Pharmaceuticals and EDCs in Water Suplies – Cause for Concern?

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Overview

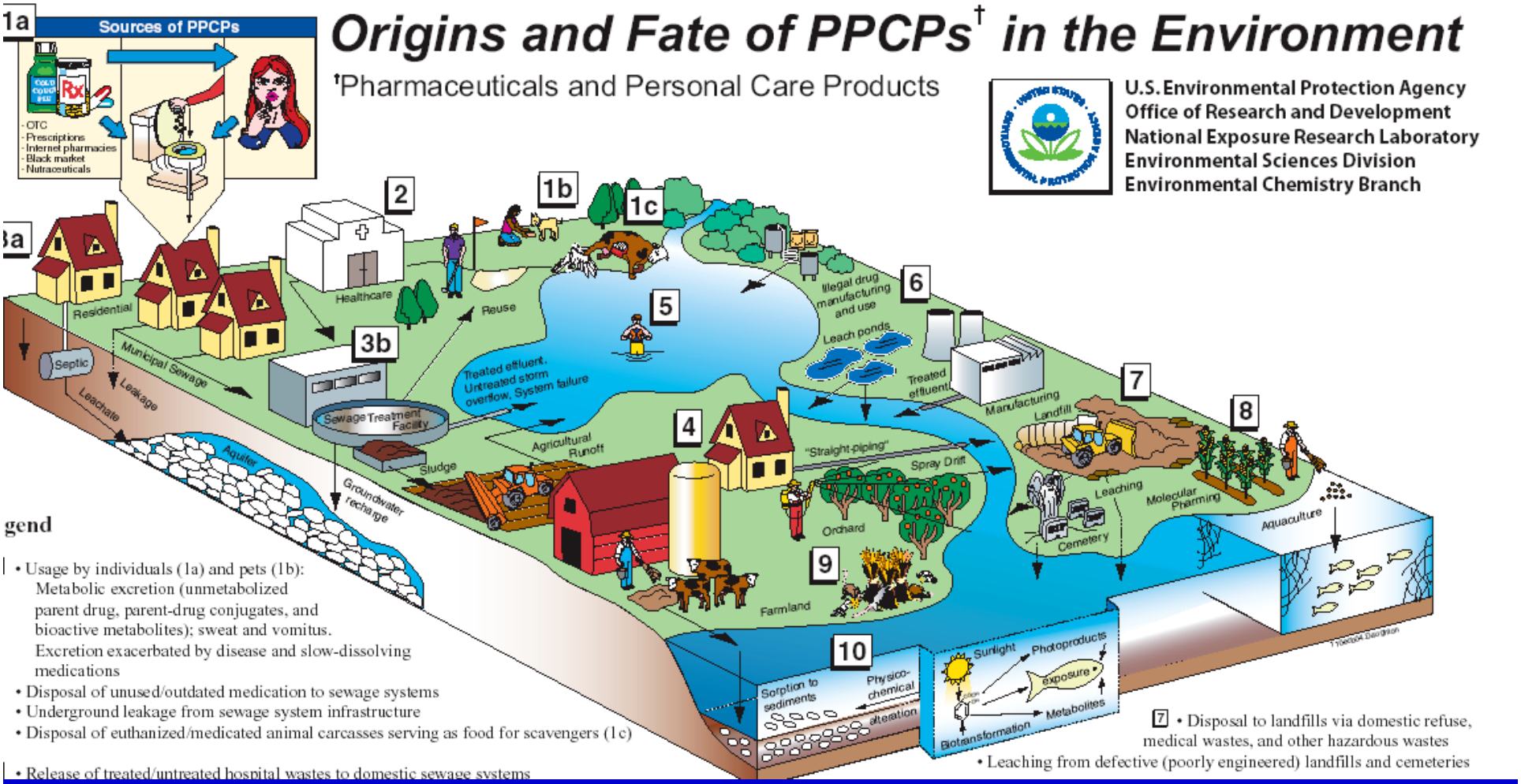
- Sources and effects of PPCPs at detected concentrations?
- Effectiveness of common water treatment technologies?
- Can water and wastewater treatment reduce the concentration of PPCPs?
- Research efforts by the consumer care and pharmaceutical industries

What are emerging contaminants?

