The Role of Pharm*E*covigilance in Reducing the Environmental Footprint of Pharmaceuticals

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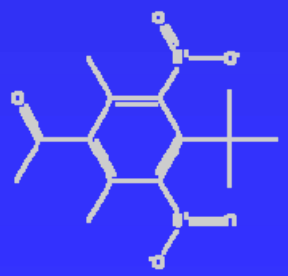
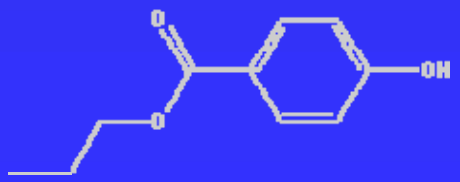
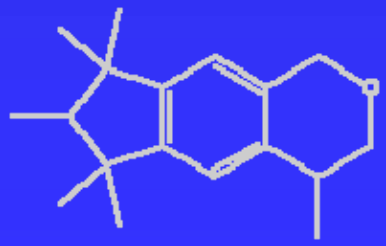
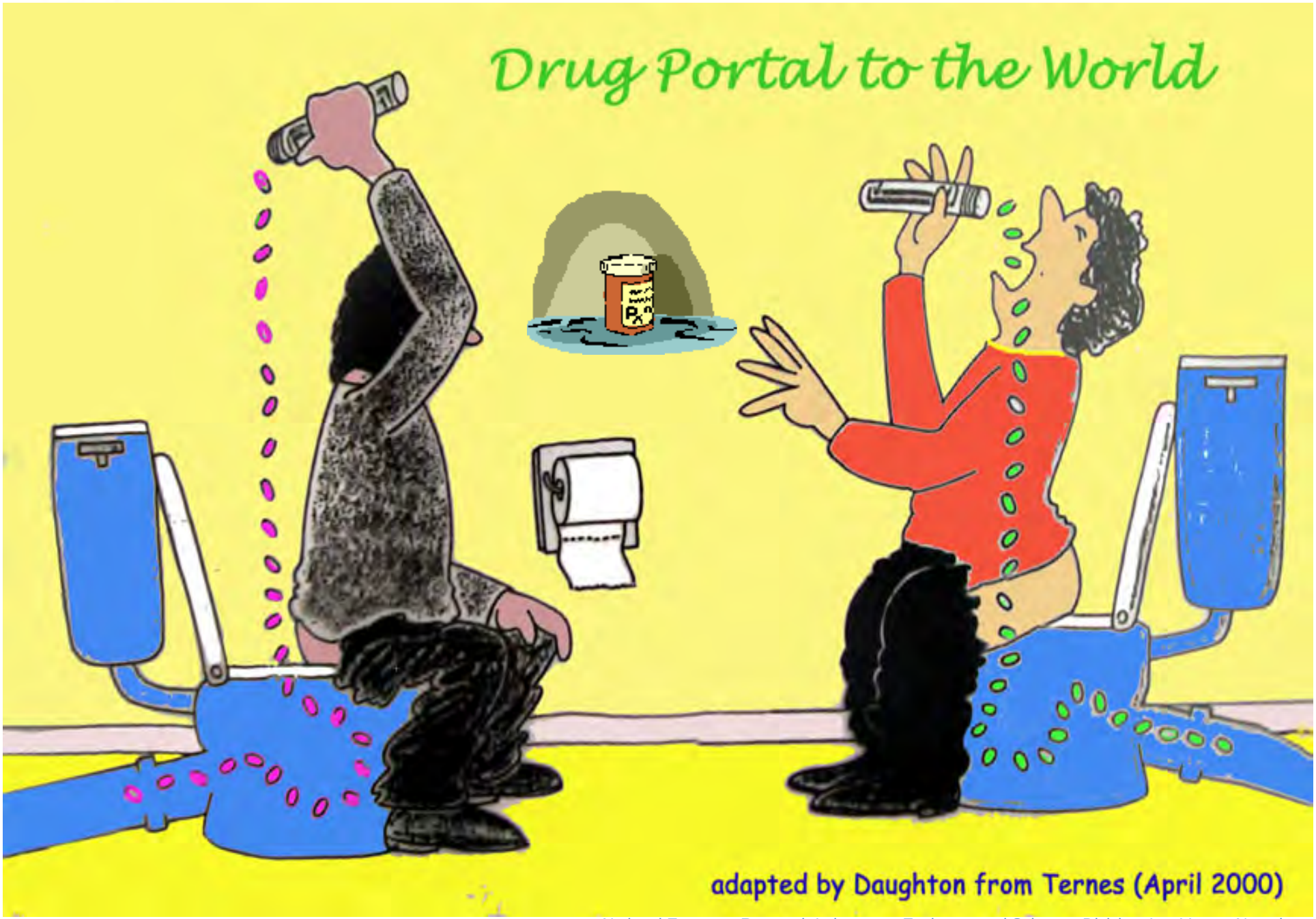
PPCPs as Environmental Pollutants?

PPCPs are a diverse group of chemicals comprising all human and veterinary drugs (available by prescription or over-the-counter, including the new genre of “biologics”), diagnostic agents (e.g., X-ray contrast media), “nutraceuticals” (bioactive food supplements such as huperzine A), and other consumer chemicals, such as fragrances (e.g., musks) and sun-screen agents (e.g., 4-methylbenzylidene camphor; octocrylene); also included are “excipients” (so-called “inert” ingredients used in PPCP manufacturing and formulation; e.g., parabens).








Drug Portal to the World
adapted by Daughton from Ternes (April 2000)

1st National Survey† Revealed Extent of PPCPs in Waterways

- **USGS "Reconnaissance" study in 1999-2000 was 1st nationwide investigation of pharmaceuticals, hormones, & other organic contaminants:**
  - 139 streams analyzed in 30 states
  - 82 contaminants identified (many were pharmaceuticals)
  - 80% streams had 1 or more contaminant
  - Average 7 contaminants identified per stream

- Since 1998, peer reviewed papers on PPCPs have increased from fewer than 200 per year to greater than 1,000 per year

† Kolpin DW,*et al.* "Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: a national reconnaissance." *Environmental Science & Technology* 2002, 36(6):1202-1211; *doi:10.1021/es011055j*

Prescription Drugs Found in Tap Water

Drug Disposal Overview

- Unused medications become pharmaceutical waste
  - Historically, consumers and other institutions have been advised to dispose of the drugs via the toilet or the trash

    Ultimately can enter the environment
  - If not disposed, concern is availability for inappropriate usage of drugs

