Silent Spring

“For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death”

Rachel Carson, 1962.
Silent Spring

“In less than two decades of their use, the synthetic pesticides have been so thoroughly distributed throughout the animate and inanimate world that they occur virtually everywhere.”

Rachel Carson, 1962.
DDT mosquito control circa 1955
Toxicology

• The science of poisons

• The study of adverse effects of chemicals on living systems
Bag of chemicals

(You)
Toxicology studies how external chemicals interact with your body’s chemicals to cause damage or illness.
Expressions of Toxicity

- Modify existing body functions
- Change speed of cellular reactions
- Reversible injury
- Irreversible injury
- Death
All substances are poisons; there is none that is not a poison.

The right DOSE differentiates a poison from a remedy

(the dose makes the poison)

Areolus Phillipus Theophrastus Bombastus von Hohenheim

Paracelsus (1493-1541)
"Honey, let's lay off the Botox for a while, shall we?"
Botulinum A Toxin: Food Poison or Wrinkle Remover? Depends on the dose.

- **Botulinum A toxin is:**
- a neurotoxin produced by the gram positive bacterium *Clostridium botulinum*
- the most potent known biologic neurotoxin
- a neuromuscular blocking agent which inhibits the release of acetylcholine
- a drug administered by intramuscular injection
- the clinically available product is botulinum toxin type A (marketed as BOTOX®)
Toxicity Testing

• Animal models will predict adverse effects in humans.

• High dose, short term, exposure of animals will predict adverse effects of low dose, long term, exposure in humans.
Toxicological effects are believed to occur either:

- **Non-Linearly (Threshold)**
  - NOAEL: No Observable Adverse Effect Level

- **Linearly (Non-Threshold)**
  - (low-dose extrapolation)
Chemical Risk Assessment:

Human Health risks

Threshold (non-cancer)
There is some dose, below which there will be no effect.

Non-threshold
Potency estimated from the probability of developing cancer over a lifetime of exposure.
Odds of cancer during lifetime ~ 1 in 4
**Excess Cancer Risk Terminology**

- U.S. cancer rate: 1 in 4 or $\frac{1}{4}$ or 0.25
- Acceptable excess cancer rate for each chemical exposure = 0.25 $\pm$ ?
- How about 0.25 + 0.000001 = .250001*
- 0.000001 = $1.0 \times 10^{-6}$, often referred to as $10^{-6}$ cancer risk, this means that assuming daily exposure over a 70 year lifetime that an individual would have a 1 in 1 million risk of cancer above normal probability.

*Population risk, individual risk will vary with genetic predisposition to cancer, lifestyle, and other factors.
Cancer Risk

Linear extrapolation

Tumor incidence

10% LED10 Dose (mg/kg-d)

STEP 1. Model the observed data down to a point of departure

STEP 2. Extrapolate to lower doses

10^{-4}, 10^{-6}?
How Do We Assess Risk?

Follow the National Academy of Sciences (NAS) four-step risk assessment paradigm*:

1. Hazard Identification
2. Exposure
3. Risk Characterization
4. Dose-Response Assessment

How Do We Assess Risk?

- **Hazard Identification**
  - What are the toxicological effects (endpoints)? For example, cholinesterase inhibition.

- **Dose-Response Assessment**
  - At what dose level do the effects occur? For example, what’s the NOAEL?

- **Exposure Assessment**
  - How much chemical is a person being exposed to?

- **Risk Characterization**
  - Combine the hazard, dose-response, and exposure information to describe the overall magnitude of the risk.
Chemicals of Concern

~84,000 chemical substances regulated in the USA.

~1000-1500 new chemicals manufactured each year.
Many chemicals, limited toxicity data

- **No of chemicals**
  - 100,106 on EINECS list, 1981
  - 75,000 upper estimate of 70,000, 1997
  - 25,000 lower estimate of 20,000, 1997

**EU priorities for risk assessment**
- c. 10,000 (IUCLID) of which
  - Limited toxicity data

**EU high production volume chemicals (HPVC)**
- c. 3,500 of which
  - 42 of which
  - 10

**EU priorities for risk assessment 1996-98**

**Risk assessment completed 1997**
- c. 2,000

**'New' chemicals marketed since 1986 (ELINCS)**
- c. 400

**'New' chemicals**

**'EXISTING' CHEMICALS**

**NEW' CHEMICALS**

**HPVC** High Production Volume Chemicals, i.e. production over 1,000 tons/year

- Little/no toxicity = less than OECD minimum for screening
- Limited toxicity data available for OECD/EU screening (e.g. only 20-30% of substances have usable data on cancer or reproduction)

