TOXICOLOGICAL CHEMISTRY of CHEMICALS, *Cont.*

Toxic Organic Compounds

1

Toxic Organic Compounds

Synthetic chemicals

- Most are derived from petroleum or natural gas
- Types:
  - **Polycyclic aromatic hydrocarbons (PAHs)**
  - **Organochlorine insecticides**
  - **Organophosphate** and **carbamate insecticides**
  - **Organic herbicides**
  - **Dioxin contaminant** of herbicides and wood preservatives

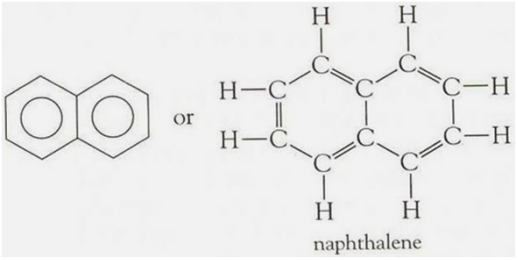
2

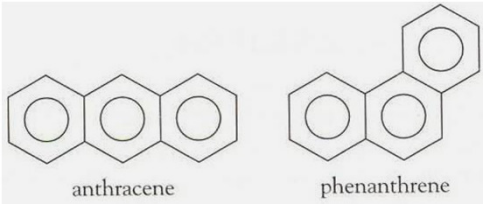
Polycyclic Aromatic Hydrocarbons (PAHs)

3

Polycyclic Aromatic Hydrocarbons (PAHs)

- PAHs consist of fused benzene rings
- *Examples:*





4

PAHs - *Cont.*

Uses:

- Only naphthalene is made commercially
  - used as precursor to plasticizers, insecticides, surfactants, etc)
- Other PAHs don't have uses

Source:

- Incomplete combustion of C-based fuel (coal, wood, diesel)
  - Diesel engine exhaust recently labeled "***probable human carcinogen***"
- "Tar" of cigarette smoke
- Surface of charred or burnt food; Smoked food

NOTE: PAHs constitute 0.1% (= 1000 ppm) of airborne particulate matter

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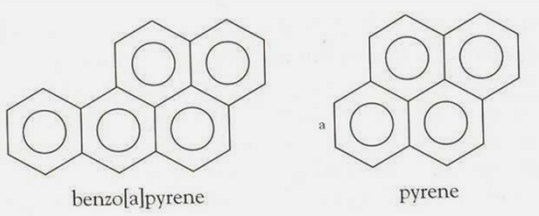
PAHs (Cont.)

Health effects:

- Carcinogenic to test animals
  - ***Probable human carcinogen***
    - Most notorious is benzo[a]pyrene

Level in several urban sites in the Great Lakes exceeds the current guidelines



- *Bioaccumulates* in the food chain => a worrisome pollutant

6

PAHs (Cont.)

Many cities in developing countries have chronic problems with carbon-based particulate air pollution. For example, the serious indoor and outdoor air pollution which arises primarily from the unvented burning of coal and biomass for cooking and heating and consists primarily of PAHs, sulfur dioxide and particulate matter, is reputed to be responsible for over one million deaths annually in China. The rate of lung cancer in Chinese women is higher than that for men, possibly due to higher exposures to PAHs from coal burning and from cooking oil fumes.

The particulate matter containing PAHs is traceable not only to smoke from the burning of coal, but also to the exhaust of diesel-fueled vehicles and of motor scooters with two-stroke engines. For example, the air in Bombay, India is of such poor quality that breathing it for a day is said to be equivalent in toxicity to smoking ten cigarettes!

Baird, p. 365

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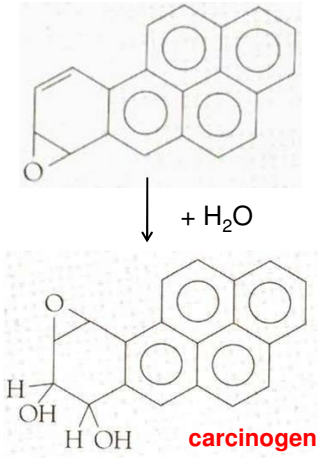
PAHs (Cont.)