    Diversion and poisonings
- Take-back events and programs
- Controlled Substances Act (CSA) 1970
- Stakeholders & Beneficiaries:

  EPA, DEA, ONDCP, FDA, USFWS, state and local governments, municipal water districts, pharmacy & pharmaceutical industries, healthcare industry, insurance industry

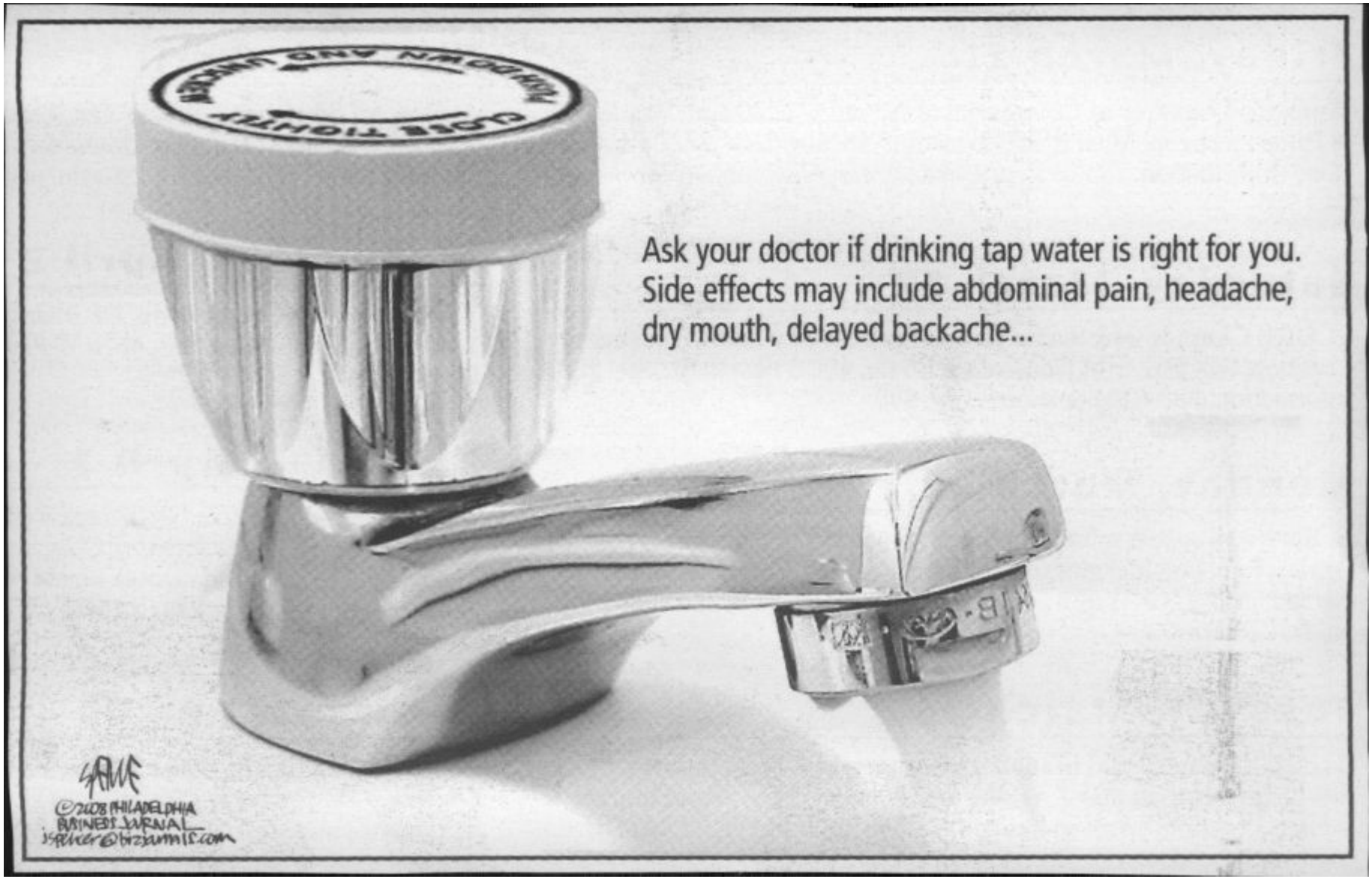

PROBE FINDS PHARMACEUTICALS IN U.S. DRINKING WATER
MOM, MAY I HAVE A GLASS OF MILK INSTEAD.
Tom Stiglich ©2008
WWW.TOMSTIGLICH.COM

Models of Change

- “Take-back” events
  - NERC
  - “No Drugs Down the Drain”
  - Great Lakes
  - US EPA grant
  - Various states
    - California, Pennsylvania, Indiana, Massachusetts, Oregon, Washington

National Guidance

- ONDCP guidelines, February 2007
  - Collaboration with FDA and EPA
  - Updated 2009, removed list of drugs to be disposed via sewers
- DEA, Controlled Substances Act
  - Recent ANPRM
    - Encouraged to standardize process for what constitutes an exemption for law enforcement personnel
    - Encouraged to standardize recordkeeping requirements
    - Define what constitutes an appropriate destruction of controlled substances
    - Asked to consider many collection options for take back programs

