Chemical toxicology

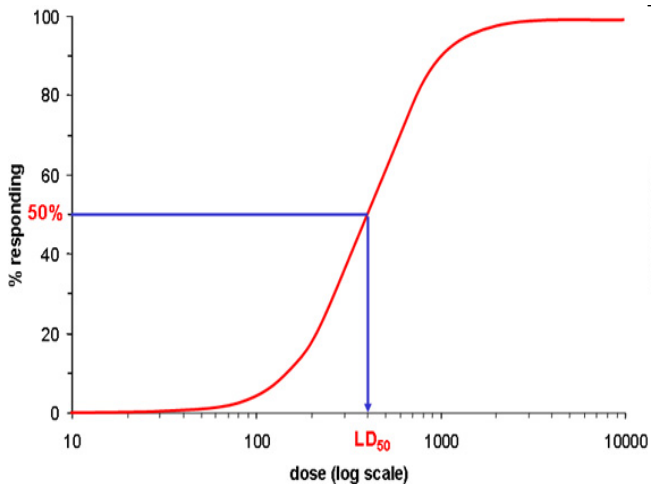
Toxicology

Toxicology studies adverse effects of chemicals on living organisms.

Chemicals exert toxic effects by disturbing the normal course of biochemical reactions. Molecular mechanism.

Quantitative relationship:

- Dose-effect
- LD_{50}

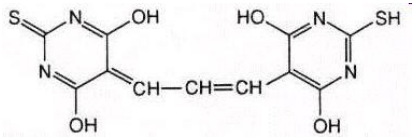


Chemical toxicology

General toxic effects

✓ *Nonspecific effects*: lipophilic and amphipathic compounds interact with cell membranes. Aliphatic alcohols: antiseptic. Depression of CNS /heart muscle.

✓ *Lipid peroxidation*: radical compounds oxidate unsaturated fatty acid derivatives. (rancid fat reaction). Detected with thiobarbituric acid → fluorescent product with malondialdehde and similar compounds



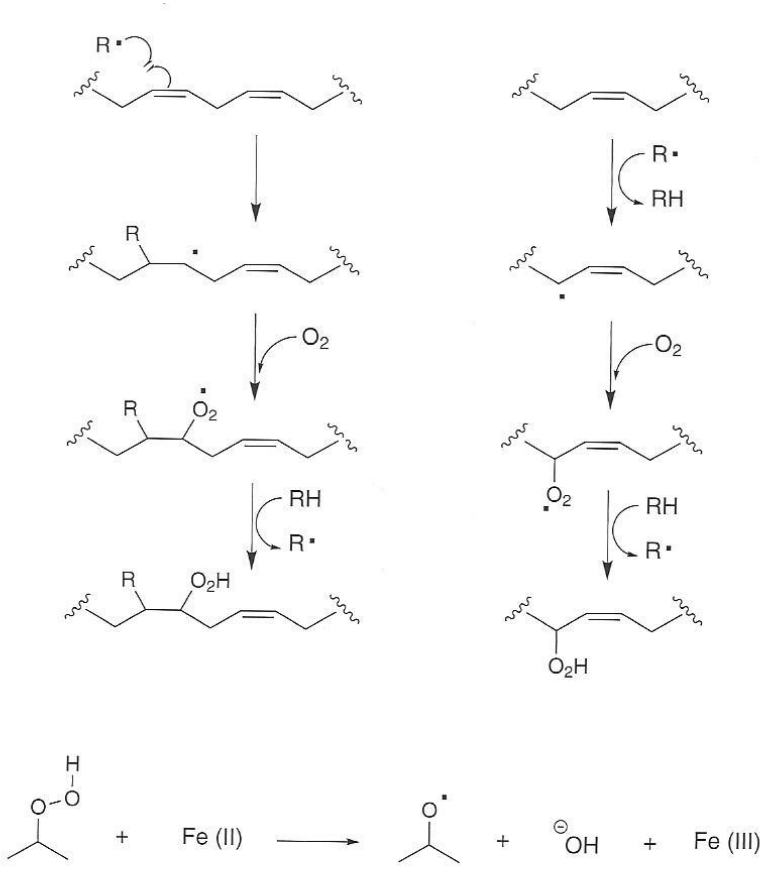


Figure 7.9 Radical-induced peroxidation of unsaturated fatty acids.

Chemical toxicology

General toxic effects

✓ *Lipid peroxidation*: 1) damage to membranes
2) damage to membrane-bound enzyme systems
3) diffusion to the nucleus and DNA-damage

✓ *Acidosis:*

pH lowering. Blood 7.35-7.40. Effect of CO_2 (lung, kidneys). Enzyme carboanhydrase catalyzes :

$$2\ H_2O + CO_2 \rightarrow H_2CO_3 + H_2O\ (HCO_3^- + H_3O^+)$$

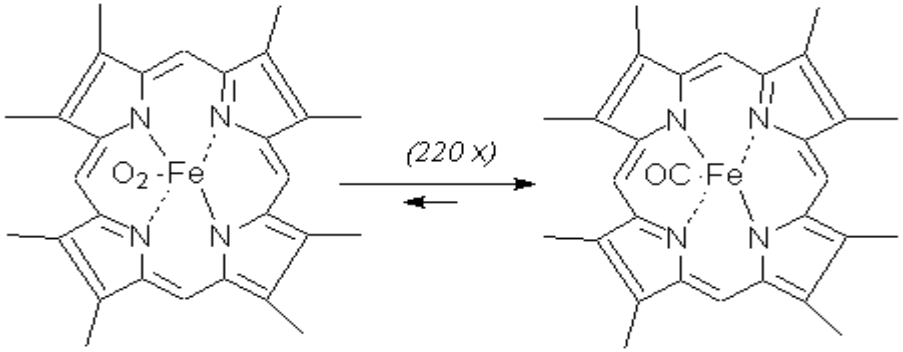
Decreasing pH → → increasing breathing frequency
Acidosis by high quantity of acid drugs: salycilic derivatives; formic acid precursors; carboxylic halides; anhydrides; metabolic carboxylic acids (oxalic acid from ethylene glycol)

Chemical toxicology

General toxic effects

✓ *Oxygen deficiency*: stops energy accumulation in the cell (ATP, GTP) and oxidative phosphorilation (respiratory chain)