Mechanism of PAH carcinogenity: Box 6-4, p. 363, Baird

- Research showed that PAHs themselves are not carcinogenic
  - Their ***metabolic products*** are carcinogenic
- **Chemical transformation:**
  (1) oxidation into an epoxide ring
  (2) Subsequent hydration produces the active carcinogen
  - Addition of H^+ forms a stable cation that can bind to DNA, inducing mutations and cancer



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PAHs (Cont.)

Environmental Chemistry of PAHs:

Transport *in the atmosphere*

- ≤ 4 fused ring remain gaseous
  - Form degradation products upon reaction with *free radicals* in the air
- > 4 fused ring have low vapor P
  - Condense and adsorb onto surface of soot and ash
  - They become ***respirable***

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PAHs - Environmental Chemistry *(Cont.)*

Transport *in the hydrosphere*

- Creosote, a coal tar derivative used as wood preservative, contains PAHs
  - Used in fishing docks (immersed in water)

PAHs leach out

Water pollution
(Lobster, fatty tissues of fish, whales)

- Oil spills from tankers, refineries and off-shore drilling sites also cause pollution of water with PAHs

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Organochlorine Insecticides

Organochlorine Insecticides

NOTE: The following information were taken from Baird, C. "Environmental Chemistry, 2nd ed. (2003), pp. 297-.

Characteristic properties

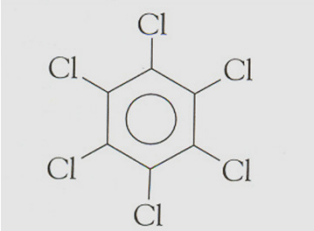
- Stable towards environmental degradation
- Low solubility in water
- High solubility in fatty materials (hydrocarbon-like) in living matter
- Relatively high toxicity to insects
- Low toxicity to humans

Properties responsible for their ***bioaccumulation***

Organochlorine Insecticides (Cont.)

Example: **HCB** or **hexachlorobenzene**

- Used as fungicide for cereal crops after WWII
- Extremely persistent => Led to its widespread env'l contamination
- Toxicity effect:
  - Carcinogenic to lab rodents
  - Probable human carcinogen



hexachlorobenzene (HCB)

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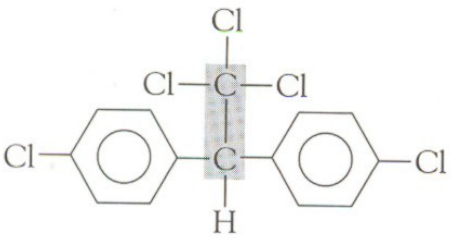
Organochlorine Insecticides (Cont.)

DDT or ***para*-dichlorodiphenyltrichloroethane**



(DDT): *para*-dichlorodiphenyltrichloroethane

Historical perspective:

- **1939**: **Paul Müller** (Swiss) discovered DDT as insecticide
  [He later received the 1948 Nobel Prize in medicine and physiology]

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DDT – *Cont.*

Historical perspective: (Cont.)

- During WWII DDT was used to combat insect-transmitted illnesses
  - Malaria
  - Yellow fever

  } Transmitted by **mosquitoes**
  - Typhus => transmitted by body lice
  - Plague => carried by fleas
- W.H.O. estimated that > 5M lives have been saved by DDT

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DDT – *Cont.*

Historical perspective: (Cont.)