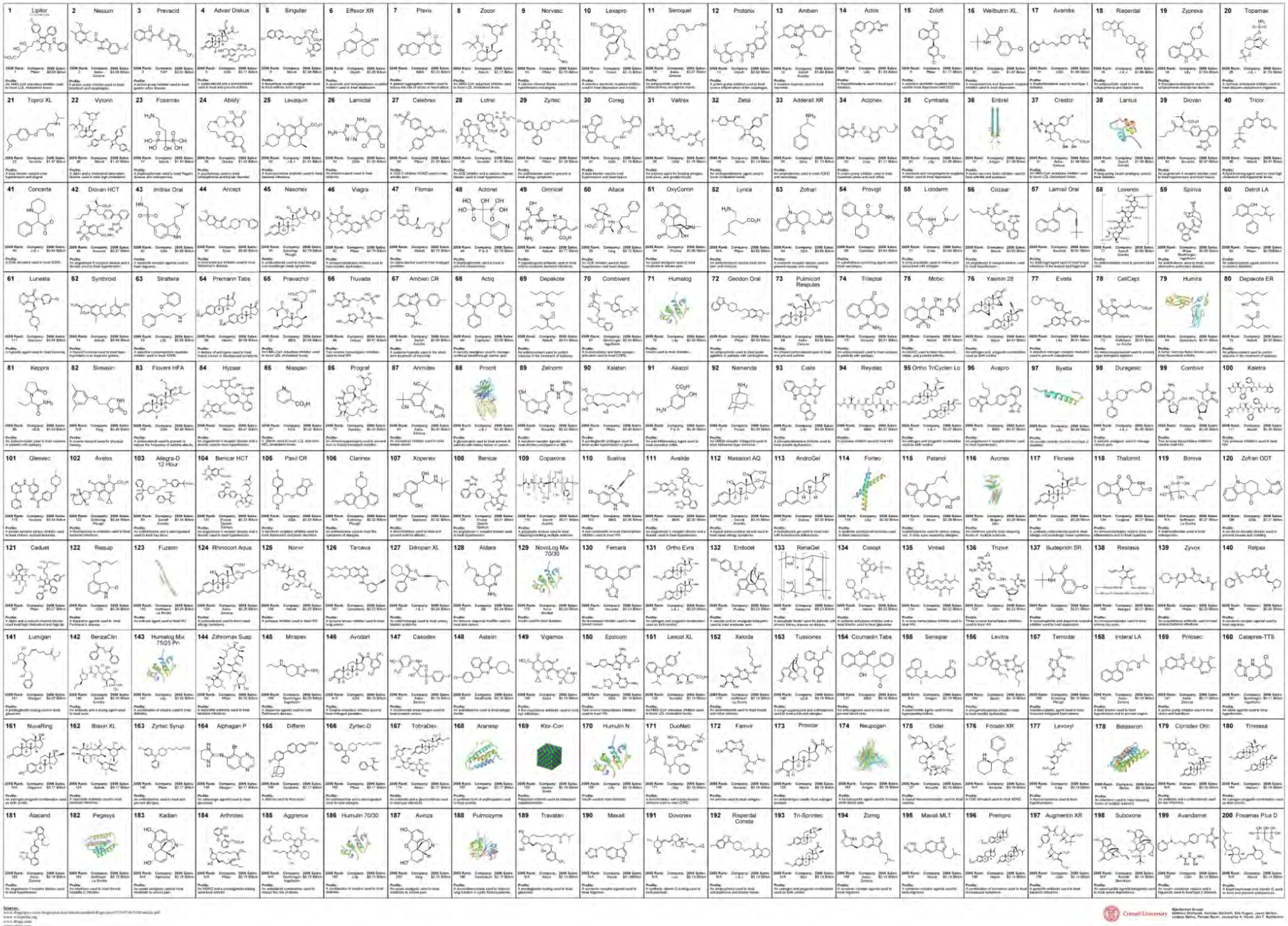

Ask your doctor if drinking tap water is right for you.
Side effects may include abdominal pain, headache,
dry mouth, delayed backache...
©2008 PHILADELPHIA
BUSINESS JOURNAL

A Clarification

In this presentation, the actual chemical substances with which we are concerned regarding contamination of the environment are the active ingredients in pharmaceuticals – known in the industry as **APIs**. But we sometimes loosely (but incorrectly) refer to drugs or pharmaceuticals as being the contaminants themselves

These terms are all often used interchangeably

200 Top-Selling Prescribed Drugs (2006)


1 Lipitor
2 Nexium
3 Prevacid
4 Advair Diskus
5 Singulair
6 Effexor XR
7 Plavix
8 Zocor
9 Norvasc
10 Lexapro
11 Seroquel
12 Protonix
13 Ambien
14 Actos
15 Zoloft
16 Wellbutrin XL
17 Avandia
18 Risperdal
19 Zyprexa
20 Topamax
21 Toprol XL
22 Vytorin
23 Fosamax
24 Abilify
25 Levaquin
26 Lamictal
27 Celebrex
28 Lotrel
29 Zyrtec
30 Coreg
31 Valtrex
32 Zetia
33 Adderall XR
34 Aciphex
35 Cymbalta
36 Enbrel
37 Crestor
38 Lantus
39 Diovan
40 Tricor
41 Concerta
42 Diovan HCT
43 Imitrex Oral
44 Aricept
45 Nasonex
46 Viagra
47 Flomax
48 Actonel
49 Omnicef
50 Altace
51 OxyContin
52 Lyrica
53 Zofran
54 Provigil
55 Lidoderm
56 Cozaar
57 Lamisil Oral
58 Lovenox
59 Spiriva
60 Detrol LA
61 Lunesta
62 Synthroid
63 Strattera
64 Premarin Tabs
65 Pravachol
66 Truvada
67 Ambien CR
68 Actiq
69 Depakote
70 Combivent
71 Humalog
72 Geodon Oral
73 Pulmicort Respules
74 Trileptal
75 Mobic
76 Yasmin 28
77 Evista
78 CellCept
79 Humira
80 Depakote ER
81 Keppra
82 Skelaxin
83 Flovent HFA
84 Hyzaar
85 Niaspan
86 Prograf
87 Arimidex
88 Procrit
89 Zelnorm
90 Xalatan
91 Asacol
92 Namenda
93 Cialis
94 Reyataz
95 Ortho TriCyclen Lo
96 Avapro
97 Byetta
98 Duragesic
99 Combivir
100 Kaletra
101 Gleevec
102 Avelox
103 Allegra-D 12 Hour
104 Benicar HCT
105 Paxil CR
106 Clarinex
107 Xopenex
108 Benicar
109 Copaxone
110 Sustiva
111 Avalide
112 Nasacort AQ
113 AndroGel
114 Forteo
115 Patanol
116 Avonex
117 Flonase
118 Thalomid
119 Boniva
120 Zofran ODT
121 Caduet
122 Requip
123 Fuzeon
124 Rhinocort Aqua
125 Norvir
126 Tarceva
127 Ditropan XL
128 Aldara
129 NovoLog Mix 70/30
130 Femara
131 Ortho Evra
132 Endocet
133 RenaGel
134 Cosopt
135 Viread
136 Trizivir
137 Budeprion SR
138 Restasis
139 Zyvox
140 Relpax
141 Lumigan
142 BenzaClin
143 Humalog Mix 75/25 Pn
144 Zithromax Susp
145 Mirapex
146 Avodart
147 Casodex
148 Astelin
149 Vigamox
150 Epzicom
151 Lescol XL
152 Xeloda
153 Tussionex
154 Coumadin Tabs
155 Sensipar
156 Levitra
157 Temodar
158 Inderal LA
159 Prilosec
160 Catapres-TTS
161 NuvaRing
162 Biaxin XL
163 Zyrtec Syrup
164 Alphagan P
165 Differin
166 Zyrtec-D
167 TobraDex
168 Aranesp
169 Klor-Con
170 Humulin N
171 DuoNeb
172 Famvir
173 Proscar
174 Neupogen
175 Elidel
176 Focalin XR
177 Levoxyl
178 Betaseron
179 Ciprodex Otic
180 Trinessa
181 Atacand
182 Pegasys
183 Kadian
184 Arthrotec
185 Aggrenox
186 Humulin 70/30
187 Avinza
188 Pulmozyme
189 Travatan
190 Maxalt
191 Dovonex
192 Risperdal Consta
193 Tri-Sprintec
194 Zomig
195 Maxalt MLT
196 Prempro
197 Augmentin XR
198 Suboxone
199 Avandamet
200 Fosamax Plus D
Sources:
Cornell University

