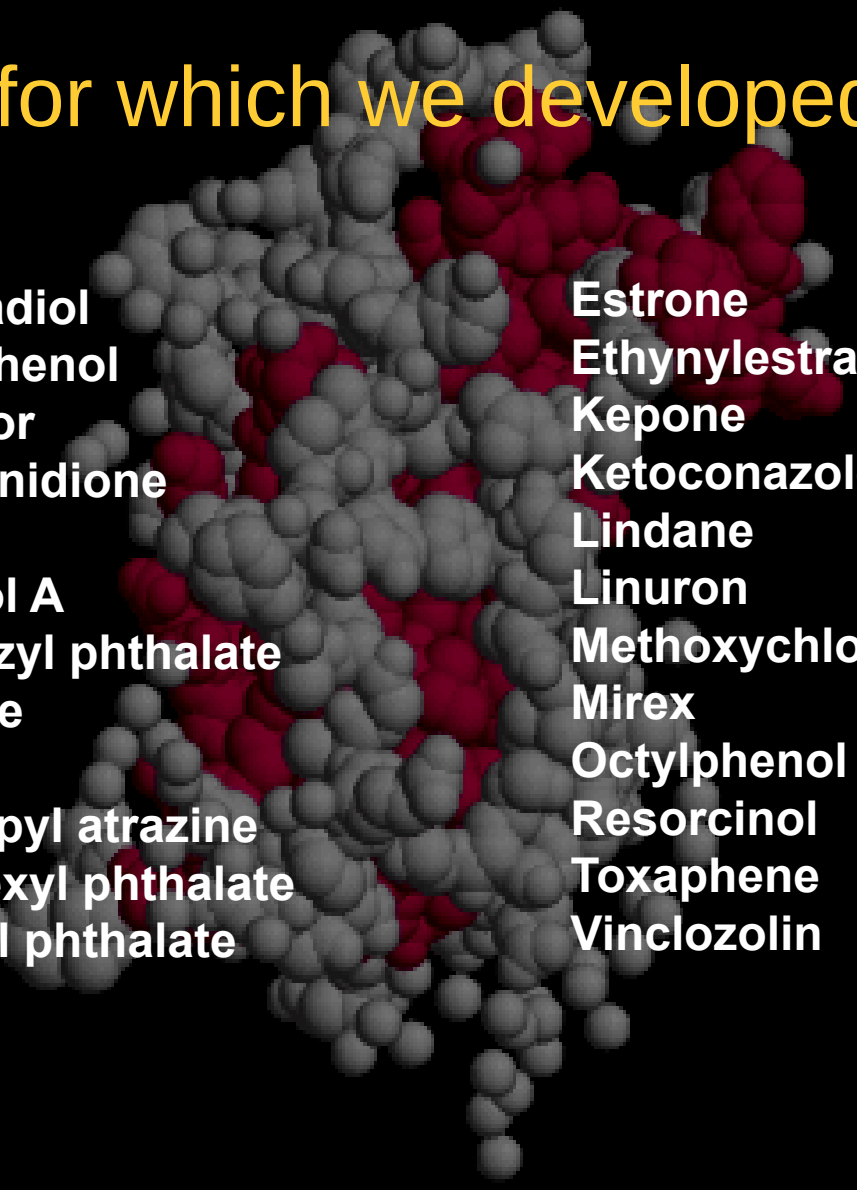
2,6-di-t-Butyl-p-cresol
Alprazolam
Amlodipine
Atenolol
Atorvastatin
Baclofen
Butylated hydroxyl-anisole
Caffeine
Carbamazepine
Chlordane
Ciprofloxacin
Citalopram
Clonidine
Cyclophosphamide
DEET
Diazepam
Diclofenac
Divalproex
Enalapril

Fluoxetine
Gemfibrozil
Ibandronate
Ibuprofen
Kepone
Ketoconazole
Ketoprofen
Lisinopril
Meprobamate
Methoxychlor
Methylphenidate
Metronidazole
Mirex
Morphine
Naproxen
Nitrofurantoin
Norfluoxetine
Olanzapine
Omeprazole