- After WWII, DDT became widely used as insecticide (accounted for 80 % of manuf. DDT)
  - Fruit trees
  - Vegetables
  - Cotton

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DDT – *Cont.*

Desirable properties of DDT as insecticide

- Persistent chemical
  - One spraying lasted for weeks or years (depending on method of application)
  - Persistence due to its:
    - Low vapor pressure *(low volatility)*
    - Low reactivity to light and microorganisms
    - Low solubility in water

  } Resisted degradation; transport

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DDT – *Cont.*

Environmental effects of DDT

- Persisted in soil for several years
  - ***Biomagnified*** in the food chain
- Some insect populations developed resistance
- Affected the reproductive abilities of birds
  - Metabolic prod. interfered with a Ca-regulating enzyme
    - Very thin shells; Baby bird unable to survive
- **1962: Rachel Carson** (biologist) published the "Silent Spring"
  Env'l problems associated with DDT
- **1973: EPA** banned all DDT uses (except those essential to public health)

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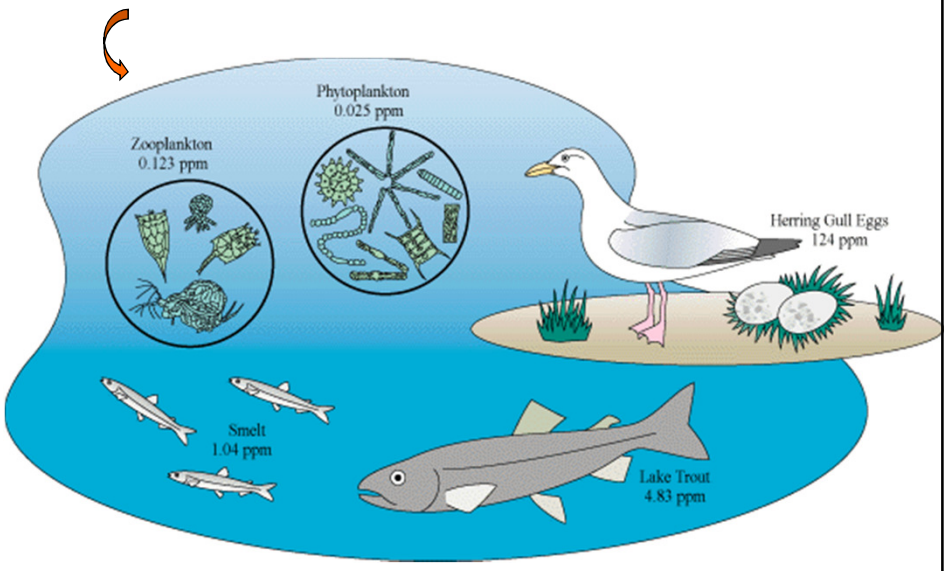
Accumulation and fate of DDT



19

DDT – *Cont.*

***Accumulation* and fate of DDT**

- DDT levels accumulated in fatty tissues => higher levels in older trout

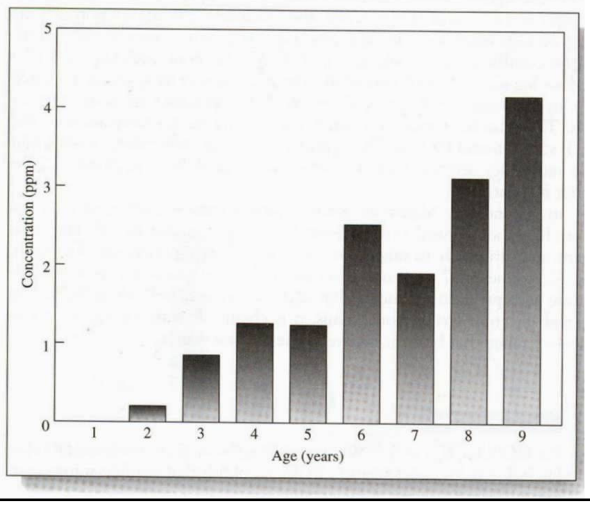


Figure 6-2
Variation with age of the average DDT concentration in Lake Ontario trout. (Source: *Toxic Chemicals in the Great Lakes and Associated Effects*, vol 1, part 2. 1991 Ottawa, Canada: Minister of Supply and Services.)