Global Problem of Humanitarian Donations

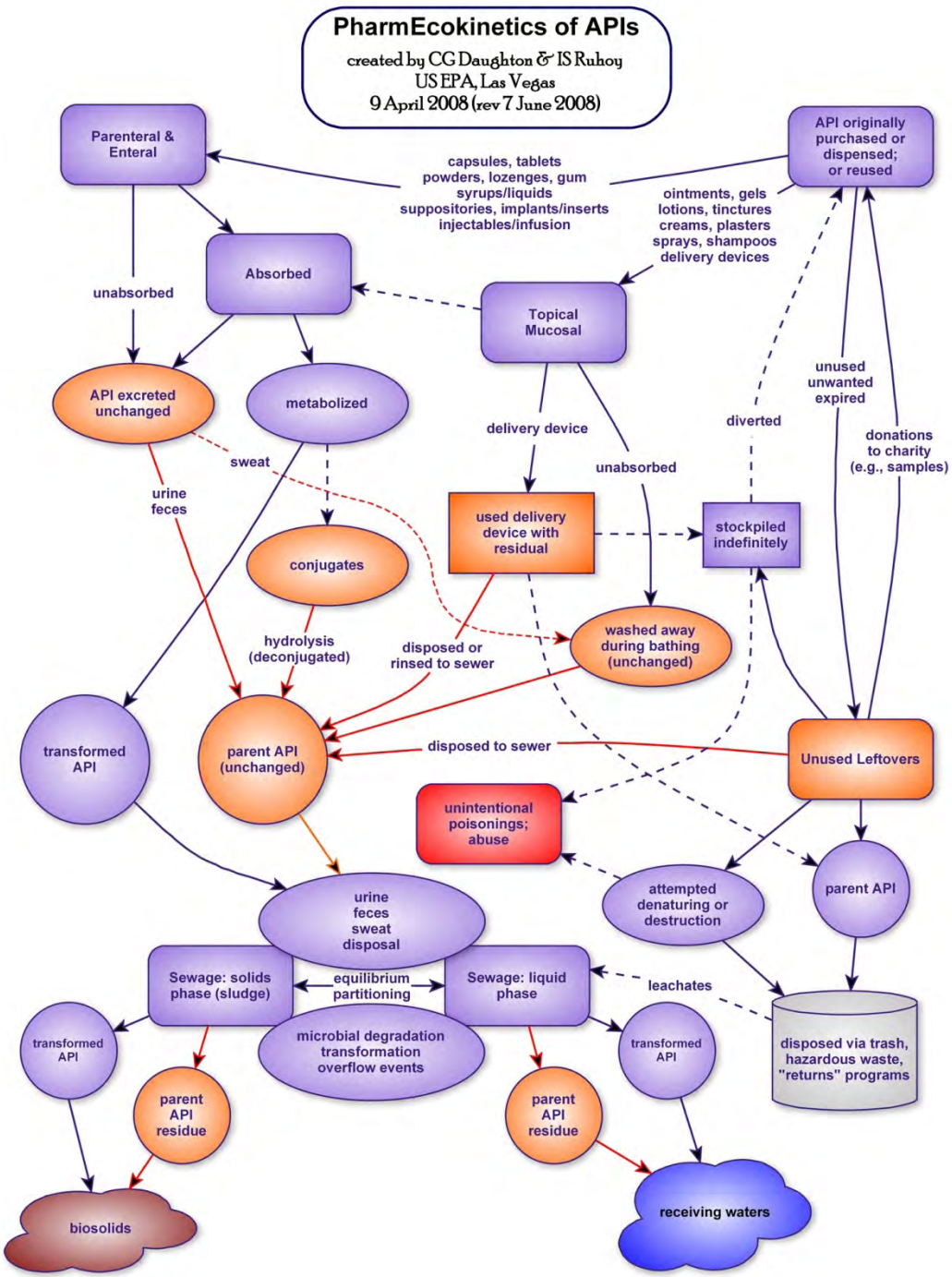
Hospital collection site for donated pharmaceuticals (Banda Aceh, Indonesia)

Environmental Impact of Disposal

- APIs enter the environment by three primary routes: excretion, bathing, and disposal of leftover, unwanted medications
  - Excretion (primarily via urine and secondarily via feces) comprises continual low-level contributions from multitudes of people
  - Bathing releases APIs from medications applied directly to the skin and excreted via sweat †
  - Disposal represents acute but transient and episodic contributions from fewer people
    - The only route that is most amenable to pollution prevention or source control measures is disposal
- Indirect entry can occur via disposal of unwanted drugs and used delivery devices to trash (e.g., in leachates from landfills)
- **Proper disposal is greatly complicated by the conflict between the need to protect public safety and the need to minimize aquatic (and terrestrial) exposure**

† Daughton CG and Ruhoy IS "Environmental Footprint of Pharmaceuticals - The Significance of Factors Beyond Direct Excretion to Sewers," *Environmental Toxicology & Chemistry*, in press.