Carbon monoxide: 0.1% in air blocks 50% of a human blood Hb



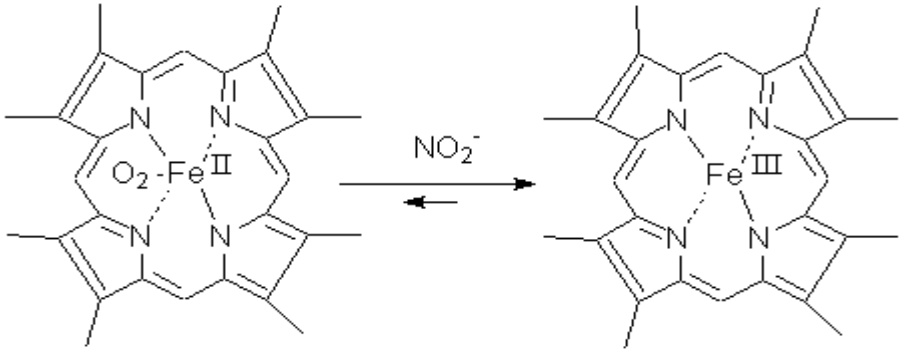
oxyhemoglobin (Fe^{2+}) carboxyhemoglobin

Chemical toxicology

General toxic effects

✓ *Oxygen deficiency*: stops energy accumulation in the cell (ATP, GTP) and oxidative phosphorilation (respiratory chain)

Methemoglobinemia: balanced by NADH-methemoglobin reductase



oxyhemoglobin (Fe^{2+}) methemoglobin

Chemical toxicology

General toxic effects

✓ *ATP deficiency*: a) inhibition of the citric acid cicle

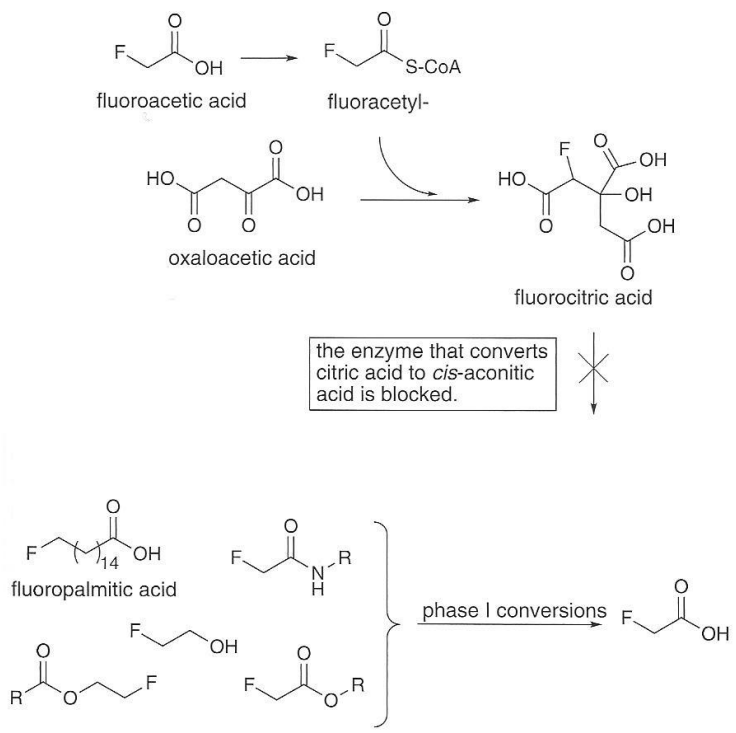
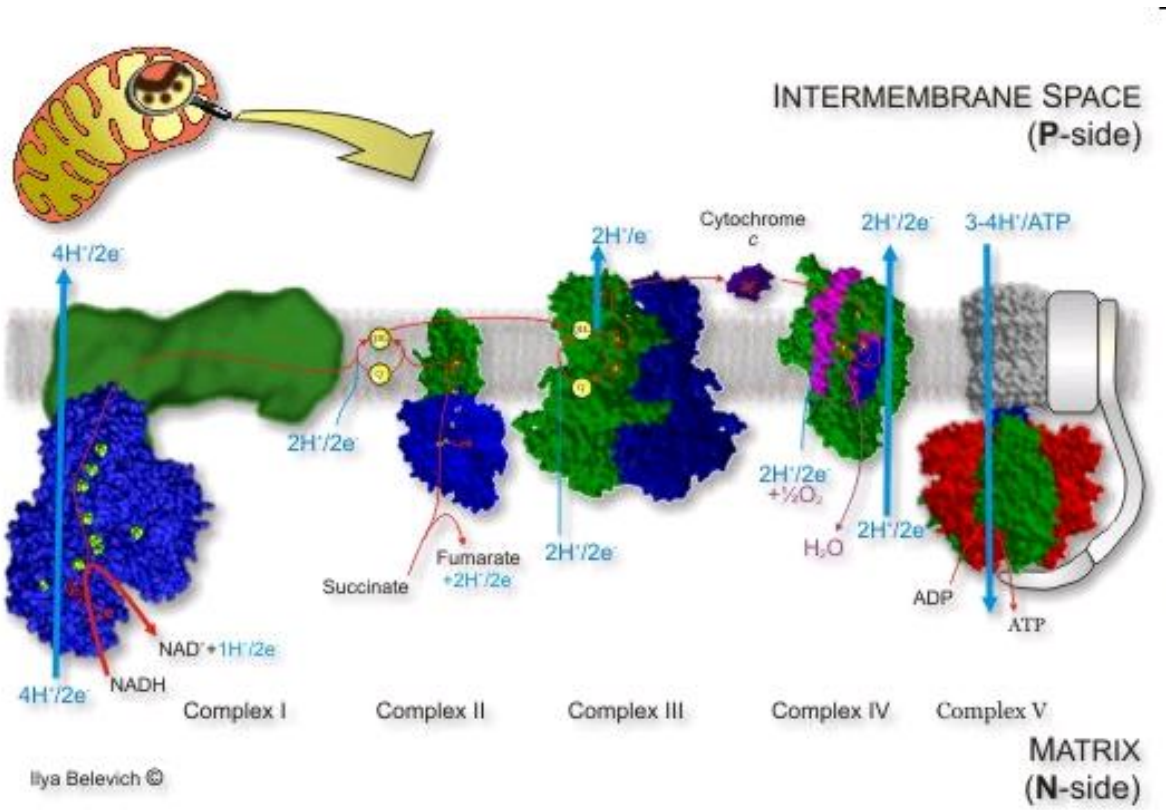


Figure 7.20 Fluoracetic acid will block the citric acid cycle.

