Head lice

- Hexit® Shampoo
  - Lindane
- Nix® cream rinse
  - Permethrin

Dibenzodioxins and dibenzofurans
- TCDD 2,3,7,8 tetrachloro-p-dioxin

**Organic chemicals as endocrine disrupters**
- Sustained increase in breast cancer
- Organic compounds mimicking the effects of estrogens
- 40% of all cancers in women are mediated by hormones

Hormones: used in signaling and regulatory mechanisms i.e. homeostasis
- A control system that responds to internal/external signals to maintain the body in a chemical equilibrium
- Regulates sexual development
- Stress response to external threats

**Mechanism of action**
- Exert their influence by:
  - Mimicking the effects of endogenous hormones such as estrogens and androgens
  - Antagonising the effects of endogenous hormones
  - Altering the pattern of synthesis and metabolism of normal hormones
  - Modifying hormone receptor levels
Effect on health

- Male:
  - Some studies indicate sperm count and semen quality decreased
  - Increase in incidence of testicular cancer, undescended testicles, various deformities of the reproductive tract has increased
  - Thought that certain chemicals can act on a male fetus during the time that sexual differentiation occurs

- Female:
  - Diethylstilbestrol - clear cell carcinoma
  - Incidence of breast cancer increased 45% 1960-1985
  - Neurological problems in PCB exposed infants (cause and effect?)

Peroxisome proliferases

- Subcellular organelles found in most plant and animal cells that perform a variety of metabolic functions including cholesterol and steroid metabolism
- Peroxisome proliferators cause a large increase in both the size and number of peroxisomes in exposed organisms
  - Herbicides 2,4-D
- Prolonged exposure results in increased liver tumours in laboratory animals—although don’t damage DNA directly
- Toxicity via endocrine disruption?

Other organic contaminants

- Pharmaceuticals
  - Human
  - veterinary
- Polynuclear aromatic hydrocarbons
  - Tobacco smoke, burning of fossil fuels ie. Benzo[a]pyrene
- Petroleum hydrocarbons
  - Crude oil - mixture of over 1000 chemicals
- Organotins
  - Tributyl tin
  - unnatural shell thickening in oysters
  - IMPOSEX (mollusc)

Biotransformation and toxic metabolites

Biotransformation of Xenobiotics can be a defense mechanism

Xenobiotic metabolism is divided into primary (Phase I) and secondary (Phase II) metabolism

<table>
<thead>
<tr>
<th>Xenobiotic</th>
<th>Phase I</th>
<th>Metabolite</th>
<th>Phase II</th>
<th>Conjugate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing polarity</td>
<td></td>
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</tbody>
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Phase I - involves oxidation, reduction and hydrolysis of the toxicant involving the Mixed Function Oxygenase (MFO) system. The most important is Cytocrome P450 (an iron containing enzyme)

- found in all vertebrates, invertebrates and most plant species.

Phase 1 metabolism

CYP 450:
- Without exception, the levels and activity of each P450 enzyme have been shown to vary from one individual to the next
- Due to both genetic and environmental factors decreased P450 enzyme activity can occur due to:
  - A genetic mutation that results in decreased synthesis of P450 protein
  - Exposure to environmental that suppresses P450 expression
  - Exposure to a xenobiotic that inhibits P450 activity
- Increased enzyme activity can occur:
  - By gene duplication
  - Exposure to xenobiotics that induce the synthesis of P450
  - Exposure to xenobiotics that stimulate preexisting P450 protein

CYP P450 isoenzymes catalyse aliphatic and aromatic hydroxylations, epoxidations, N-oxidations, sulfoxidations, dealkylations, deaminations, dehalogenations
Phase II reactions

- Conjugation reaction:
  - joining together two compounds
  - an energy-consuming process
- Glucuronidation
- Sulfation
- Glutathione

Case Study
Feminisation of fish in English rivers

- Vitellogenin is a precursor of egg yolk
  - Synthesized in developing liver under the control of endogenous estradiol (can be measured)
  - Levels of estradiol undetectable in male fish so the gene responsible for vitellogenin synthesis is normally not expressed
  - In the presence of estradiol male fish can synthesis vitellogenin