Environmental Life-Cycle of Pharmaceuticals
created by CG Daughton
US EPA, Las Vegas
2 December 2006
transformation/degradation
mineralization
stewardship opportunities
Manufacturer
Commerce distribution
Wholesalers Distributors
Agriculture (e.g., orchards)
runoff
excrement
pets
euthanized carcasses
potential for acute/chronic poisoning of wildlife scavengers
carcasses of medicated animals
domestic animals
airborne dusts (e.g., medicated feed)
occupational human pulmonary exposure
CAFOs
Aquaculture
physician samples
Physicians
Feedstores
Vet use
prescribing
dispensing pharmacies Rx & OTC
unsold product
Reverse distributors
waste residuals pretreatment
humanitarian donations: excess or unusable leftovers
atmospheric release (e.g., anaesthetics)
sloughing of antibiotic-resistant bacteria/genes
Waste Treatment (e.g., lagoons)
manure solids
Soil amendment/ disposal
Take-Backs, Mail-Backs, Collection events
Human consumer use
Gene Exchange multi-drug resistance
exposure to resistant bacteria
naturally occurring bacteria
Incineration
unused/expired leftovers
LTCFs Hospitals Hospice
Leftover medications
Stored awaiting disposal
Diversion Abuse (e.g., pharming)
acute poisonings: accidental & purposeful
diversion by gleaners
Landfill
trash
RCRA Hazardous Waste
release of dermal products from bathing
excretion from oral & parenteral use
Disposal by consumer
trash
Incineration
Waste Treatment
toilet
groundwater (artificial recharge, colloidal transport)
Aquatic exposure
toilet or sewerage
Disposal by Coroner's
research of Ruhoy 2006
optional
Law enforcement (controlled substances)
sediments (sorption)
straightpiping & overflow events
runoff
leachates
landfill
Plant-Made Pharmaceuticals (PMPs)
finished drinking water treatment
receiving waters
Waste Treatment
Sludge Biosolids
Soil Amendment
groundwater
Molecular Pharming
"toilet-to-tap"
drug residues & transformation by-products
Recreation
Advanced Treatment (recycling)
aqueous effluent
irrigation
PMPs cross-contaminating food supply
Wildlife exposure from grazing/ foraging
Chronic, Low-Level, Incidental Human Exposure
Oral & Dermal
uptake by plants & crops
uptake by soil-dwelling organisms


PharmEcokinetics of APIs
created by CG Daughton & IS Ruhoy
US EPA, Las Vegas
9 April 2008 (rev 7 June 2008)
Parenteral & Enteral
capsules, tablets
powders, lozenges, gum
syrups/liquids
suppositories, implants/inserts
injectables/infusion
API originally purchased or dispensed; or reused
ointments, gels
lotions, tinctures
creams, plasters
sprays, shampoos
delivery devices
unabsorbed
Absorbed
Topical Mucosal
API excreted unchanged
metabolized
delivery device
diverted
unused unwanted expired
donations to charity (e.g., samples)
sweat
urine
feces
unabsorbed
used delivery device with residual
stockpiled indefinitely
conjugates
hydrolysis (deconjugated)
disposed or rinsed to sewer
washed away during bathing (unchanged)
transformed API
parent API (unchanged)
disposed to sewer
Unused Leftovers
unintentional poisonings; abuse
attempted denaturing or destruction
parent API
urine
feces
sweat
disposal
Sewage: solids phase (sludge)
equilibrium partitioning
Sewage: liquid phase
leachates
transformed API
microbial degradation
transformation
overflow events
transformed API
disposed via trash, hazardous waste, "returns" programs
parent API residue
parent API residue
biosolids
receiving waters


I'M GOING TO PRESCRIBE A BIRTH CONTROL PILL AND AN ANTIBIOTIC AND A TRANQUILIZER! OR YOU CAN DRINK TWO QUARTS OF TAP WATER, AND CALL ME IN THE MORNING!
3/11
DARKOW
COLUMBIA DAILY TRIBUNE
CAGLECARTOONS.COM
2008

Environmental Concerns

- Treatment (palliative, symptomatic and sometimes curative) and prevention of disease, together with improved quality of life, are highly visible aspects of a global pharmaceutical industry with sales in 2007 exceeding US$700BN

- Medicines are designed to have biological effects in small doses
  - Non-target organisms can be exposed
  - Possible subtle effects in aquatic organisms at very low concentrations (as low as ng/L or parts per trillion [ppt])
- There are thousands of chemically distinct APIs in medicines
  - Potential for synergistic effects with other medicines and/or other contaminants

Environmental Concerns

- Pharmaceutical Facility Waste Streams
  - India; in one instance, the levels of the most abundant API [ciprofloxacin] reached 31 mg/L [31 ppm] at a waste treatment facility, orders of magnitude higher than had ever been reported (*Larsson et al. 2007*)
  - "Health facilities flush estimated 250M pounds of drugs a year"

  USA Today, 9/08

Environmental Pollution

- Water treatment
  - Situations where sewage receives minimal or no treatment
    - Septic systems, straight-piping, storm over-flow
  - Conventional
    - Flocculation, coagulation, filtration
  - Advanced
    - Chlorination
    - Ozonation, reverse osmosis, activated carbon, nanofiltration
- Some APIs are STILL refractory
  - For example, carbamazepine, ibuprofen, 17α-ethinylestradiol, meprobomate, dilantin, contrast agents, chemotherapeutics, some β-blockers
  - Not just parent APIs
    - Some metabolites, degradates, and transformation products can be more mobile, more persistent, and potentially as toxic

Effects on Aquatic Organisms: Cause for Concern

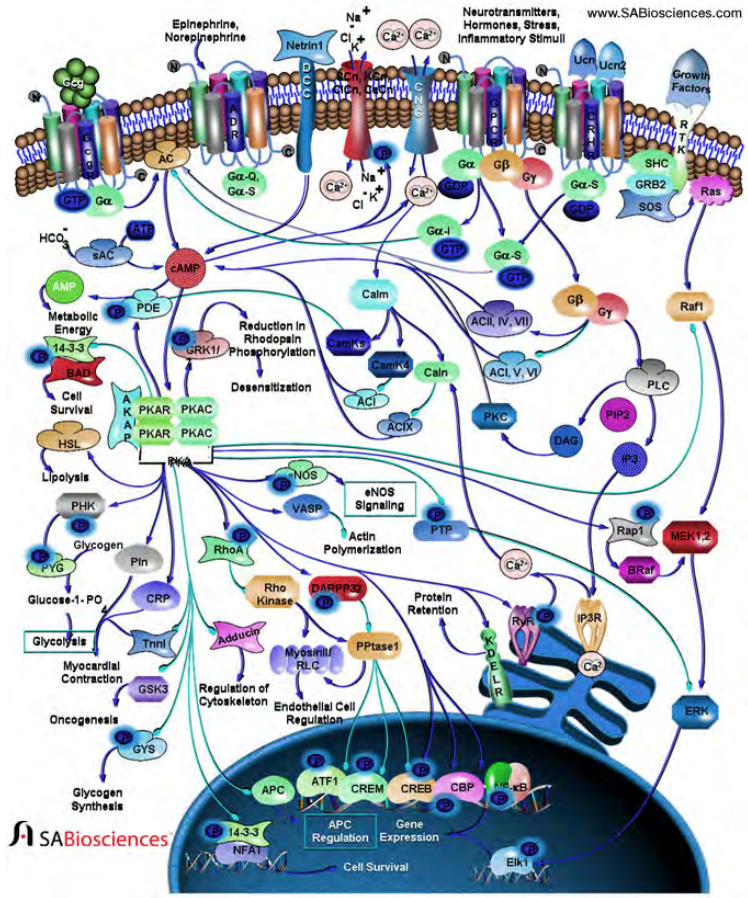
- "Pseudo-persistence"
  - –Continuous, multigenerational exposure
- May be endocrine disruptors
  - –alterations to sexual differentiation
    - Boulder Creek (feminization)
    - Potomac River (intersex)
  - –reproduction and growth impairments
    - Antidepressants and frogs
  - –subtle, behavioral effects
- More questions than answers about effects of APIs on aquatic species and the possibility of chronic effects in sensitive subpopulations of humans