Dichapetalum cimosum (CH_2F-COOH)

General toxic effects

✓ *ATP deficiency*: b) inhibition of the respiratory chain



Chemical toxicology

General toxic effects

✓ *ATP deficiency*: b) inhibition of the respiratory chain

Hydrogen cyanide

Hydrogen sulphide

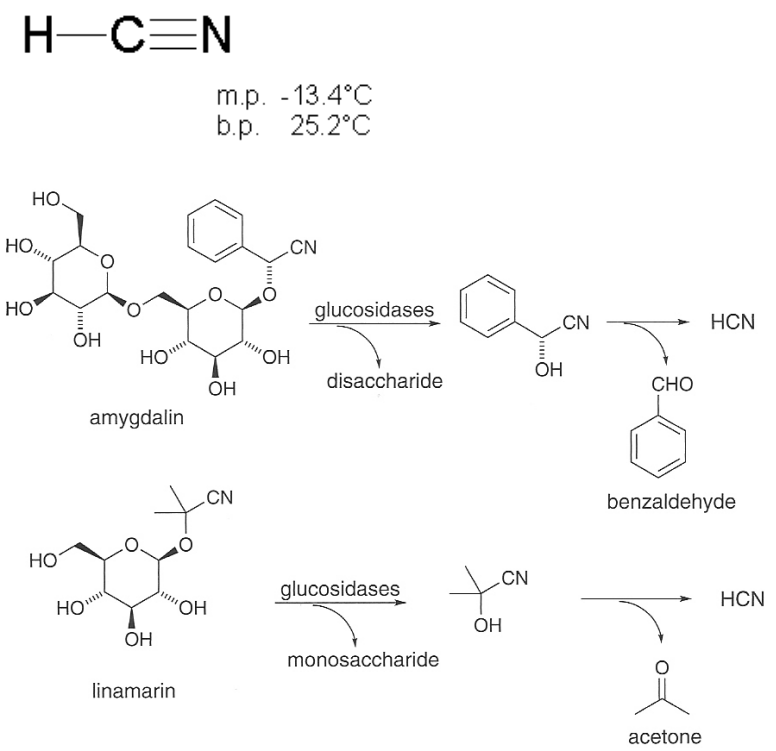


Figure 7.22 Enzymatic hydrolysis of cyanogenic glucosides.

Chemical toxicology

Specific toxic effects

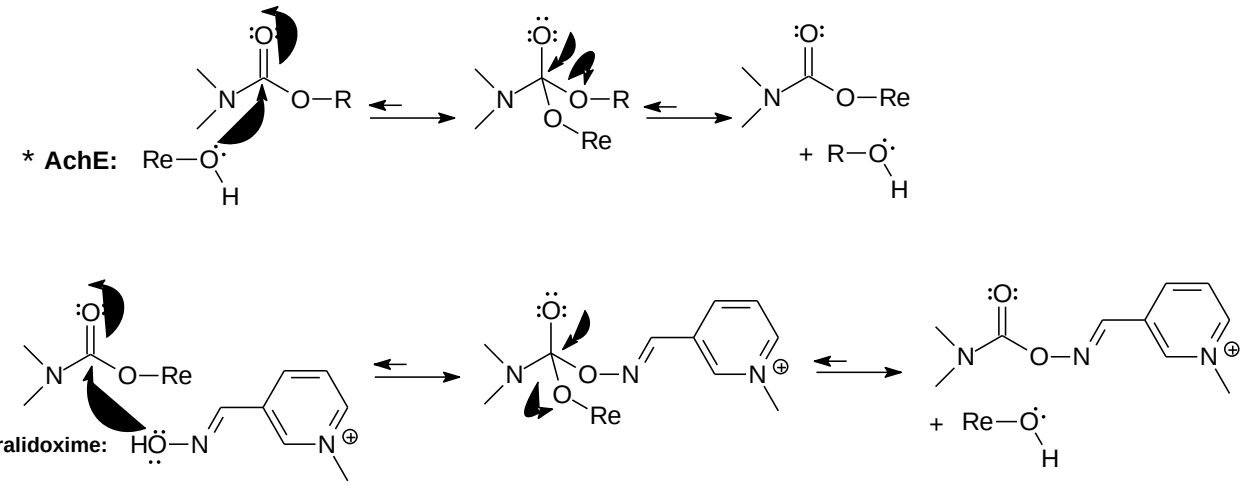
✓ *Effects on the blood*: O_2 / oxyhemoglobin. Hypoxia (CO-Hb, metHb). Aplastic anemia: reduction of blood cell formation. Leukemia: leukocytes cancer.

✓ *Effects on the cardiovascular system*: Bradycardia, tachycardia, arrhythmia (heart). Arteriosclerosis / atherosclerosis (vases). Acrolein, As.

Specific toxic effects

✓ *Effects on the nervous system*:

- interaction with receptors and ion channels (1. Agonistic or antagonistic effect on receptors; 2. Agonistic effect on receptors 3. Antagonistic effect on receptors; 4) neurotransmitter metabolic enzymatic inhibition (Acetylcholine esterase, AchE*); 5) ion channels blocking)
- inhibition of ATP production;



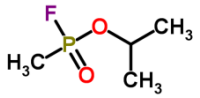
Chemical toxicology

Specific toxic effects

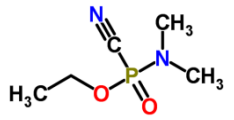
✓ *Effects on the nervous system*: AchE: inhibitors

Organophosphate military poisons:
nerve gases; irreversible AchE inhibitors. Among the most toxic synthetic compounds ever made (World War II)

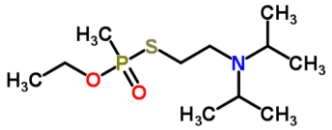
✓ **Sarin:** isopropyl methylphosphonofluoridate**.** Systemic poison to CNS. One drop can kill a human. LD_{50} 0.01 mg/Kg; mp -58°C, bp 147°C.
☠ *Tokyo 1995,* terroristic attack to the subway by オウム真理教 (Aum Shinrikyo, new religious movement")



✓ **Tabun:** ethyl dimethylphosphoramidocyanidate.
LD_{50} (mouse, i.p.) 0.6 mg/Kg; mp -49°C, bp 238°C.