- Personal care products – deodorants, shampoos, hair products, perfumes
- Pharmaceuticals, including lifestyle drugs

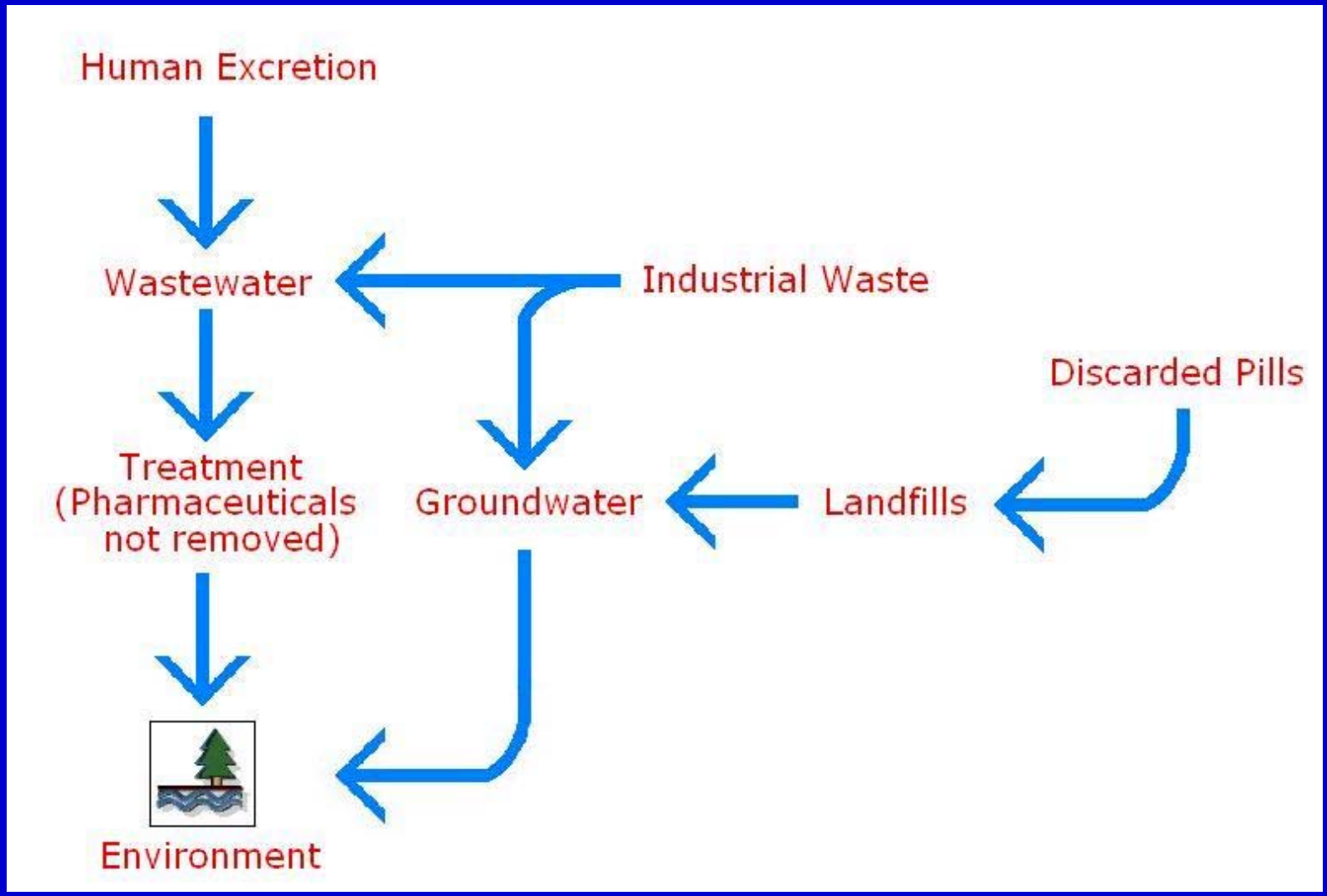
"Everything can be found everywhere"