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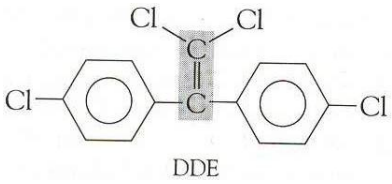
Accumulation and fate of DDT

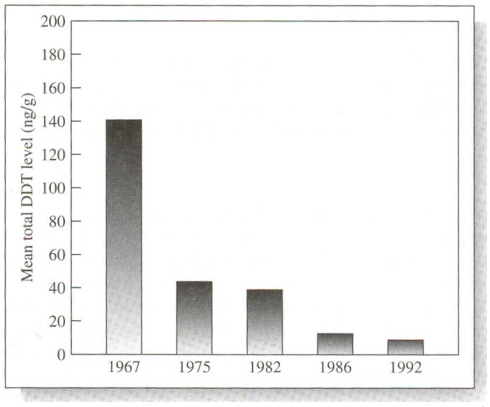
DDT in humans is slowly eliminated

- Stored in human fat mostly as its metabolic product DDE



DDE

Source: *Toxic Chemicals in the Great Lakes and Associated Effects*, vol 1, part 2. 1991 Ottawa, Canada: Minister of Supply and Services.



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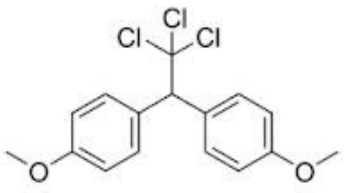
Organochlorine Insecticides - Analogs to DDT

DDT Analogs

- Same insecticidal properties as DDT
- Reasonably biodegradable
  - No bioaccumulation
- Best known is ***methoxychlor*** (insecticide)
  - Used domestically and in agriculture

Controls flies; mosquitoes



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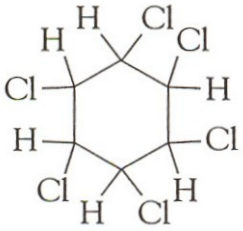
Other Organochlorine Insecticides

Lindane

- Contains one of 8 isomers of hexachlorocyclohexane
  - Called gamma isomer = has insecticidal properties
  - Same isomer in medical preparations for lice and scabies control
  - Treatment of seeds and seedlings



1, 2, 3, 4, 5, 6-hexachlorocyclohexane

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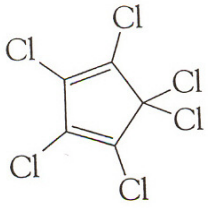
Other Organochlorine Insecticides – *Cont.*

Chlorinated cyclodienes

- ***Aldrin***, ***Dieldrin, Chlordane, Heptachlor***, etc.
  - Used to control various pests:
    - ✓ *Fire ants; cockroaches; termites; locusts*



Chlorinated cyclodienes

Undesirable properties

- Persistent chemicals; *Bioaccum.* due to solubility in fatty tissues
- Caused liver *cancer* in test animals
- Some are *teratogenic*

Prohibited use in the U.S.

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Modern Insecticides: Organophosphates and Carbamates

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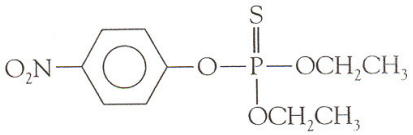
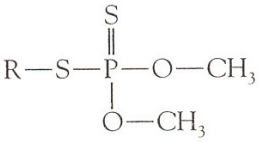
Organophosphate Insecticides

- Esters, amides, or simple derivatives of phosphoric acid

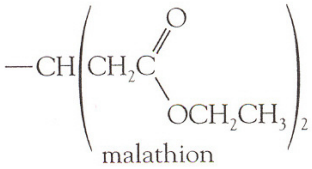
- Nonpersistent
  - Decompose within days or weeks
- Much more acutely toxic to humans and other mammals than are organochlorines
- Function as nerve poisons to insects
  - Inhibit enzymes in the insects' nervous system



parathion



where R =



malathion

Organophosphate (Cont.)