Oseltamivir
Oxcarbazepine
Pentoxyfylline
Phenytoin
Pravastatin
Pregabalin
Primidone
Resorcinol
Risperidone
Salicylic acid
Simvastatin
Simvastatin hydroxy acid
Sulfamethazine
Sulfamethoxazole
TCEP
Thiabendazole
Timolol
Triclosan
Trimethoprim

Source: http://www.flickr.com/photos/bill_horne/1796280595/

EDCs for which we developed ADIs



17ß-Estradiol
4-Nonylphenol
Acetachlor
Androstenidione
Atrazine
Bisphenol A
Butylbenzyl phthalate
Chlordane
p,p-DDE
Deisopropyl atrazine
Diethylhexyl phthalate
Di-n-butyl phthalate
Estrone
Ethynylestradiol
Kepone
Ketoconazole
Lindane
Linuron
Methoxychlor
Mirex
Octylphenol
Resorcinol
Toxaphene
Vinclozolin

Source: http://scienceray.com/biology/human-biology/the-human-endocrine-system/

Basis of ADIs

Derived using Decision Tree approach (WRF-05-005), based on lowest value from:

- ***Noncancer effects from animal toxicity studies***– either the **lowest observed adverse effect level** (LOAEL) or the highest dose that causes no effect (**no observed adverse effect level**, NOAEL) ÷ uncertainty factors ("RfD approach")
- ***Lowest therapeutic dose*** *(TD)* ÷ uncertainty factors*
- ***Carcinogenic tumor incidence*** ("slope factor approach")
- ***Threshold of toxicologic concern*** (TTC)

* Comparisons suggest that for nongenotoxic, noncarcinogenic pharmaceuticals, basing ADI on therapeutic dose is health protective

Source: http://compgen.unc.edu/wp/wp-content/uploads/2009/03/ccmice.png

Examples: our approach

(screening level values)

Compound	Method	Effect Dose	Effect	UF	ADI (µg/kg-d)
Furosemide	Toxicity data-based	25 mg/kg-d (LOAEL)	Reproductive/ developmental; rabbits	3000	**8.3**
	Therapeutic dose-based	20 mg/d	Treatment for edema	3000	**0.097**
	TTC-based	0.15 µg/d	Compounds with structural alerts for genotoxicity	NA	**0.0021**
	Cancer slope factor-based	SF = 0.0086 $(mg/kg\text{-}d)^{-1}$	Mammary, thyroid, and pituitary tumors in rodents	NA	**0.12**

Drinking Water Equivalent Levels (DWELs)

Non cancer

- Consume 2 liters of water per day
- 70 kg body weight

$$\text{DWEL } (\mu g/L) = \frac{\text{ADI}\,(\mu g/kg-d) \times 70\text{ kg}}{2\text{ L/d}}$$

Carcinogens

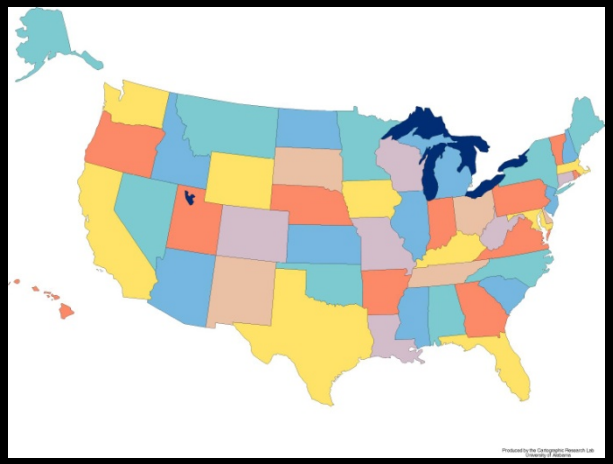
- Acceptable risk of 1 in 1,000,000 (10^{-6}) and exposure for 30 years over a 70 year lifetime

$$\text{DWEL } (\mu g/L) = \frac{10^{-6} \times 70\text{ kg} \times 70\text{ yr}}{\text{SF}\,(\mu g/kg-d)^{-1} \times 2\text{ L/d} \times 30\text{ yr}}$$