**EINECS**: European Inventory of Existing Commercial Chemical Substances

**IUCLID**: International Uniform Chemical Information Data Base

- Adequate toxicity for EU risk assessment (including some cancer/reproductive/neurotoxic data) but inadequate data on consumer or environmental exposures

**ELINCS**: European List of Notified Chemical Substances (New Substances)

- Limited data available for basic toxicity screening
- 400 risk assessments carried out by Member States (confidential data)

**Note**: In addition to the EU existing chemicals risk assessment programme, both the OECD and WHO/IPCS have completed detailed risk assessments covering about 200 priority chemicals.

## Chemicals Evaluated as Carcinogenic

<table>
<thead>
<tr>
<th>Category</th>
<th>Prop.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>chemicals tested in rats &amp; mice</td>
<td>350/590</td>
<td>59</td>
</tr>
<tr>
<td>naturally occurring chemicals</td>
<td>79/139</td>
<td>57</td>
</tr>
<tr>
<td>synthetic chemicals</td>
<td>271/451</td>
<td>60</td>
</tr>
</tbody>
</table>

Chemicals Evaluated as Carcinogenic

<table>
<thead>
<tr>
<th></th>
<th>Prop.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>chemicals tested in rats or mice</td>
<td>702/1384</td>
<td>52</td>
</tr>
<tr>
<td>natural pesticides</td>
<td>37/71</td>
<td>52</td>
</tr>
<tr>
<td>chemicals in roasted coffee</td>
<td>21/30</td>
<td>70</td>
</tr>
<tr>
<td>Mold toxins</td>
<td>14/23</td>
<td>61</td>
</tr>
</tbody>
</table>

# Chemicals Evaluated as Carcinogenic

<table>
<thead>
<tr>
<th>Category</th>
<th>Prop.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs w/ reported cancer tests</td>
<td>117/241</td>
<td>49</td>
</tr>
<tr>
<td>FDA drug submissions</td>
<td>125/282</td>
<td>44</td>
</tr>
</tbody>
</table>

---

Chemical classes of concern

phenols
substituted phenols
organonitrogen compounds
low molecular weight PAHs
high molecular weight PAHs
pesticides
volatile halogenated alkanes
volatile halogenated alkenes
chlorinated aromatic hydrocarbons
chlorinated aliphatics
Chemical classes of concern (continued)

- pthalates
- halogenated ethers
- polychlorinated biphenyls (PCBs)
- volatile unsaturated carbonyls
- volatile chlorinated aromatics
- volatile ethers
- metals
- dioxins
- surfactants
- cyanide
- asbestos
Low molecular weight polynuclear aromatic hydrocarbons (PAHs)

Acenaphthene
Naphthalene
Acenaphthylene
Anthracene
Fluorene
Phenanthrene

anthracene
Organochlorine insecticides

dieldrin

DDT
Chlorinated aromatic hydrocarbons

1,2,4-trichlorobenzene
Hexachlorobenzene
2-chloronaphthalene
1,2-dichlorobenzene
1,3-dichlorobenzene
1,4-dichlorobenzene
Polychlorinated biphenyls

PCB–1242 (Arochlor 1242)
PCB–1254 (Arochlor 1254)
PCB–1221 (Arochlor 1221)
PCB–1232 (Arochlor 1232)
PCB–1248 (Arochlor 1248)
PCB–1260 (Arochlor 1260)
PCB–1016 (Arochlor 1016)
Metals

Antimony silver
Arsenic zinc
Beryllium
Cadmium
Chromium
Copper
Lead
mercury
nickel
selenium
TCDD

Polychlorinated dibenzo-p-dioxins, including 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD)
Polychlorinated dibenzofurans
Chemical Structures: Herbicides

Triclopyr
Chemical Structures: Herbicides

Glyphosate
Chemical Structures:
Insecticides

Avermectin
Chemical Structures:
Organophosphate Insecticides

Chlorpyrifos

[Chemical structure diagram]
Persistent Organic Pollutants (POPs)

PCBs
Dioxins
Dibenzofurans
Aldrin
Dieldrin
DDT
Endrin
Chlordane

Hexaclorobenzene
Mirex
Toxaphene
Heptachlor
Persistent Organic Pollutants (POPs)

• 2001 Stockholm Convention: a treaty curtailing the manufacture and use of 12 POPs

• US supports treaty, but cannot join without amendments to FIFRA and TSCA
Persistent Bioaccumulative Toxins (PBTs)