Undesirable properties

- Exposure by inhalation, swallowing or absorption th/ the skin can lead to immediate health problems

Clinical Signs (Organophospahe toxicity, http://www.michigan.gov/dnr/)

- ✓Excess salivation, lacrimation, abdominal pain, vomiting, and diarrhea.
- ✓Bronchoconstriction and an increase in bronchial secretions
- ✓Involuntary irregular, violent muscle contractions and weakness of voluntary muscles.
- ✓Death occurs as a result of respiratory failure.

- Concentrates in fatty tissues

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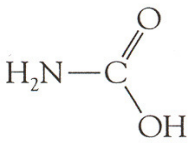
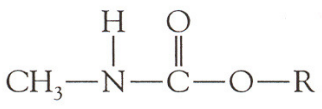
Carbamate Insecticides

Carbamates



carbamic acid



the general formula of a carbamate

- Nonpersistent
  - Decompose upon reaction with water, forming nontoxic products
- Low dermal toxicity
- Examples: *Carbaryl; Aldicarb; Carbofuran*
  - Lawn and garden insecticide
  - Low toxicity to mammals
  - Toxic to honeybees

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Naturally-Occurring Pesticides

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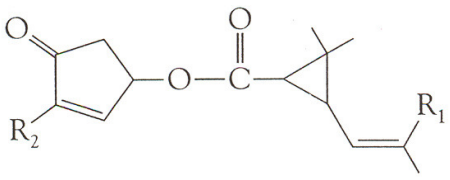
Natural Insecticides

- Manufactured by plants as defensive mechanism against insects
- Examples: *Nicotine; Rotenone; Pheromones and Juvenile hormones*

Pyrethrins

- Obtained from crysanthemum (certain species)
- Have been used by humans for centuries



general pyrethrin structure

Ex. Ground up dried flower heads used to control body lice during the Napoleonic times

- Paralyze insects (like organophosphates)

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Pyrethrins (Cont.)

Desirable properties

- Generally safe to use
- Mode of action: Cause paralysis on insects

Undesirable properties

- Photodecomposition

Synthetic pyrethrins = designed to withstand sunlight

- Outdoor application
- Names end in *-thrin*: *Ex*. Permethrin

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Organic Herbicides

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Herbicides

- Prior to use of organic pesticides:
  - Inorganic compounds like sodium <u>arsenate</u> were used as weed-killers

Toxic to humans;
Persistent chemicals

- Organic pesticides now dominate the market
  - High <u>selectivity</u> for certain plants

Leave other plants unharmed

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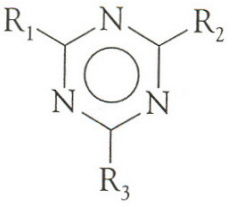
Organic Herbicides

Triazines

- Alternating N & C atoms in a six-membered ring



In herbicidal triazines, R_1 = Cl and R_2, R_3 = amino

general formula of the triazines

- Useful triazine herbicides contain Cl and -NH_2 or -NHR groups bonded to the ring carbon (next slide)

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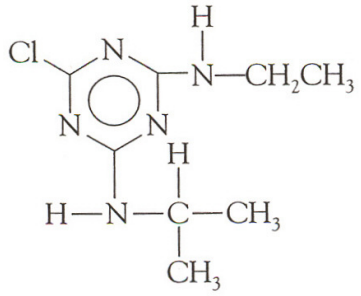
Triazines (Cont.)

- Best known is ***atrazine***



atrazine

Atrazine

Mode of action (as herbicide)

- Blocks photosynthesis
  - Higher plants (e.g. corn) are not affected because they rapidly degrade atrazine

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Atrazines (Cont.)