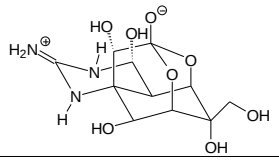
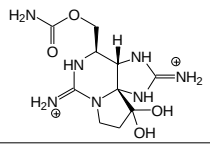
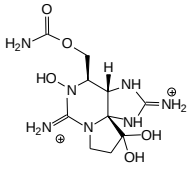
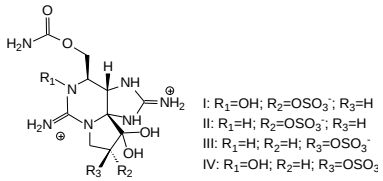
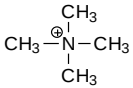


✓ **VX:** O-Ethyl S-[2-(Diisopropylamino)ethyl]methyl-phosphonothioate



Chemical toxicology

Specific toxic effects ✓ *Effects on the nervous system*: ion channels blockers

Name	***Structure***	***Formula and MW***	***action***
Tetrodotoxin (TTX)		319 ($C_{11}H_{17}N_3O_8$)	Blocks sodium channels **LD_{50} 10 µg/Kg**
Saxitoxin (STX)		301 $(C_{10}H_{19}N_7O_4)^{2+}$	Blocks sodium channels
Neosaxitoxin (NeoSTX)		317 $(C_{10}H_{19}N_7O_5)^{2+}$	Blocks sodium channels
Gonyautoxin (GTX)	 I: R_1=OH; R_2=OSO_3^-; R_3=H II: R_1=H; R_2=OSO_3^-; R_3=H III: R_1=H; R_2=H; R_3=OSO_3^- IV: R_1=OH; R_2=H; R_3=OSO_3^-	I, IV: 380; II, III: 364	Blocks sodium channels
Tetramine (TTM)		74 ($C_4H_{12}N$)	Ganglionic blocking agent (curare like)

Chemical toxicology

Specific toxic effects

✓ *Effects on the liver*: fatty liver (radicals, CCl_4) / liver cancer.
Induction of cytochrome P450
(vinyl chloride → epoxide)

✓ *Effects on the kidneys*: acidosis, oxalic acid, metals (Hg, Cd)

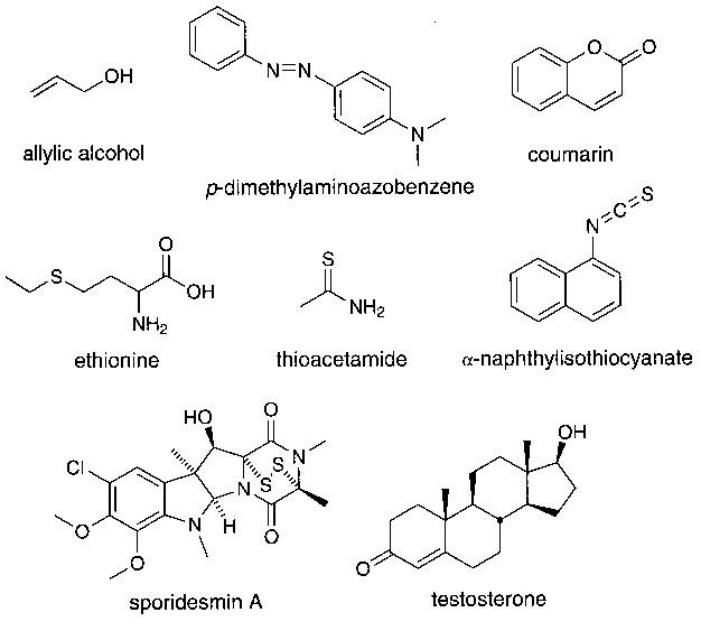


Figure 7.26 Compounds toxic to the liver.

Chemical toxicology

Specific toxic effects

✓ *Effects on the respiratory system*:
lung cancer (smoke). Paraquat radical. Pyrrolizidine alkaloids.

✓ *Effects on the skin*: Local effects of strongly reactive compounds: chemical burns. Photosensitization.

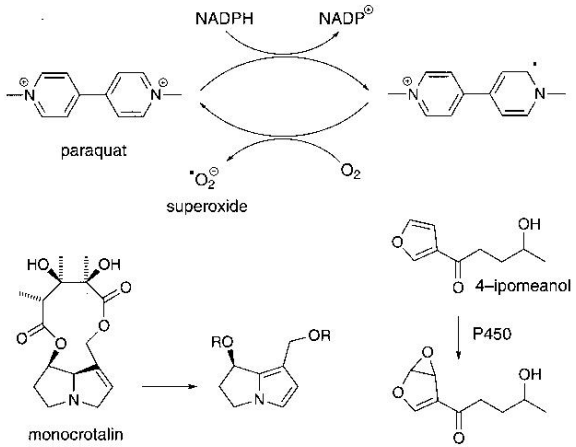


Figure 7.27 Compounds that are toxic to the lung.

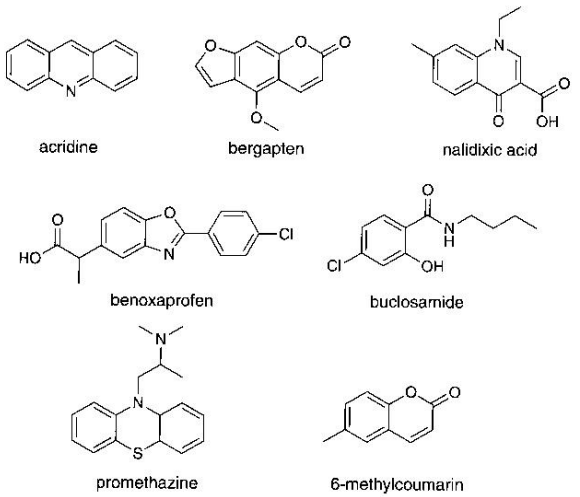


Figure 7.28 Phototoxic and photoallergic compounds.

Lime juice (bergapten) + sun

Specific toxic effects

✓ *Effects on the immune system*:

Physiological function: protection against microorganisms, viruses, malignant cells. Troublesome hyper-reaction of immune system: allergy:

- non specific allergic reaction: phagocytosys, inflammation
- specific allergic reaction: determination of self/foreign nature with antibody (by B-cells) and lymphocytes (by T-cells) production. Antigenes: MW > 5000 Da. Haptene: small molecule + protein

Sensitization: generation of long-lived memory cells that enable tho body to remember that an antigen is foreign. Quick reaction (minutes vs. 12-48 h of normal immune reaction).

Chemical toxicology

Specific toxic effects

✓ **Chemical allergenes:** *immediate hypersensitivity*: antibody mediated asthma and contact dermatitis.

Anaphylactic shock. Cross-reactivity: different diisocyanates.