• Chemicals that are:
  – man-made and naturally occurring substances
  – toxic, persist in the environment, and bioaccumulate in food chains
  – pose risks to human health and ecosystems.
<table>
<thead>
<tr>
<th>EPA Priority Level-1 PBTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldrin/Dieldrin</td>
</tr>
<tr>
<td>Alkyl-lead</td>
</tr>
<tr>
<td>Benzo(a)Pyrene</td>
</tr>
<tr>
<td>Toxaphene</td>
</tr>
<tr>
<td>Chlordane</td>
</tr>
<tr>
<td>DDT, DDD, DDE</td>
</tr>
<tr>
<td>Dioxins/Furans</td>
</tr>
<tr>
<td>Hexachlorobenzene</td>
</tr>
<tr>
<td>Mercury, Mercury Compounds</td>
</tr>
<tr>
<td>Mirex</td>
</tr>
<tr>
<td>Octachlorostyrene</td>
</tr>
<tr>
<td>PCBs</td>
</tr>
</tbody>
</table>
Pharmaceuticals and Personal Care Products (PPCPs)

In addition to antimicrobials and steroids, over 50 individual PPCPs or metabolites, from > 10 broad classes of therapeutic agents or personal care products, have been identified in Environmental samples; mainly in sewage, surface, and ground waters.
Pharmaceuticals and Personal Care Products (PPCPs)\(^1\)

- analgesics/non-steroidal anti-inflammatory\es\)
- antimicrobials
- antiepileptics
- antihypertensives (betablockers, beta- adrenergic receptor inhibitors)
- antineoplastics
- antiseptics
- contraceptives

\(^1\)reported in environmental samples as of 1999
Pharmaceuticals and Personal Care Products (PPCPs)\(^1\)

- b2-sympathomimetics (bronchodilators)
- lipid regulators (anti-lipidemics; cholesterol-reducing agents; and their bioactive metabolites)
- musks (synthetic)
- anti-anxiety/hypnotic agents
- sun screen agents
- X-ray contrast agents

\(^1\)reported in environmental samples as of 1999
### Example analgesics/non-steroidal anti-inflammatories

<table>
<thead>
<tr>
<th>Brand name</th>
<th>generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol</td>
<td>acetaminophen</td>
</tr>
<tr>
<td>Voltaren</td>
<td>diclofenac</td>
</tr>
<tr>
<td>Advil</td>
<td>ibuprofen</td>
</tr>
<tr>
<td>Oruvail</td>
<td>ketoprofen</td>
</tr>
<tr>
<td>Naprosyn</td>
<td>naproxen</td>
</tr>
</tbody>
</table>
USGS Reconnaissance of Emerging Contaminants in US Streams:
Veterinary and Human Antibiotics

<table>
<thead>
<tr>
<th>Tetracyclines</th>
<th>Norfloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlortetracycline</td>
<td>Sarafloxacin</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Macrolides</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>Erythromycin-H2O</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>(metabolite)</td>
</tr>
<tr>
<td></td>
<td>Tylosin</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Roxithromycin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td></td>
</tr>
</tbody>
</table>
**USGS Reconnaissance of Emerging Contaminants in US Streams:**
**Human Drugs (prescription)**

<table>
<thead>
<tr>
<th>Metformin (antidiabetic)</th>
<th>Paroxetine (antidepressant, antianxiety)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine (antacid)</td>
<td>Warfarin (anticoagulant)</td>
</tr>
<tr>
<td>Ranitidine (antacid)</td>
<td>albutamol (antiasthmatic)</td>
</tr>
<tr>
<td>Enalaprilat (antihypertensive)</td>
<td>Gemfibrozil (antihyperlipidemic)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Diltiazem (antihypertensive)</td>
</tr>
<tr>
<td>Digoxigenin (metabolite)</td>
<td>Fluoxetine (antidepressant)</td>
</tr>
<tr>
<td>Dehydronifedipine (antianginal metabolite)</td>
<td></td>
</tr>
</tbody>
</table>
USGS Reconnaissance of Emerging Contaminants in US Streams: Human Drugs (non-prescription)

- Acetaminophen (analgesic)
- Ibuprofen (anti-inflammatory, analgesic)
- Codeine (analgesic)
- Caffeine (stimulant)
- 1,7-Dimethylxanthine (caffeine metabolite)
- Cotinine (nicotine metabolite)
USGS Reconnaissance of Emerging Contaminants in US Streams:
Industrial and Household Wastewater Products