"The dose determines the poison"



Credit: US EPA, Las Vegas

Modes of Pharmaceutical Entry



German Study, 1998 (Ternes)

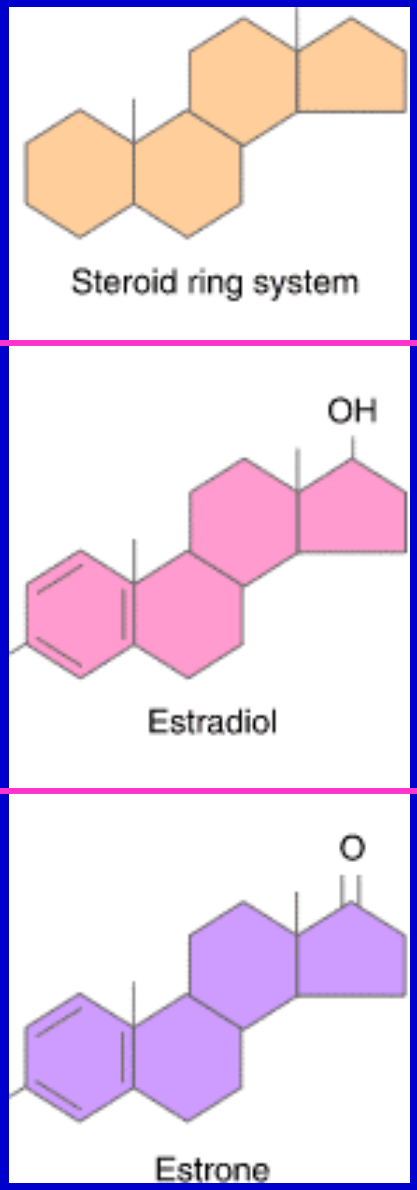
- First major assessment of multiple chemicals in wastewater and surface water
- Analyzed concentrations of 32 pharmaceuticals in six different classes
- Many pharmaceuticals classified as “relevant environmental chemicals” as a result of study

U.S. Geological Survey, 2002

- Most comprehensive assessment to date of chemicals in surface water
- Analyzed concentrations of 95 pharmaceuticals, hormones, and organic contaminants
- Detectable levels of chemicals found at 111 of 139 sites

Endocrine Disruption?