Risk Assessment of PPCPs and EDCs

Comparison to water concentrations

- **AwwaRF/WRF 3085/04-003**
  - Analyses of finished and distribution drinking water for 20 PPCPs and metabolites, 10 EDCs, and 3 steroid hormones
  - 18 DWTPs and 15 distribution system locations nationwide
  - Also analyses of source water



Source: http://alabamamaps.ua.edu/contemporarymaps/usa/basemaps/usa.jpg

Risk Assessment of PPCPs

Comparison to water concentrations

Compound	Frequency of Detection Finished dw, distribution	ADI (µg/kg-d)	DWEL (µg/L)	Maximum conc. (µg/L)*	Minimum margin of safety
Atenolol	8/18, 8/15	2.0##	70	0.026	2,700
Carbamazepine	8/18, 6/15	0.34**	12	0.018	670
Diazepam	1/18, 0/15	1.0***	35	0.00033	110,000
Fluoxetine	2/18, 1/15	0.97***	34	0.00082	41,000
Norfluoxetine	0/18, 1/15	0.97***	34	0.00077**	44,000
Gemfibrozil	7/18, 4/15	1.3#	45	0.0021	21,000
Meprobamate	14/18, 12/15	7.5***	260	0.043	6,000
Phenytoin	10/18, 11/15	0.19#	6.8	0.032	210
Risperidone	0/18, 1/15	0.014**	0.49	0.0029**	170
Sulfamethoxazole	4/18, 1/15	510***	18,000	0.0030	6,000,000
Triclosan	1/18, 0/15	75***	2,600	0.0012	2,200,000

ND = Atorvastatin, o-hydroxy atorvastatin, p-hydroxy atorvastatin, Diclofenac, Enalapril, Naproxen, Simvastatin, Simvastatin hydroxy acid, Trimethoprim

*AwwaRF/WRF 3085/04-003—Analyses by SNWA (Snyder et al., 2008)

Risk Assessment of EDCs

Comparison to water concentrations

Chemical	Basis of ADI	ADI (µg/kg-d)	DWEL (µg/L)	Frequency of Detection Finished dw, distribution*	Maximum conc. (µg/L)**	Minimum margin of safety
Atrazine	Developmental	0.1	3 (MCL)	15/18, 13/15	1	3
Bisphenol A	Developmental	50 (RfD)	1,800	1/18, 0/15	0.025	72,000
Linuron	Hematological	2.0 (RfD)	70	2/18, 0/18	0.0083	8,400
4-Nonylphenol	Developmental	50	1,800	2/18, 2/15	0.11	16,000
Butylbenzyl phthalate	Repro/ developmental	100*	3,500	ND	<0.050	>70,000
Diethylhexyl phthalate	Repro/ developmental	12*	420	ND	<0.10	>4,200
17ß-Estradiol	Endocrine (human)	0.017	1.8	ND	<0.00050	>3,600
Estrone	Endocrine (human)	0.050	0.46	ND	<0.00020	>2,300
Ethynylestradiol	Endocrine (lowest therapeutic dose)	0.0001	0.0035	ND	<0.0010	>3.5
Lindane	Systemic	0.3 (RfD)	20	ND	<0.010	>2,000
Methoxychlor	Developmental	0.020*	0.70	ND	<0.010	>70
Octylphenol	Developmental	150	5,300	ND	<0.025	>210,000
Vinclozolin	Systemic	12*	420	ND	<0.010	>42,000

*n = 18 finished drinking water and 15 distribution system samples

**AwwaRF/WRF 3085/04-003—Analyses by SNWA (Snyder et al., 2008)

***Compound has a higher U.S. EPA RfD; later studies show effects at lower doses

INTERTOX

Risk Communication

How many (8 oz) glasses of water per day to equal the ADI?

Atrazine
~ 26 (8 oz) glasses

Bisphenol A
~ 610,000 (8 oz) glasses

Carbamazepine
~ 5,600 (8 oz) glasses

Phenytoin
~ 1,800 (8 oz) glasses

Hypothetical

*Assuming exposure to the maximum-detected concentration in finished or distribution water

What’s coming down the track?