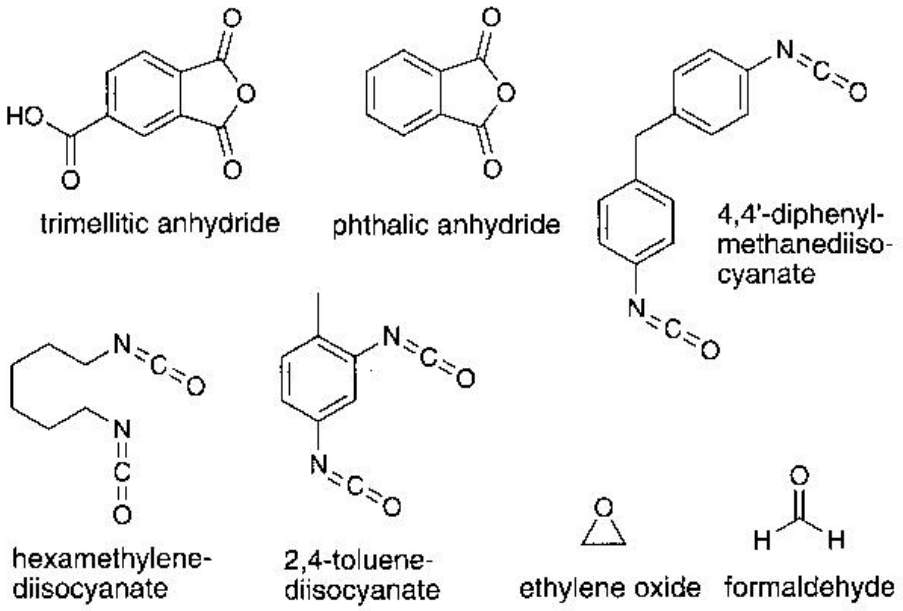


Figure 7.30 Examples of chemicals that give immediate hypersensitivity.

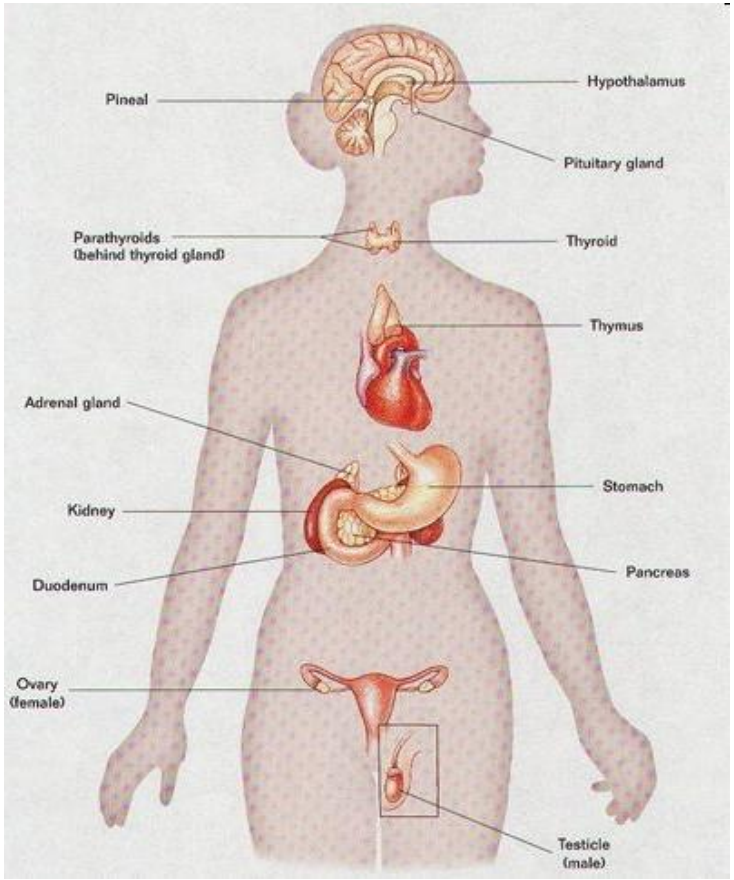
Chemical toxicology

Specific toxic effects

✓ **Endocrine disruptors:** *effects on endocrine system*:
regulation of blood pressure
regulation of body temperature
reproduction
building of muscle mass and bones

Toxicity: agonists / antagonists

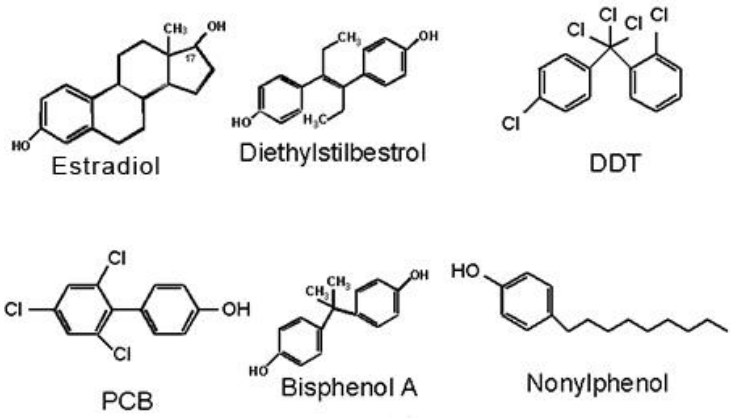
Environmental toxicants



Chemical toxicology

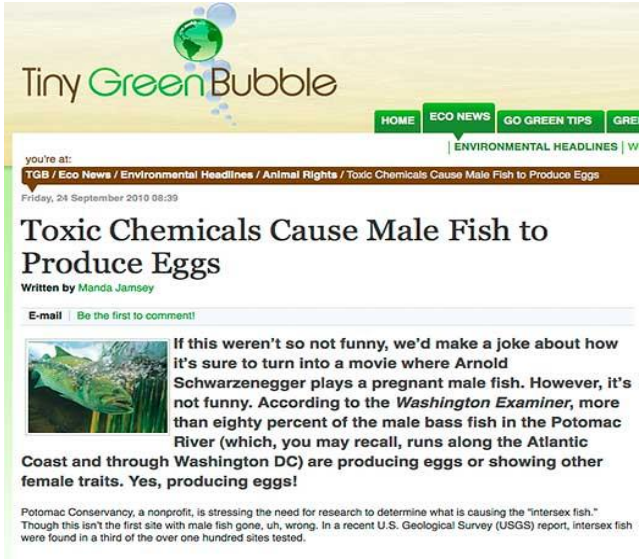
Specific toxic effects

✓ **Endocrine disruptors: estrogenic compounds**



*Environmental Science and Technology 2009, **43**, 597.* SPE; GC-MS; LC-MS.