Effects

- Ecological
  - Sex ratios
  - Feminization
  - Behavioral/Social
  - Neurological
  - Growth
- Human Effects
  - Largely unknown
  - Food chain
  - Antibiotic resistance
- Unintended Exposure in Vulnerable Populations
  - Faeroe Island Statement

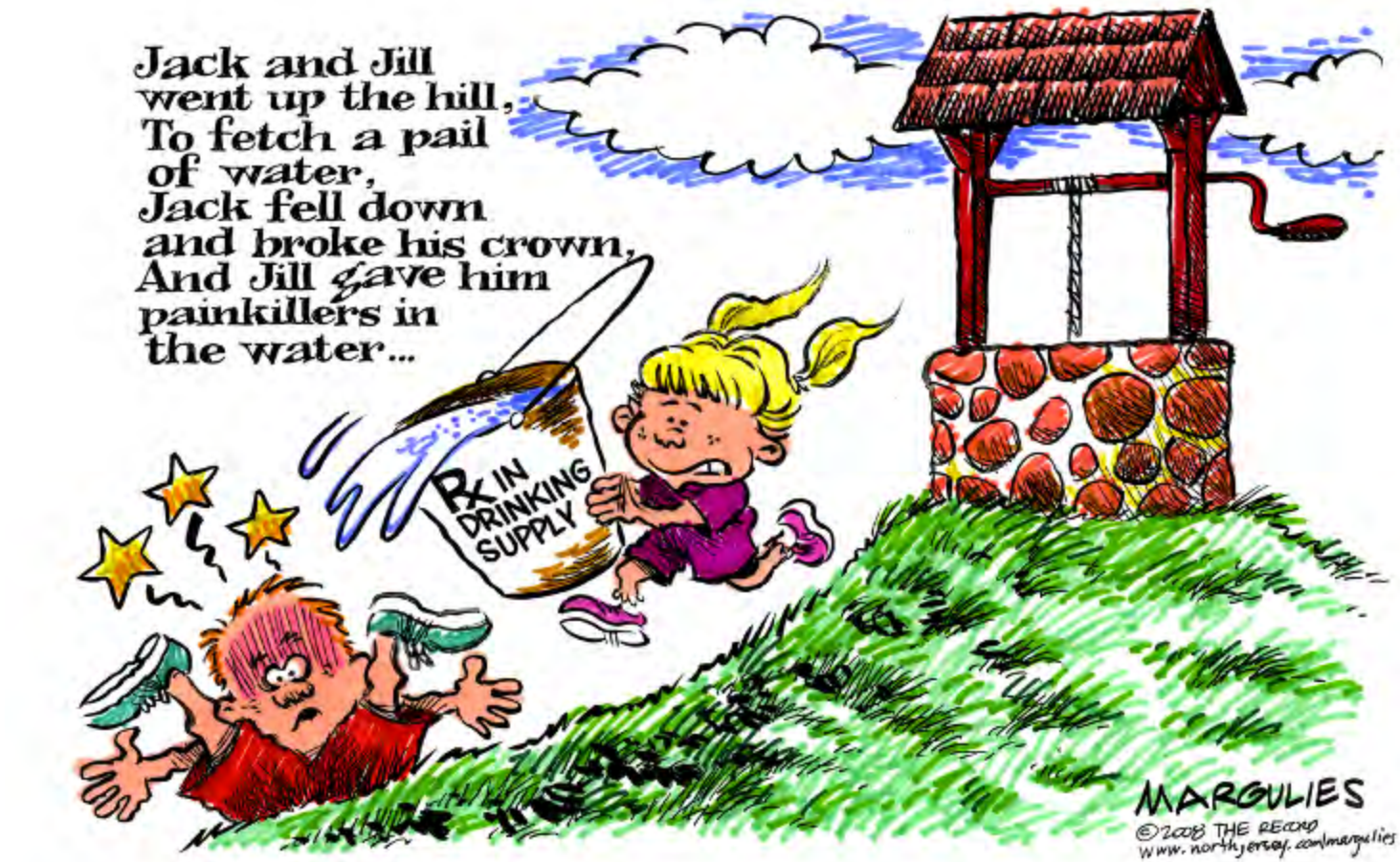
FDA – environmental risk assessment

  - Short term tests that measure how much of a compound is required to kill an organism outright or stunt its growth in a matter of days