The fundamentals

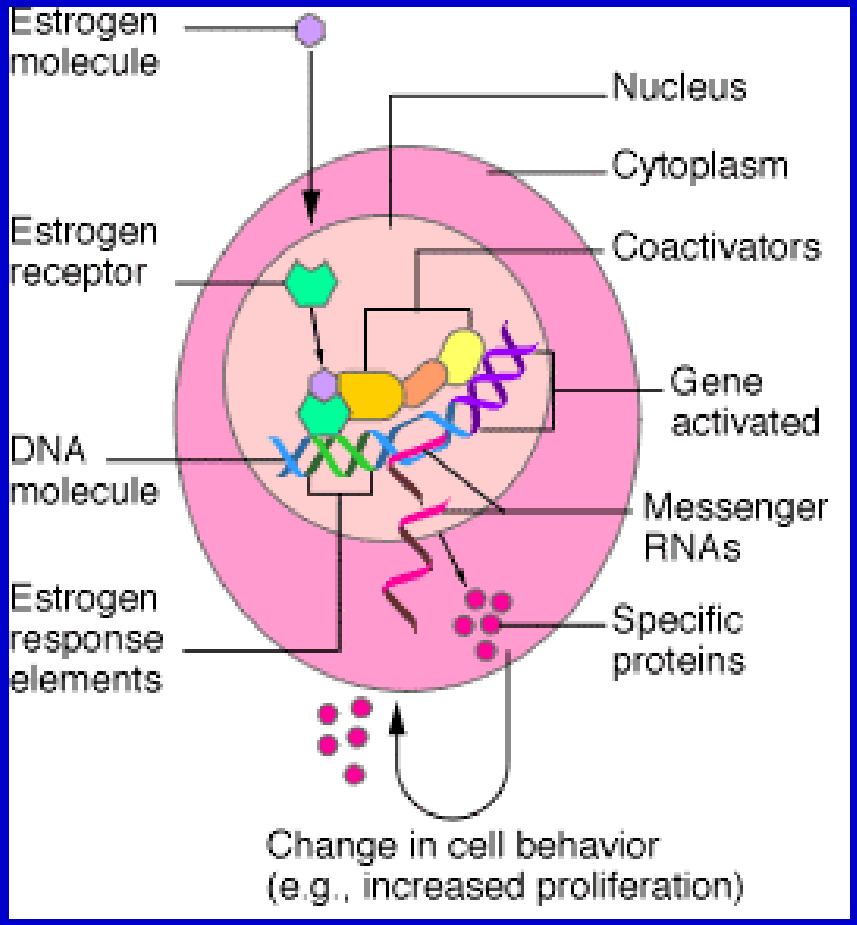


Estrogen Structure and Function

- Member of the steroid family of molecules with fused carbon rings
- Significant role in reproduction
- Imperative in the proper functioning of mammary gland, cardiovascular system, and bone maintenance

★ Estrogens also produced in males, but the reason remains unclear.