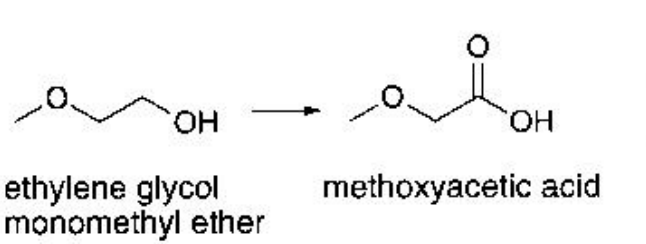
		source (n = 19)		
	MRL	max.	med.	no.
known or potential EDCs				
atrazine	0.25	870	32	15
17β-estradiol	0.50	17	17	1
estrone	0.20	0.90	0.30	15
17α-ethynylestradiol	1.0	1.4	1.4	1
bisphenol A	5.0	14	6.1	3
butylbenzyl phthalate	50	54	53	2
diethylhexyl phthalate	120	170	150	2
galaxolide	25	48	3	4
linuron	0.50	9.3	4.1	5
nonylphenol	80	130	100	8
progesterone	0.50	3.1	2.2	4
testosterone	0.50	1.2	1.1	2



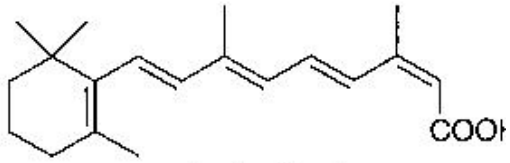
Chemical toxicology

Specific toxic effects

✓ **Chemical teratogenes:** *Effects on the embryo*: first 8 weeks gestation (histogenesis). Influence the following organogenesis (weeks 3-9). There are also physical and biological t. More than 1000 chemicals are teratogens on rodents (pH of rodent embryo blood > maternal: trapping of weak acids). Approx. 30 are teratogen for humans. Hg (Minamata), Pb, Cd, As; thalidomide (day 23-38 from conception, 10000 cases in the 60s)

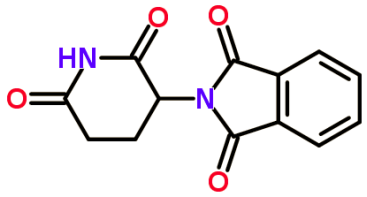


ethylene glycol monomethyl ether — methoxyacetic acid



isotretinoin

Figure 7.32 Examples of teratogenic compounds.



thalidomide

Chemical toxicology

Genotoxic effects

DNA as molecular target:

✓ chemical origin. Known from 1775, Dr Percivall Pott: scrotal cancer was the first occupational (chimney sweeps) link to cancer.

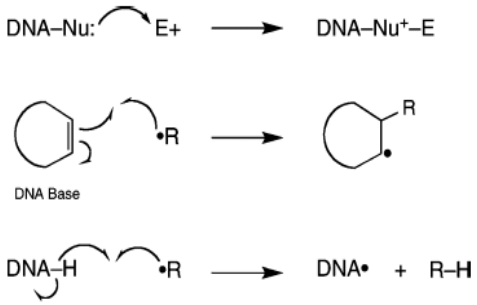
- environmental toxicology
- epidemiology

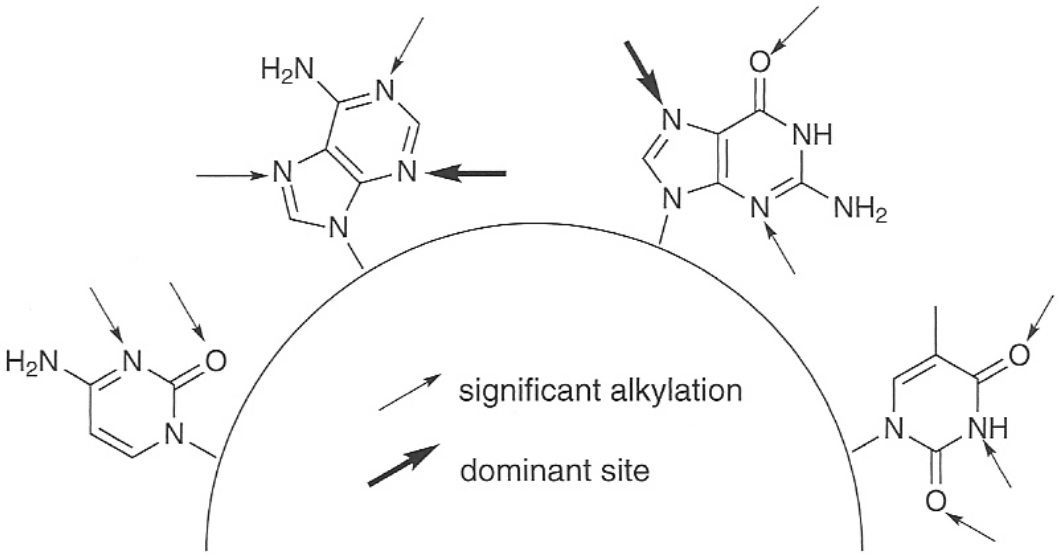
Chemical toxicology

Genotoxic effects

DNA bases modification:

- ✓ with exogenous chemicals
  - *electrophiles*
  - *radicals (or reactive products formed from)*
  - *metals*





t½ guanine 15000000 h

t½ 7-alkylguanine 200 h

Figure 8.5 The most frequent sites for alkylation of the bases in double-stranded DNA.

Chemical toxicology

Genotoxic effects

DNA bases modification:

- *bifunctional electrophiles*

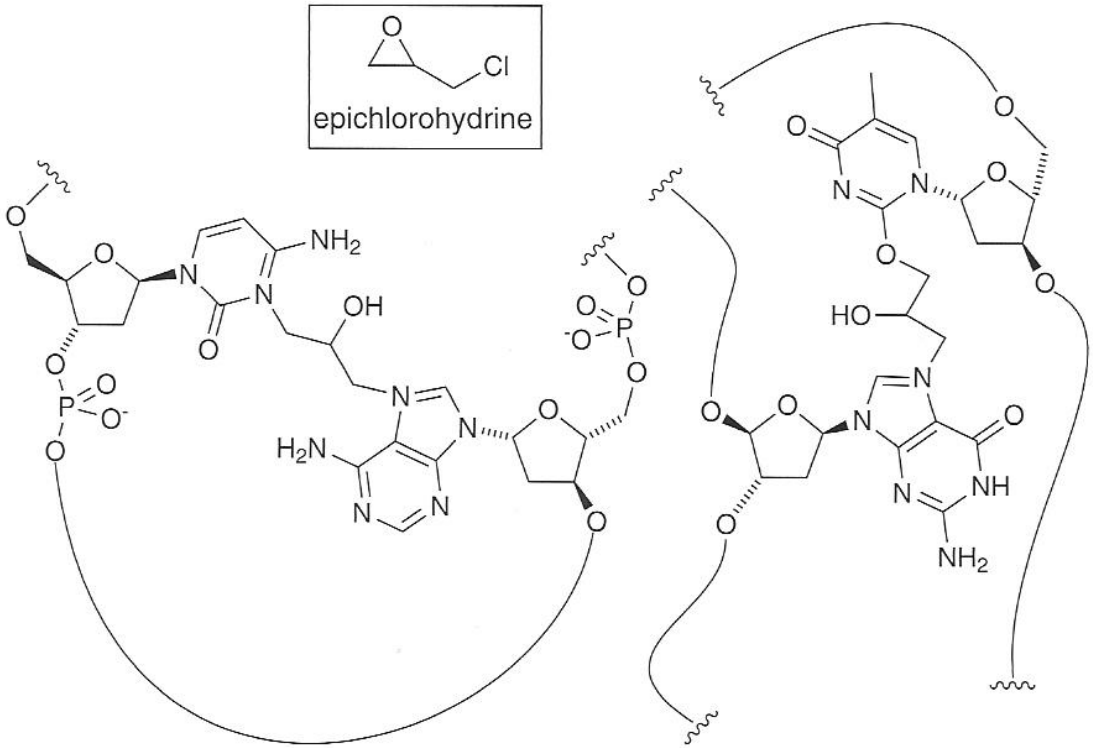


Figure 8.6 Intra- and interstrand cross links by the bifunctional epichlorohydrin, which to the left has reacted with adenine and cytosine in the same strand and to the right with guanine and thymine in opposite strands.

Chemical toxicology

Genotoxic effects

DNA bases modification:

- *radicals*

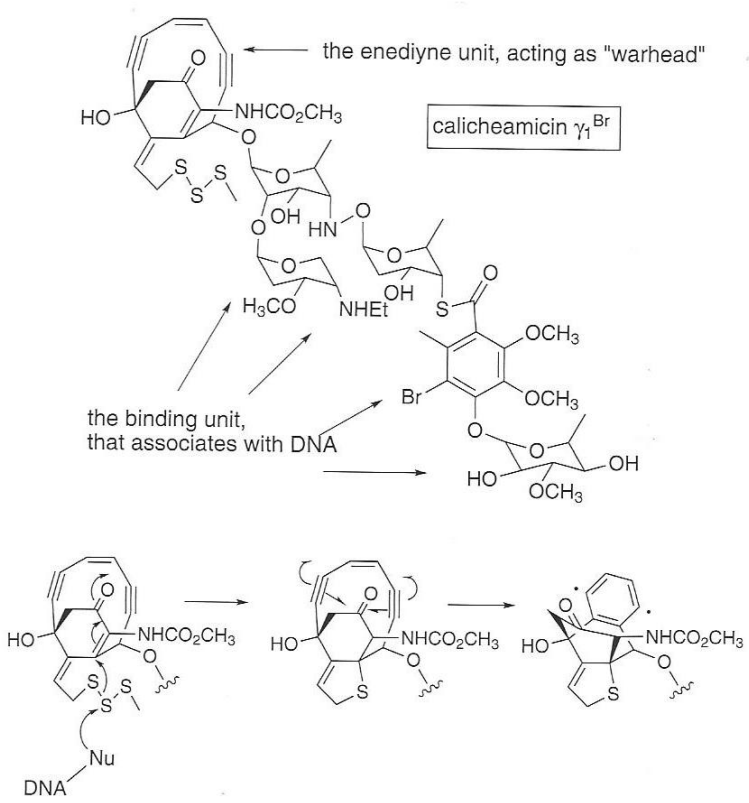


Figure 7.4 The antitumor antibiotic calicheamicin γ_1^{Br} and its interaction with DNA.

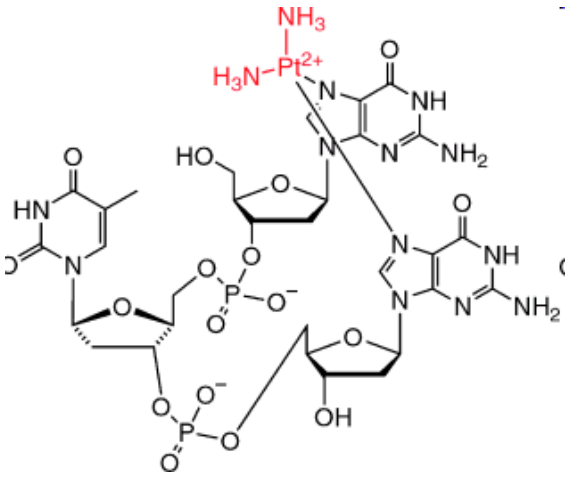
both strands cutting → chromosomal aberration

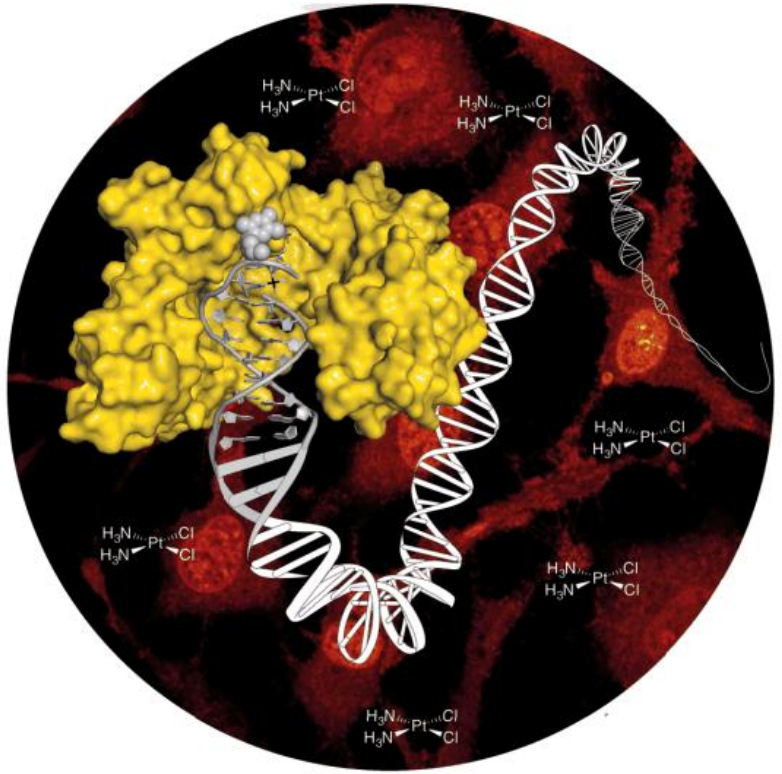
Chemical toxicology

Genotoxic effects

DNA bases modification:

- *metal ions* (Ni^{2+}, Cd^{2+}, Cr^{6+})
- *metal complexes* (Pt^{2+})





Angewandte Chemie International Edition **2010**, 49, 2949

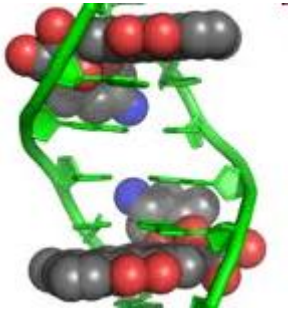
Chemical toxicology

Genotoxic effects

Intercalation:

✓ flat molecules

- *PAH*
- *aflatoxins*
- *daunomycin*



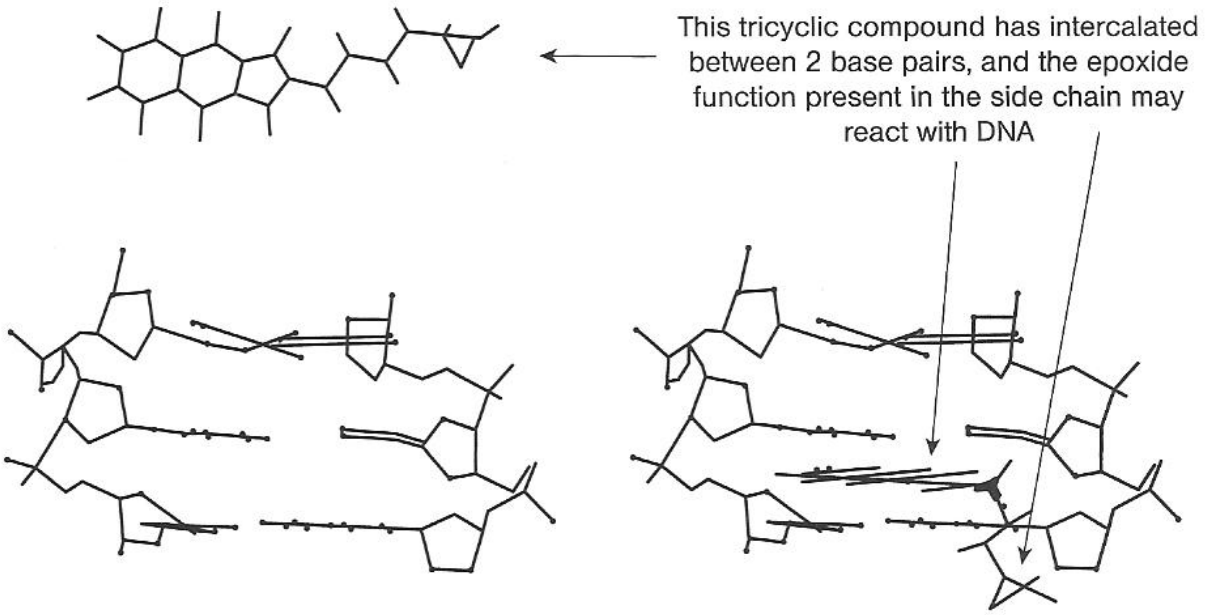


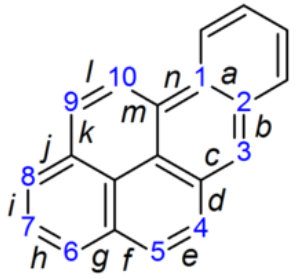
Figure 8.7 Intercalation.

Chemical toxicology

Genotoxic effects

Intercalation:

✓ flat molecules: **PAHs**: Formed by incomplete combustion of other hydrocarbons. Condensed ring system with high C/H ratio. Sources include engine exhaust, wood stove smoke, cigarette smoke, charbroiled food, tires, creosote. Poorly water soluble: soil accumulation.



Pyrene nomenclature

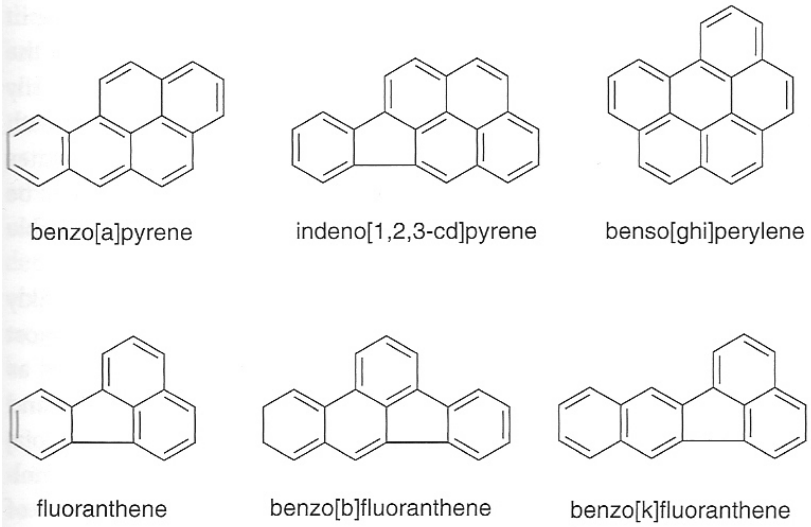
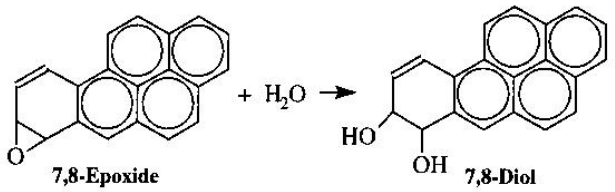
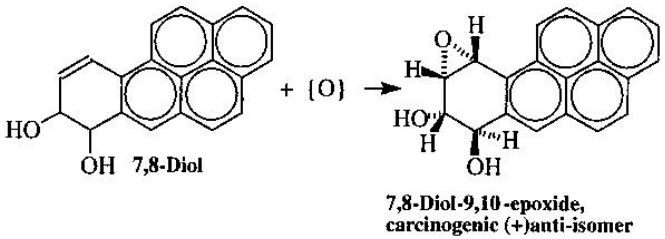


Figure 9.1 Examples of relatively common and dangerous PAHs.





Chemical toxicology

Genotoxic effects

Microtubules damage:

✓ Microtubules are protein structures that move chromosomes during mitosis

- *colchicine*