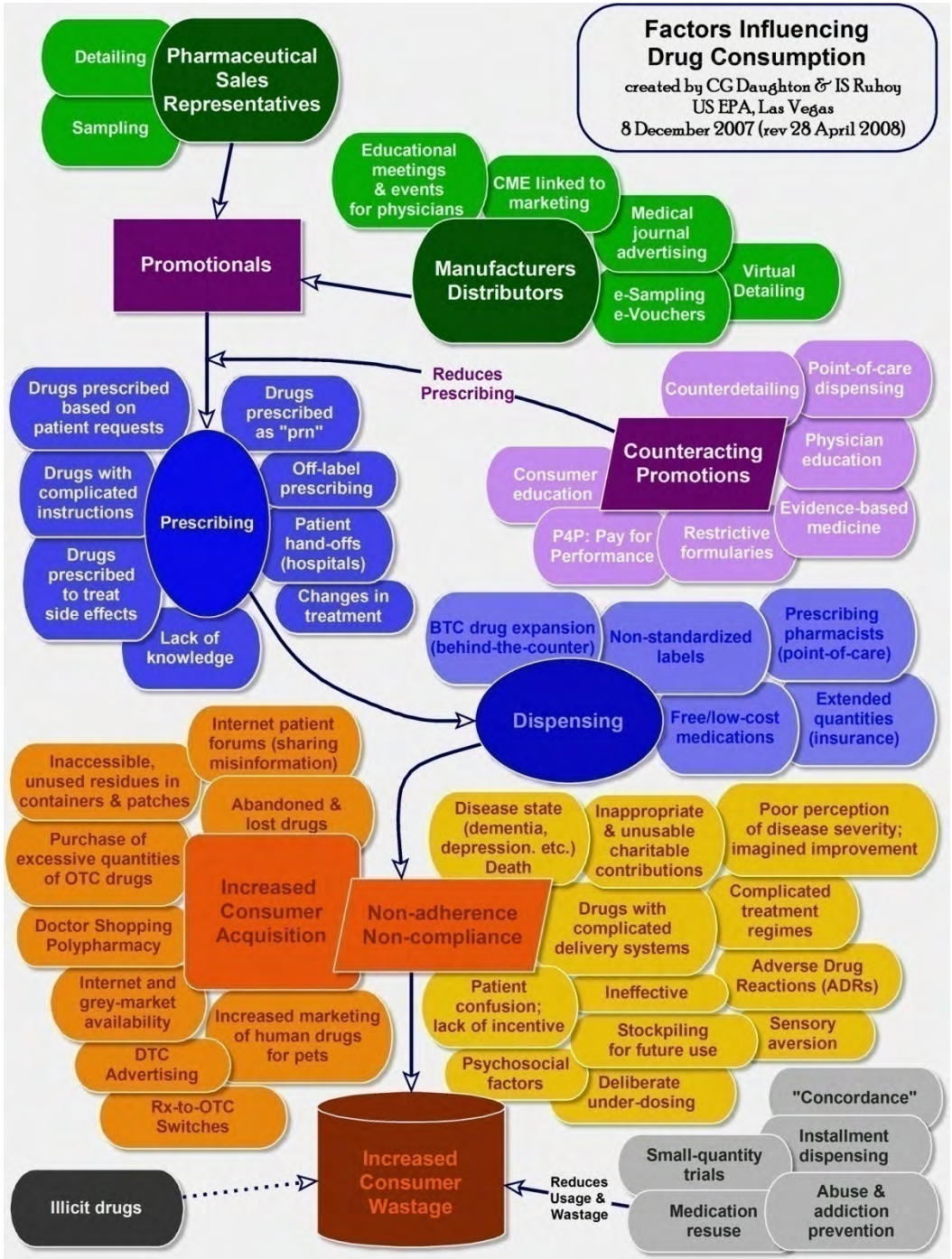


Human Exposure

- Function of:
  - Identities, quantities, & geographic distribution of APIs
  - ADME
  - Major source of unchanged APIs: unwanted, leftover drugs
  - Environmental transport
  - Environmental fate
  - Exposure routes


Jack and Jill
went up the hill,
To fetch a pail
of water,
Jack fell down
and broke his crown,
And Jill gave him
painkillers in
the water...
Rx IN DRINKING SUPPLY
MARGULIES
©2008 THE RECORD
www.northjersey.com/margulies

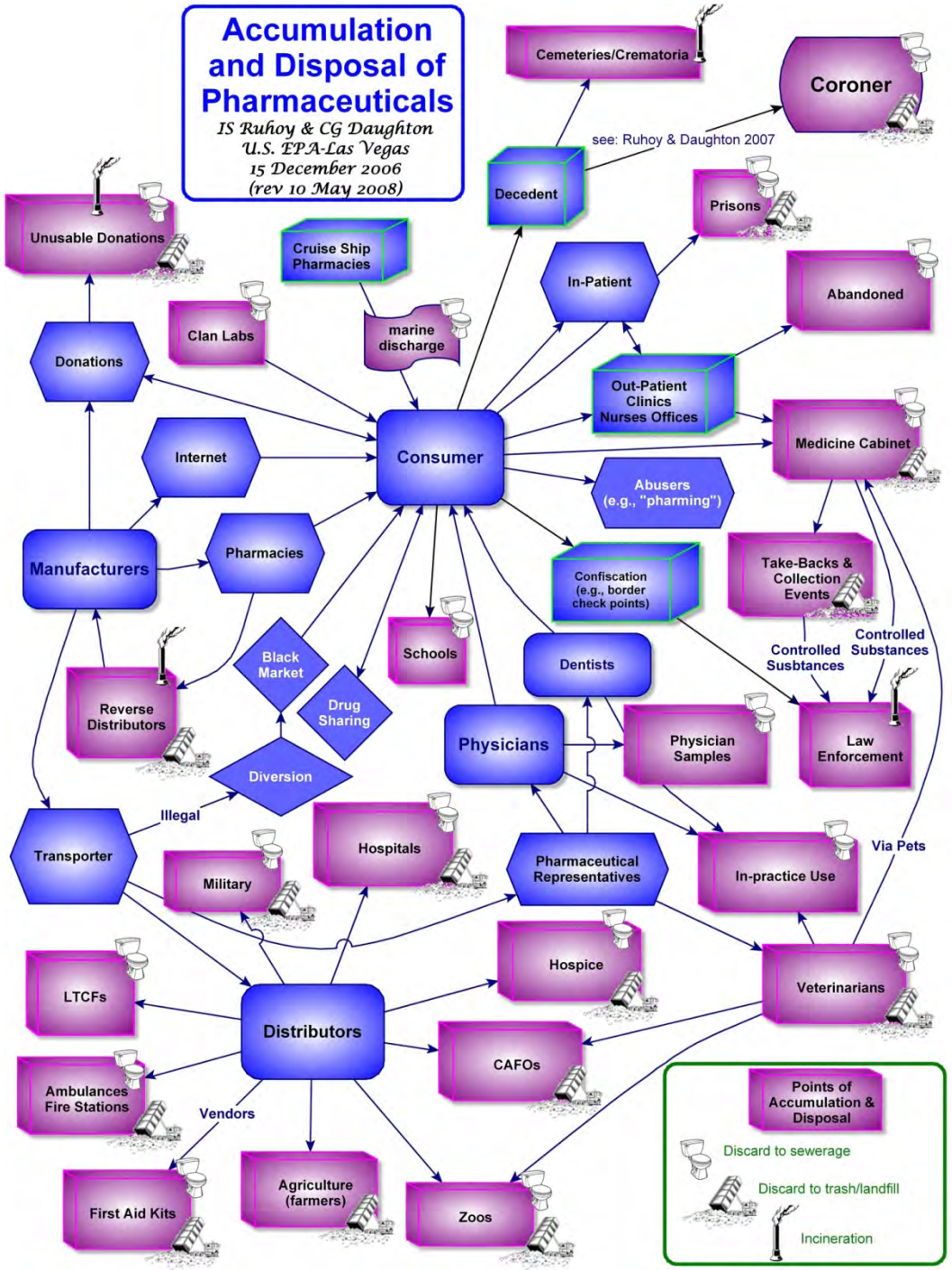

I'M NOT FEELING WELL. I'M GOING TO RUN OVER TO THE PHARMACY.
LAS VEGAS SUN 2008 KING FEATURES SYNDICATE
MIKE SMITH



Ruhoy IS and Daughton CG "Beyond the Medicine Cabinet: An Analysis of Where and Why Medications Accumulate," *Environ. Internat.*, **2008**, *34*(8):1157-1169; doi:10.1016/j.envint.2008.05.002; available: http://www.epa.gov/nerlesd1/bios/daughton/EnvInt2008.pdf