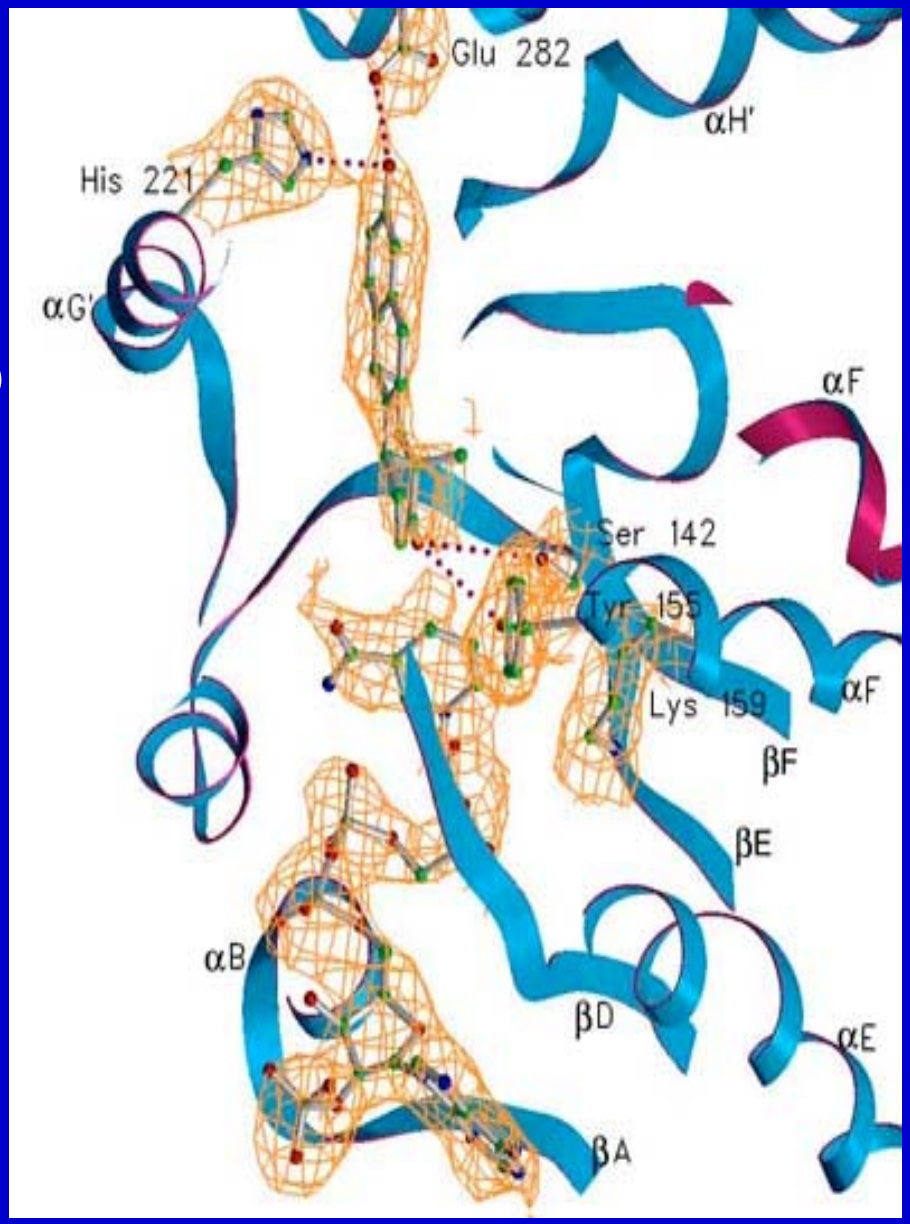
Mechanism of Estrogen Action

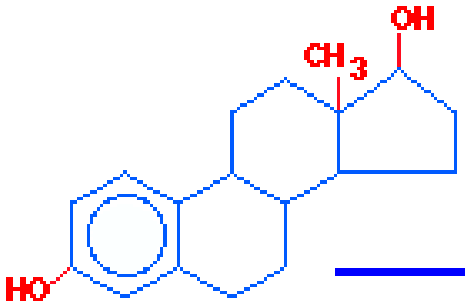


- Estrogenic compound diffuses across membrane
  - ★ LIPOPHILIC
- Binds to receptor in the nucleus
- Activates DNA transcription, producing mRNA
- mRNA exits nucleus and travels into the cytoplasm
- mRNA is translated into a specific protein
- Protein elicits a cellular response

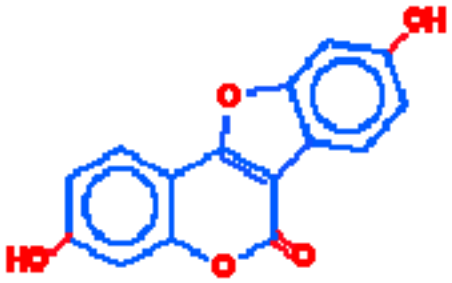
Estrogen Receptors (ERs)

- Ligand-inducible nuclear receptors
- Composed of 595 amino acid residues
- Conformational change upon binding, creating DNA-binding domain
- Transcription and translation induced
- Two types of ERs – ERa and ERß

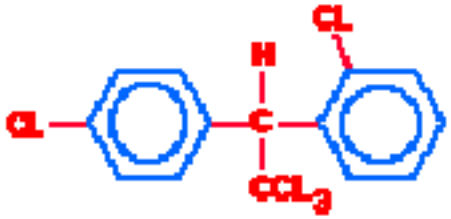




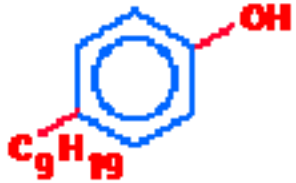
Estradiol: The Natural Ligand



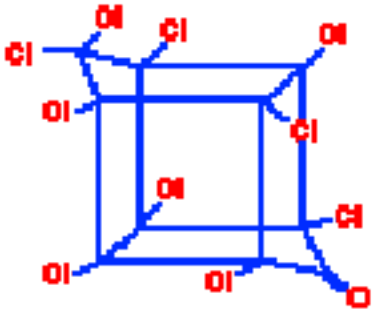
Coumestrol



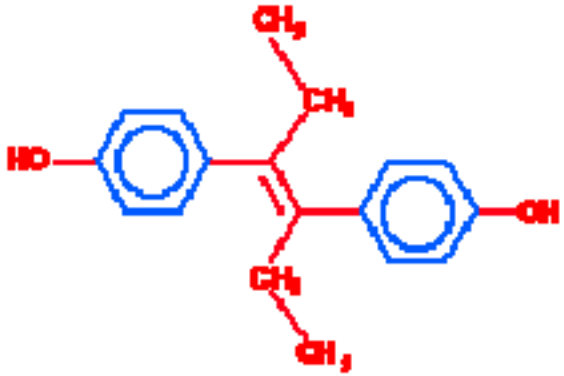
o,p'-DDT



4-nonylphenol (NP)