<table>
<thead>
<tr>
<th>Insecticides</th>
<th>Plasticizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazinon</td>
<td><em>bis</em>(2-Ethylhexyl)adipate</td>
</tr>
<tr>
<td>Carbaryl</td>
<td>Ethanol-2-butoxy-phosphate</td>
</tr>
<tr>
<td>Chlorpyrifos</td>
<td><em>bis</em>(2-Ethylhexyl)phthalate</td>
</tr>
<tr>
<td><em>cis</em>-Chlordane</td>
<td>Diethylphthalate</td>
</tr>
<tr>
<td>N,N-diethylyltoluamide (DEET)</td>
<td>Triphenyl phosphate</td>
</tr>
<tr>
<td>Lindane</td>
<td></td>
</tr>
<tr>
<td>Methyl parathion</td>
<td></td>
</tr>
<tr>
<td>Dieldrin</td>
<td></td>
</tr>
</tbody>
</table>
USGS Reconnaissance of Emerging Contaminants in US Streams: Industrial and Household Wastewater Products

<table>
<thead>
<tr>
<th>Detergent metabolites</th>
<th>PAHs¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \rho )-Nonylphenol</td>
<td>Naphthalene</td>
</tr>
<tr>
<td>Nonylphenolmonoethoxylate</td>
<td>Phenanthrene</td>
</tr>
<tr>
<td>Nonylphenol diethoxylate</td>
<td>Anthracene</td>
</tr>
<tr>
<td>Octylphenol monoethoxylate</td>
<td>Fluoranthene</td>
</tr>
<tr>
<td>Octylphenol diethoxylate</td>
<td>Pyrene</td>
</tr>
<tr>
<td>Fire retardants</td>
<td>Benzo((a))pyrene</td>
</tr>
<tr>
<td>Tri(2-chloroethyl)phosphate</td>
<td>¹fossil fuel and fuel combustion indicators</td>
</tr>
<tr>
<td>Tri(dichloroisopropyl)phosphate</td>
<td></td>
</tr>
</tbody>
</table>
### USGS Reconnaissance of Emerging Contaminants in US Streams: Industrial and Household Wastewater Products

<table>
<thead>
<tr>
<th>Antioxidants</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,6-di-tert-Butylphenol</td>
<td>Tetrachloroethylene (solvent)</td>
</tr>
<tr>
<td>5-Methyl-1H-benzotriazole</td>
<td>Phenol (disinfectant)</td>
</tr>
<tr>
<td>Butylatedhydroxyanisole</td>
<td>1,4-Dichlorobenzene (fumigant)</td>
</tr>
<tr>
<td>Butylatedhydroxytoluene</td>
<td>Acetophenone (fragrance)</td>
</tr>
<tr>
<td>2,6-di-tert-Butyl-p-benzoquinone</td>
<td>p-Cresol (wood preservative)</td>
</tr>
<tr>
<td></td>
<td>Phthalic anhydride (plastics)</td>
</tr>
<tr>
<td></td>
<td>Bisphenol A (polymers)</td>
</tr>
<tr>
<td></td>
<td>Triclosan (disinfectant)</td>
</tr>
</tbody>
</table>
USGS Reconnaissance of Emerging Contaminants in US Streams:
Sex and Steroidal Hormones

<table>
<thead>
<tr>
<th>Biogenics</th>
<th>Pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>17β-Estradiol</td>
<td>17α-Ethynylestradiol (ovulation inhibitor)</td>
</tr>
<tr>
<td>17α-Estradiol</td>
<td>Mestranol (ovulation inhibitor)</td>
</tr>
<tr>
<td>Estrone</td>
<td>19-Norethisterone (ovulation inhibitor)</td>
</tr>
<tr>
<td>Estriol</td>
<td>Equilenin (hormone replacement)</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Equilin (hormone replacement)</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Sterols</td>
</tr>
<tr>
<td>cis-Androsterone</td>
<td>Cholesterol (fecal indicator)</td>
</tr>
<tr>
<td></td>
<td>3β-Coprostanol (carnivore fecal)</td>
</tr>
<tr>
<td></td>
<td>Stigmasteranol (plant sterol)</td>
</tr>
</tbody>
</table>
Chemical Concern du jour: Brominated Flame Retardants

- tetrabromobisphenol A
- hexabromocyclododecane
- polybrominated diphenyl ethers (PBDE)

Why a concern?

- Widespread production and use
- strong evidence of increasing contamination of the environment, wildlife, and people
- limited knowledge of potential adverse effects