Source: http://www.ulricianum-aurich.de/lk05/bilder/boyle/balboa%20park/31_train_tra

More compounds
Other sources of exposure
Toxicology of mixtures

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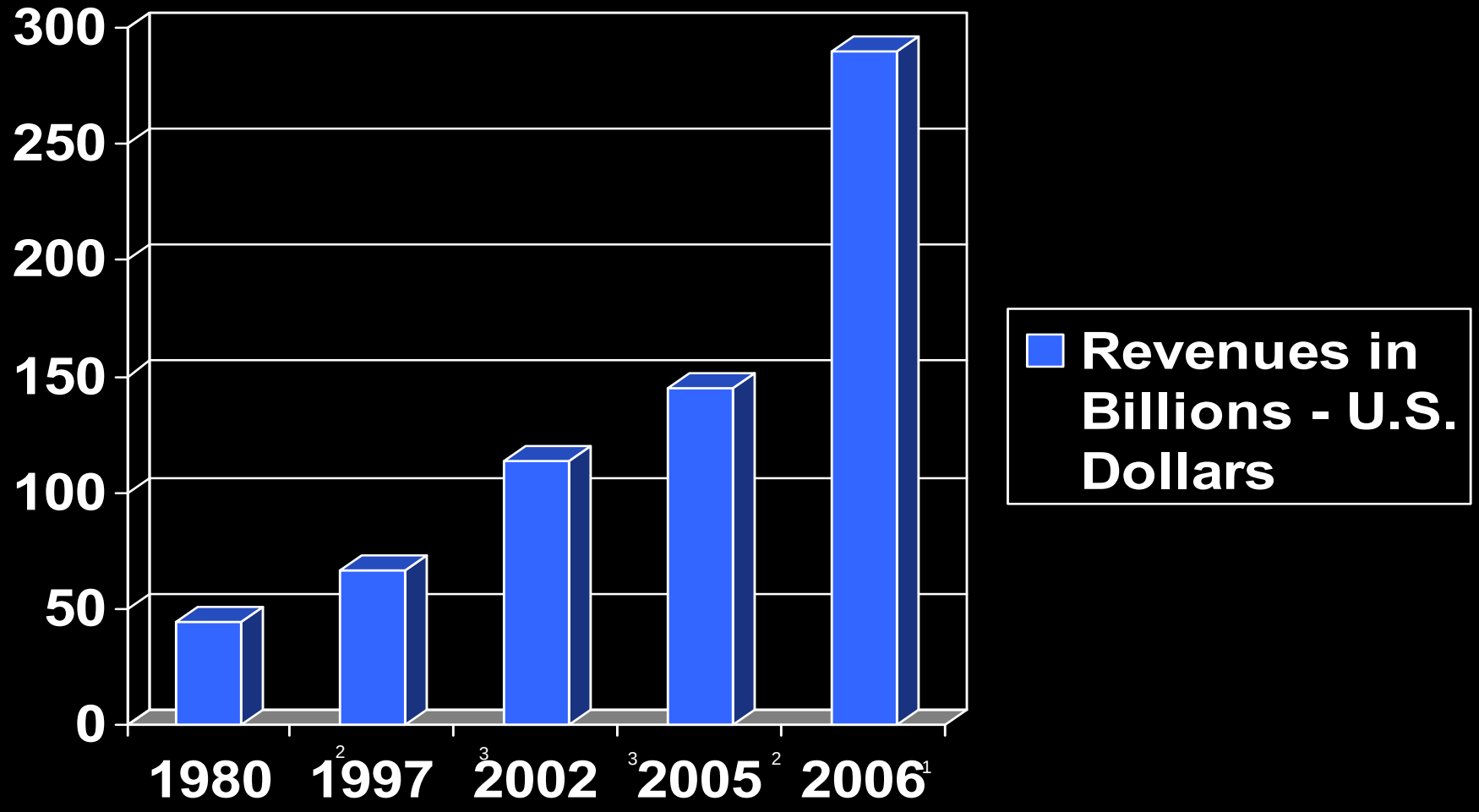
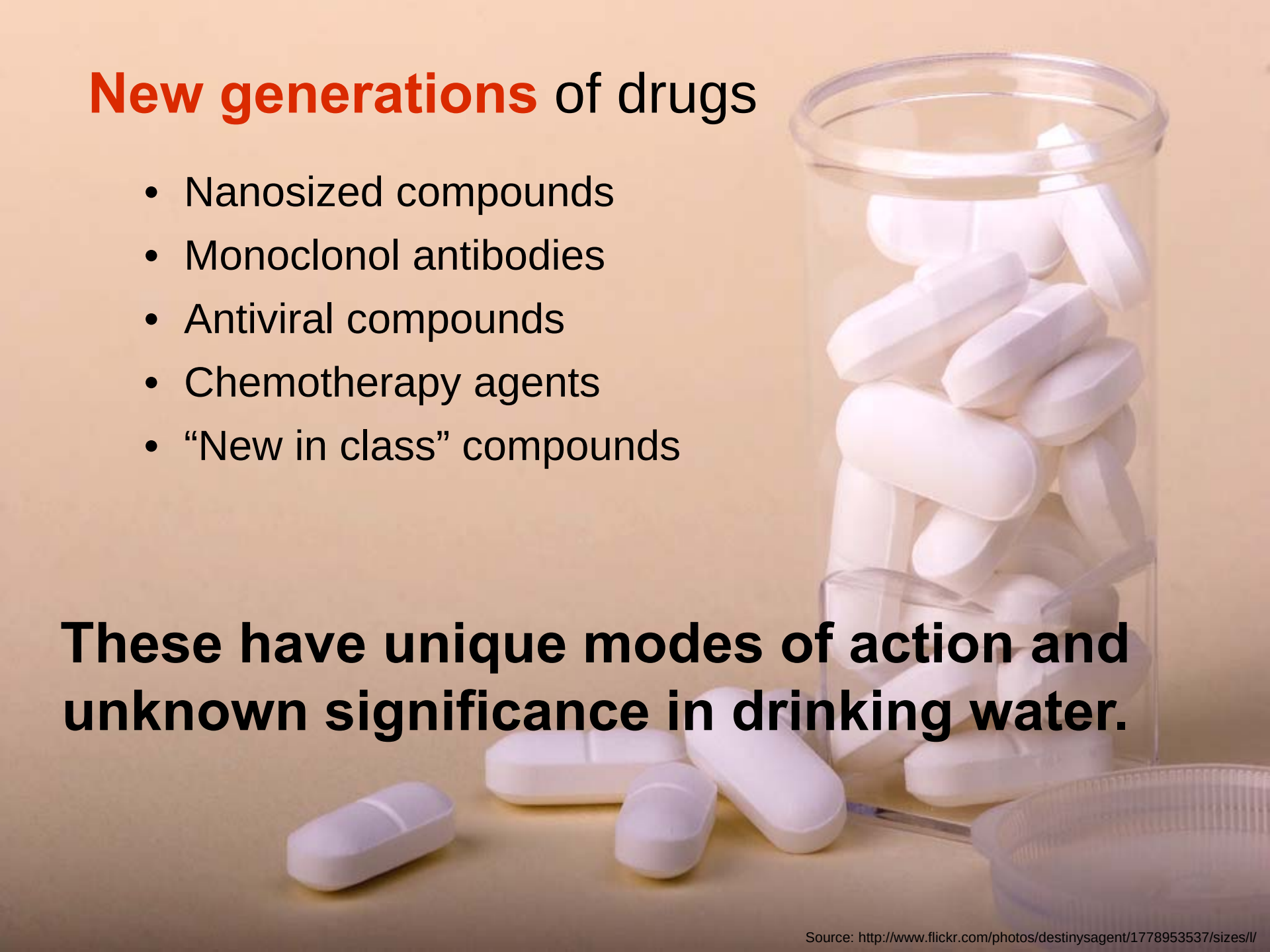
Pharmaceutical revenues
-United States-