Kepone
(chlordecone)



Diethylstilbestrol (DES)

Ligand – a substance that binds naturally

ER promiscuity + xenoestrogens = ENDOCRINE DISRUPTION

Structural features of common EDCs

- **phenolic ring**
- **H-bond capability (E2-OH)**
- **precise steric hydrophobic centers**
- **general hydrophobicity**
- **ring structure**

HOWEVER…

The heavy metal cadmium is considered an EDC, as it interacts with the receptor.

Diethylstilbestrol (DES): Infamous EDC

- **Initially used as a pharmaceutical**
- **Became used in agriculture to stimulate cow growth**
- **Estradiol has a binding affinity 1.57 times more potent than DES**

BUT DES has increased bioavailability and longer receptor association!



EDCs, ERs, and the Environment

Endocrine disruption in the environment is determined by three factors:

- **Expression of ERs**
- **Effects of development and reproduction on the regulation of ERs**

  Example: Lake Apopka, Florida

3. **Structure of ER**

Pharmaceuticals

- Detected in lakes, streams, rivers, and bodies as large as the North Sea
- Analytical extraction/concentration methods and newer detection methodologies have allowed the routine detection of ug/L and ng/L quantities of various pharmaceuticals
- But, what do those values mean? How do we place them in context?

Hazard Assessment

$$\mathrm{PEC} = \frac{A \times (100 - \sum R_i)}{V \times D} \times E$$

where: PEC = predicted environmental conc
A = amount of chemical entering system (kg)
R = rate of removal from depletion mechanisms
V = volume of flow (L / day)
D = dilution factor (assumed by FDA ~ 10)
E = conversion factor (kg to ug)

$$\mathrm{PNEC} = \frac{\mathrm{L(E)C_{50}\ from\ acute\ toxicity\ test}}{\mathrm{assessment\ factor}}$$

where: PNEC = predicted no-effect concentration
$L(E)C_{50}$ = lethal or effect concentration affecting 50% of a test population
Assessment factor = data-based 'fudge' factor, usually 10-1000

Concerns?

- Chronic toxicity studies are expensive to conduct and are rarely obtained
- Some recent studies use extremely high (unrealistic) concentrations of pharmaceuticals
- Pharmaceuticals very rarely exceed 1 ug/L in WWTP effluent
- Synergistic effects? Effects of a class of drugs and not just an individual drug?
- Humans usually excrete a metabolite and not the parent compound

Effects?

- Ryan and Orvos (1999) reviewed data from the FDA on over three dozen compounds that were not bactericidal or antibiotics and found only one, thioridazine, exhibited a 24 h EC50 less than 1.0 mg/L. These data support the current position of FDA (1998).
- However, the EC10 of ethinyl estradiol to *D. magna* reproduction was reported to be 2.5 μg/L (Kopf, 1995) indicating the need for industry and regulators to consider non-acute endpoints.