Uses

- Kills grassy weeds in corn and soybean fields

Undesirable properties

- Concentrations can build up in dry soil => No moisture to degrade it
  - Can eradicate all plants
  - High levels used to clear vegetation to create parking lots
- Widespread use can kill sensitive plants in water systems close to agricultural fields
- A possible human carcinogen (EPA list)

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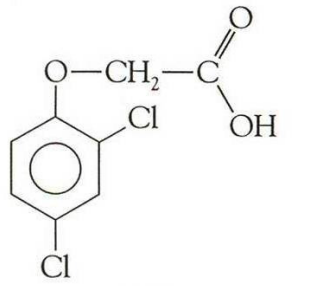
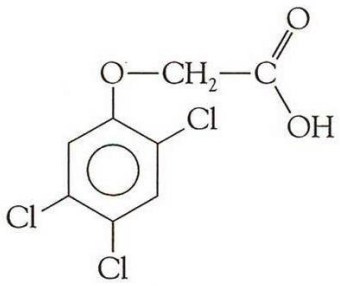
Other Organic Herbicides

Phenoxy herbicides

- Introduced as weed-killers after WWII
- Prepared from phenol
- Examples: ***2,4-D*** and ***2,4,5-T***



2,4-D
2,4-dichlorophenoxyacetic acid



2,4,5-T
2,4,5-trichlorophenoxyacetic acid

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Phenoxy Herbicides (Cont.)

2,4-D & 2,4,5-T

Uses

- **2,4-D**: Control of broad-leaf weeds in lawns, golf course greens and agricultural fields
- **2,4,5-T**: Clearing bush on roadsides and power line corridors

Undesirable properties

- Increased incidence of the cancer ***non-Hodgkin's lymphoma*** among farmers in the Midwest who applied large quantities of 2,4-D

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Dioxin Contamination of Herbicides

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Cause of Dioxin Contamination

Synthesis of 2,4,5-T Do this on the board

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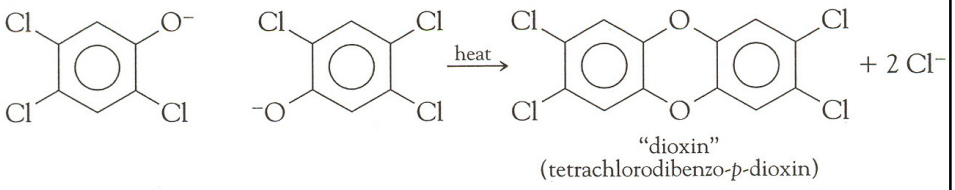
Cause of Dioxin Contamination (Cont.)

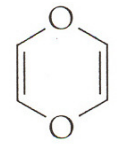
- Trichlorophenol is a ***weak acid***
  - Ionizes to a small extent into trichloro**phenoxy ion**
  - Self-reaction of phenoxy ion at **high T** produces ***"dioxin"***



"dioxin"
(tetrachlorodibenzo-*p*-dioxin)

  - High T and high [phenoxide] => higher levels of dioxin formed

Structure of real **dioxin**



1,4-dioxin

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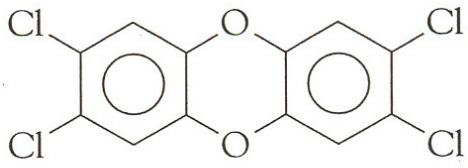
Dioxin Contamination: Historical Perspective

Agent Orange

- A **1:1 mixture** of **2,4-D** and **2,4,5-T**
- Used as defoliant during the Vietnam war
- Contains about ***10 ppm dioxin*** as contaminant! HOW come?



"dioxin"
(tetrachlorodibenzo-*p*-dioxin)

http://www.landscaper.net/agent.htm

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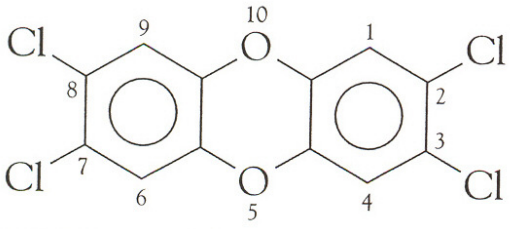
Dioxin Nomenclature

- The three-ring unit is called **dibenzo-*p*-dioxin**
- Carbons shared between 2 rings (and thus are not bound to H) are not numbered --- *can't take any more substituent*
- C #ing follows a clockwise pattern from C-1