1. http://en.wikipedia.org/wiki/Pharmaceutical_companies
2. http://www.upmc-biosecurity.org/website/resources/presentations/2007-01-15-globalbiotechandpharma/index.html
3. http://factfinder.census.gov/servlet/SAFFEconFacts?_event=&geo_id=01000US&_geoContext=01000US&_street=&_county=&_cityTown=&_state=&_zip=&_lang=en&_sse=on&ActiveGeoDiv=&_useEV=&pctxt=bg&pgsl=010&_submenuId=business_2&ds_name=&_ci_nbr=&qr_name=&reg=null%3Anull&_keyword=&_industry=325412

New generations of drugs

- Nanosized compounds
- Monoclonol antibodies
- Antiviral compounds
- Chemotherapy agents
- “New in class” compounds



These have unique modes of action and unknown significance in drinking water.

Source: http://www.flickr.com/photos/destinysagent/1778953537/sizes/l/

Other sources of exposure: Endogenous compounds

17β-Estradiol:

Finished drinking water: **<0.5 ng/L***

human breast milk: **36-45 ng/L**

cow's milk: **3.5-60 ng/L**

ADI-DWEL: **1,800 ng/L**

Estrone:

Finished drinking water: **<0.5 ng/L***

human breast milk: **3.4-5.5 ng/L**

cow's milk: **9.1-260 ng/L**

ADI-DWEL: **460 ng/L**

*AwwaRF/WRF 3085/04-003; Snyder et al., 2008

Source: http://www.flickr.com/photos/pankaspe/1604067666/

Other sources of exposure: Exogenous compounds

Bisphenol A:

Finished drinking water: (1/18 samples) **25 ng/L***

Baby formula: (2 of 4 brands) **3,100-5,500 ng/L ***

ADI-DWEL: **1,800,000 ng/L**

Nonylphenol:

Finished drinking water: (2/18 samples) **110 ng/L***

Vegetable juice (4 of 4 brands): **700-1,400 ng/L**

ADI-DWEL: **1,800,000 ng/L**

***AwwaRF/WRF 3085/04-003 : Snyder et al., 2008**

Source: http://www.cfs.gov.hk/english/programme/programme_haccp/images/control_juice.jpg

Toxicology of Mixtures

- Research with xenobiotics suggests that at low doses, additivity of dose or response is reasonable for chemicals that impact the same receptor
- Significant uncertainties for EDCs
  - Multitudes of possible mechanisms of action
  - Varying exposure levels, both exogenous and endogenous
  - Exposures at sensitive life stages may exert effects later