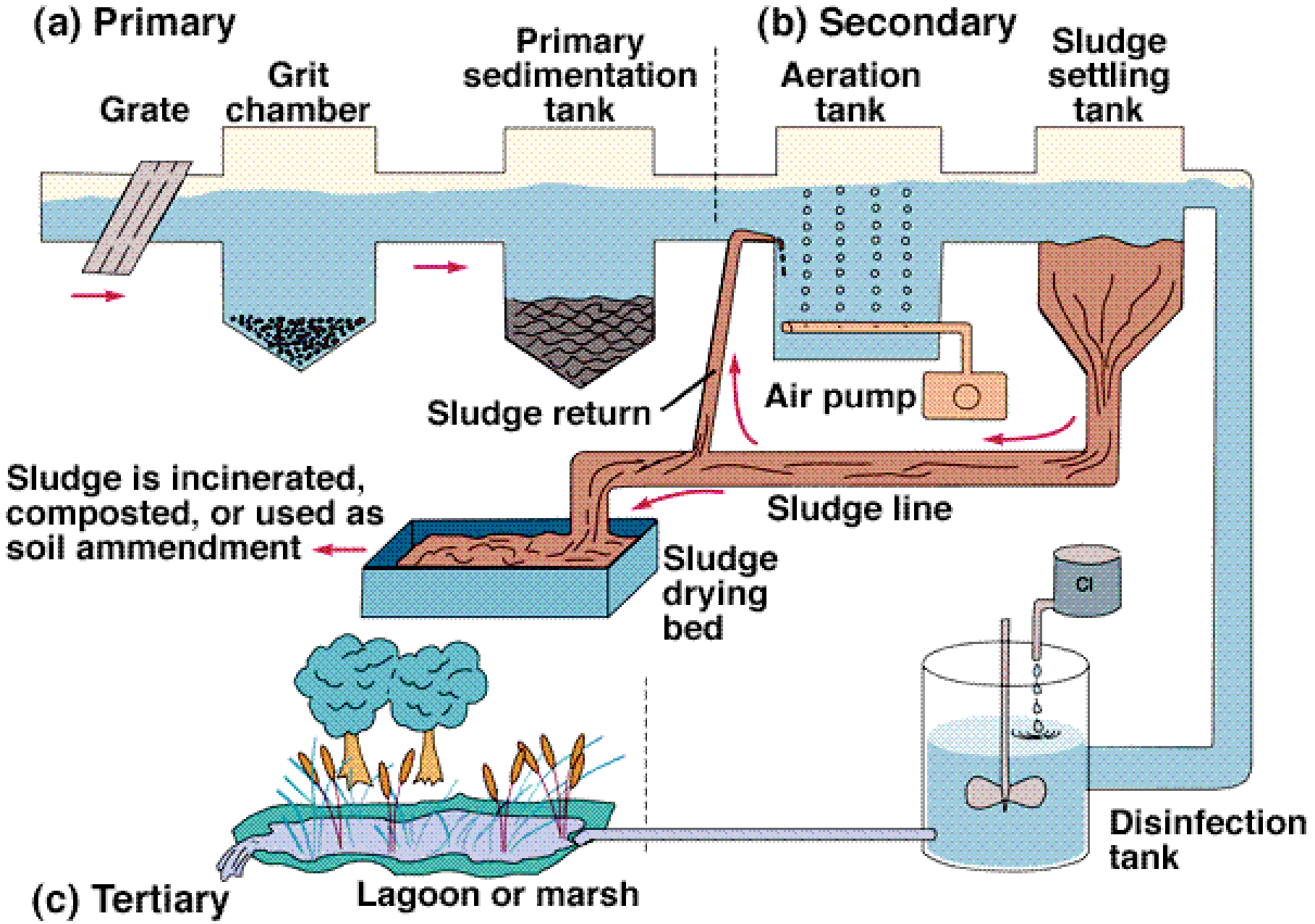
Effects?

- Company-submitted environmental assessments often lack sufficient data for estimating environmental hazard. Some include depletion mechanisms, such as algae biotransformation of finasteride (Venkataramani et al., 1994), that may be of little consequence in the environment.

Effect of Water Treatment Technologies

- Sand filtration
- Chlorination
- Charcoal/Coal
- Ultraviolet light
- Ozonation

Three types of sewage treatment.



Effect of Wastewater Treatment

- Sorption
- Biodegradation
- Volatilization
- Disinfection

Industrial Research Programs

- Procter & Gamble, Environmental Safety Department
- Merck & Co.
- Pfizer Central Research
- SmithKline Beecham, Environmental Research Laboratory
- Dow Chemical

Clinton Administration's initiative to reduce government regulation had a *dramatic effect* on these industry-funded operations – if you weren't required to do something, then why do it?

P&G's Experimental Stream Facility

A former industrial scientist's perspective

- A great deal of useful data exist under the shroud of 'confidentiality'
- Spend less $$ on detection and more $$ on potential human and ecological effects
- Realize the amount of toxicological and biodegradation data available, albeit mammalian in nature
- Make investigations as realistic as possible, examine synergistic effects and multiple drugs