Pharmaceutical Accumulation

- Consumer Homes
  - Both human and animal medicine
- Physician Offices and Clinics
  - Samples and in-office procedure use
- Veterinarian Offices
- Animal Shelters
- Dental Offices
- Hospitals
- Long-Term and Chronic Care Facilities
- Decedent Homes
- Donations
- Schools (confiscation and health care offices)
- Military Bases
- Shelters
- Dialysis Centers
- Transfusion Centers
- First Responder Services
- First-Aid Kits
- Border Check Points
- Customs (airline and freight)
- Confined Animal Feeding Operations (CAFOs)
- Agriculture
- Aquaculture
- Zoos
- Clan Labs
- Cemeteries
- Cruise Ships
- Prisons and Jails
- Humanitarian Organizations



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Major Unknown

- **What fractions of drug residues occurring in the ambient environment result from discarding leftover drugs?**
  - No studies provided objective data from well-defined populations to support any type of conclusion
  - Data are needed on the types, quantities, and frequencies with which drugs accumulate as household waste

Mining Data for Types and Quantities of Disposed Drugs

- Understanding the categories and quantities of drugs disposed facilitates assessing potential impacts on both the environment and human health by helping:
  - health care practitioners to address inefficient prescribing and dispensing practices and patient non-compliance
  - environmental scientists to better target APIs for monitoring purposes
  - assessment of risk to human health from chronic and/or acute exposures
  - policymakers (including those in the insurance industry) to begin to understand and confront the growing issue of wasted and discarded medications.

Summary of API Masses Disposed to Sewerage by a Coroner Office during a 12-Month Period: Categorized by Therapeutic Class

ATC Code	ATC Main Group	Quantity (mg) disposed	#of APIs	% of Total
A	Alimentary Tract	18,685,271	56	34.6
N	Nervous System	16,510,963	95	30.6
C	Cardiovascular System	6,331,976	71	11.7
J	Anti-infectives	5,608,735	45	10.4
M	Musculoskeletal System	3,851,949	21	7.1
R	Respiratory System	984,780	16	1.8
B	Blood	721,450	9	1.3
V	Various	622,800	1	1.2
P	Antiparasitics	236,269	2	0.44
L	Antineoplastics	186,013	14	0.34
G	GU System & Sex Hormones	146,440	23	0.27
H	Hormonal Preparations	50,601	10	0.09
S	Sensory Organs	4,375	1	0.008
D	Dermatologicals	3,420	3	0.006
TOTAL		53,945,042	367	

Ruhoy IS and Daughton CG "Beyond the Medicine Cabinet: An Analysis of Where and Why Medications Accumulate," *Environ. Internat.*, **2008**, *34*(8):1157-1169; doi:10.1016/j.envint.2008.05.002; available: http://www.epa.gov/nerlesd1/bios/daughton/EnvInt2008.pdf

Ultimate Objective: <u>No Leftover Drugs</u>

long-term focus should not be on how to properly dispose of drugs, but rather how to minimize the creation of drug waste

Actions to reduce APIs in the environment and protect human health & safety

- Unit dosing
- Trial scripts
- Low-quantity packaging of OTC medications
- Increased monitoring of patient
- Implement practice of concordance
- Samples and donations
- Reduce incentives for excessive purchasing
- Personalized medicine (e.g., lower doses)
- Reduce polypharmacy
- Lower doses via non-racemic APIs
- Prescribers to account for possible environmental impact
- Widespread implementation of sustainable take-back programs

Key questions

- Pharmaceutical occurrence in point-of-use drinking water and in foods
- Toxicological significance of long-term human exposure to multiple pharmaceuticals
- Vulnerable sub-populations
- Prioritization of individual drug entities with respect to human hazard
- Portion of residues that originates from disposal of unwanted medications versus excretion
- Portion of human poisonings resulting from accidental ingestion and abuse of diverted drugs that are stored
- Significance of antibiotic residues in environment with respect to evolution of pathogen resistance

Current Federal Activities

- Research—USEPA, USGS, FDA, CDC, NOAA, FWS, ARS, and others are evaluating environmental occurrence, effects, and treatment & stewardship options; coordination through Interagency PiE working group (under CENR).
- Policy
  - USEPA – UWR & Health Services Industry Study
  - DEA – CSA & impact on drug "take backs"
- Disposal guidelines
  - Office of National Drug Control Policy (revised 3/09)
  - US Fish & Wildlife/APhA/PhRMA SMARxT program


Mike Keefe THE DENVER POST 05/13/08
ASK YOUR DOCTOR IF TAP WATER IS RIGHT FOR YOU.

Pharm*Eco*vigilance

Conventional pharmacovigilance expanded beyond conventional focus on ADRs to encompass environmental concerns

Unify the parallel but interconnected needs for protecting both human and ecological health

Daughton CG and Ruhoy IS "The Afterlife of Drugs and the Role of PharmEcovigilance," *Drug Safety,* **2008**, *31*(12):1069-1082; doi: 10.2165/0002018-200831120-00004.

Models of Change

- European Union
  - "Green" drugs – requires pharmaceutical companies to analyze environmental risks of new drugs
    - Database available to physicians
- KNAPPE
  - **K**nowledge and **N**eed **A**ssessment on **P**harmaceutical **P**roducts in **E**nvironmental Waters
- In Sweden systems for classification of drug environmental risk and hazard have been used for 5 years
- High Performance Pharmacy Framework

Stewardship

- Stewardship involves much more than prudent disposal of leftover drugs
  - Actions taken to reduce PPCPs in the environment will have collateral benefits in also capturing chemicals we are currently not aware of and may lessen human morbidity and mortality

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The Role of Pharm*E*covigilance in Reducing the Environmental Footprint of Pharmaceuticals

GreenPharma Summit Webinar

Institute for International Research

April 14, 2009