Source: http://www.flickr.com/photos/virtually_supine/2111582580//

Toxicology of Mixtures

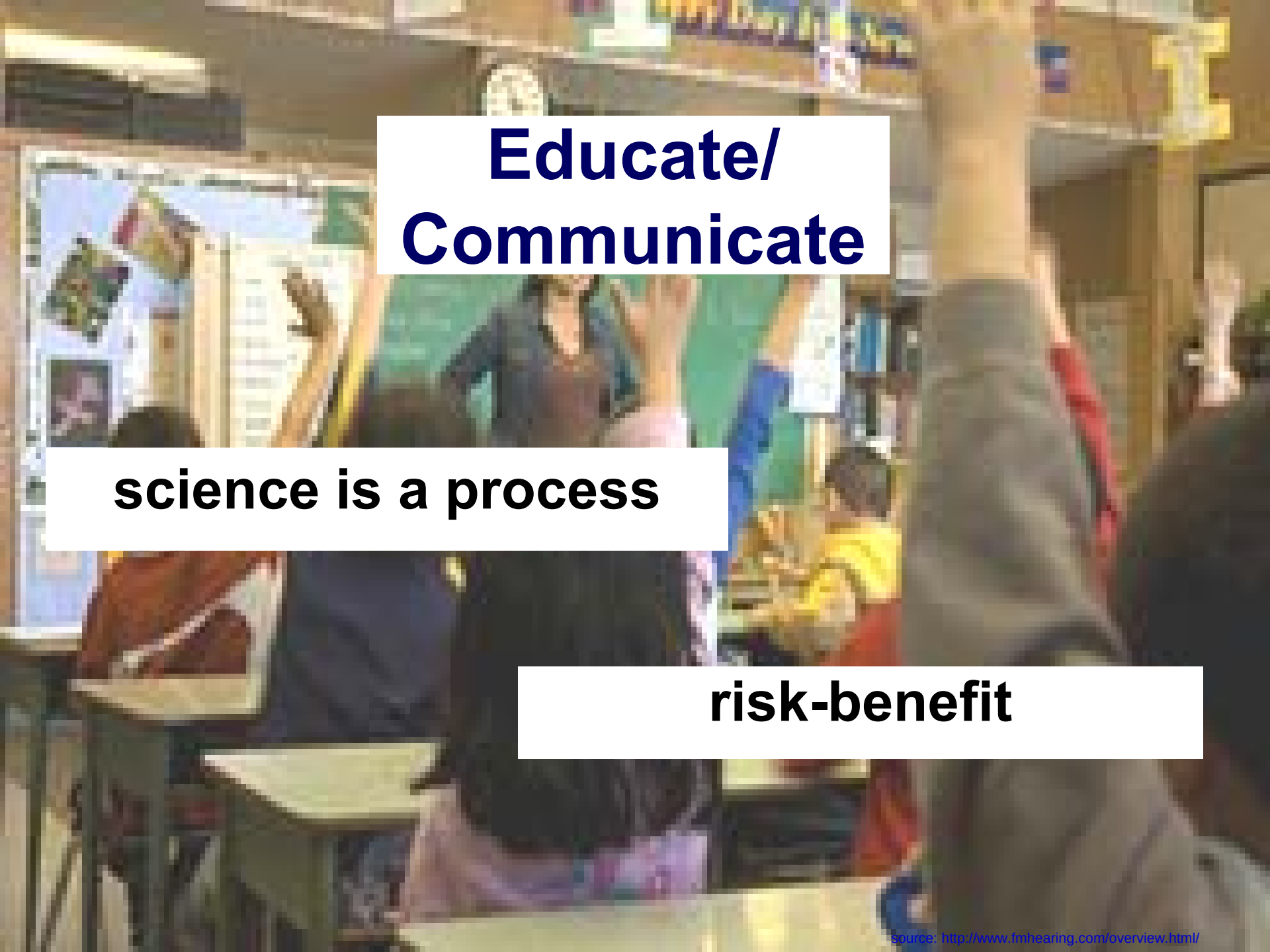
Chemical	Assumed primary mode of action
Bisphenol A	estrogenic
Butylbenzyl phthalate	estrogenic
17ß-Estradiol	estrogenic
Estrone	estrogenic
Ethynylestradiol	estrogenic
Kepone	estrogenic
Methoxychlor	estrogenic
4-Nonylphenol	estrogenic
Octylphenol	estrogenic
4,4-DDE	anti-androgenic
Di-n-butyl phthalate	estrogenic, anti-androgenic
Ketoconazole	anti-androgenic
Linuron	anti-androgenic
Mirex	anti-androgenic
Vinclozolin	anti-androgenic
Androstenidione	androgenic
Chlordane	androgenic
Methoxychlor	androgenic

- Compounds can have multiple MOAs and interact in complex ways
- This is only a *subset* of all possible compounds that may act on these endpoints:
  - Drugs
  - Industrial chemicals
  - Naturally present compounds
  - Endogenous hormones

Source: http://http://www.flickr.com/photos/ms_carrie-face/3402875218/

Conclusions

- Tens of thousands of PPCPs and EDCs potentially present in water
- No evidence of human health risk at current concentrations in drinking water *for compounds that have been measured*
- Continuing uncertainties and challenges
  - New compounds
  - Toxicology of mixtures
  - Considering other sources of exposure



Educate/ Communicate

science is a process

risk-benefit

source: http://www.fmhearing.com/overview.html/

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