2,3,7,8-tetrachlorodibenzo-*p*-dioxin
(2,3,7,8-TCDD)

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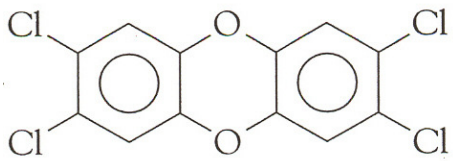
Dioxin Congeners

Congeners

- Members of a chemical family that differ only in the number and position of the same substituents
- There are **75** dioxin congeners



"dioxin"
(tetrachlorodibenzo-*p*-dioxin)

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Dioxin: Health and Environmental Effects

Health Effects

- One of the most toxic of all synthetic substances to some animals
  - LD_{50} of 0.6 ug/Kg body mass in male guinea pigs
- The type and degree of its toxicity to humans is largely unknown
  - Known to cause a severe skin condition called ***chloracne***

Environmental Effects

- A stable, ***persistent*** environmental pollutant
- Emission product from incineration of organochlorine compounds

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Dioxins

"**Dioxin**" is a general term for a group of hundreds of chemicals that are highly persistent in the environment.

- The most toxic compound is 2,3,7,8-tetrachlorodibenzo-p-dioxin or **TCDD**.

TCDD structure. Image available at http://www.greener-industry.org/pages/chlorine/3chlorine_Issues.htm

Reference: Dioxin Homepage at http://www.ejnet.org/dioxin/

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Dioxins

Dioxin is formed as an unintentional **by-product** of many industrial processes involving ***chlorine***, such as:

- Waste incineration,
- Chemical and chlorinated pesticide manufacturing,
- Production of polyvinyl chloride (PVC) plastics and
- Pulp and paper bleaching

Dioxin was the primary toxic component of ***Agent Orange***, was found at **Love Canal** in Niagara Falls, NY and was the basis for evacuations at Times Beach, MO and Seveso, Italy.

Reference: **Dioxin Homepage at** http://www.ejnet.org/dioxin/

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In January 2001, the U.S. National Toxicology Program upgraded **2,3,7,8-TCDD** from "Reasonably Anticipated to be a Human Carcinogen" to "***Known to be a Human Carcinogen***.

Reference: **Dioxin Homepage**

http://www.ejnet.org/dioxin/

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Levels of Dioxin in Food Supply (N. America)

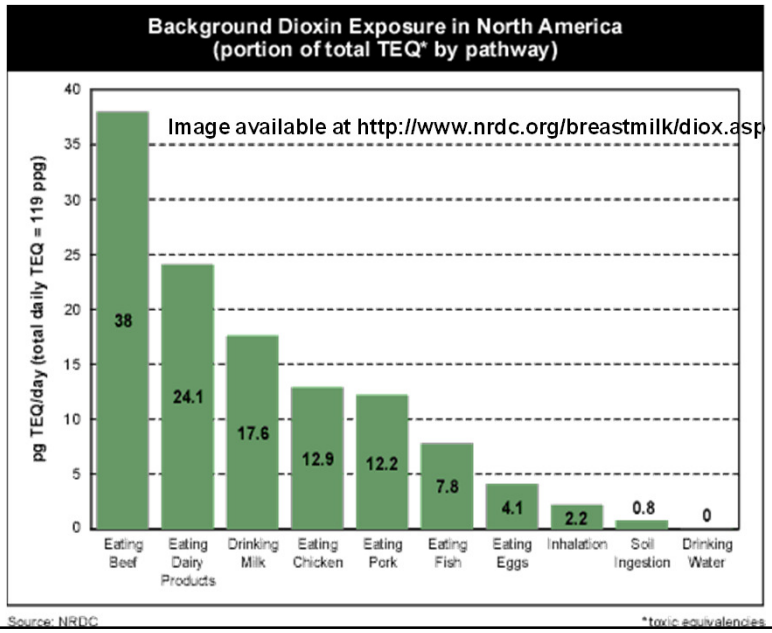

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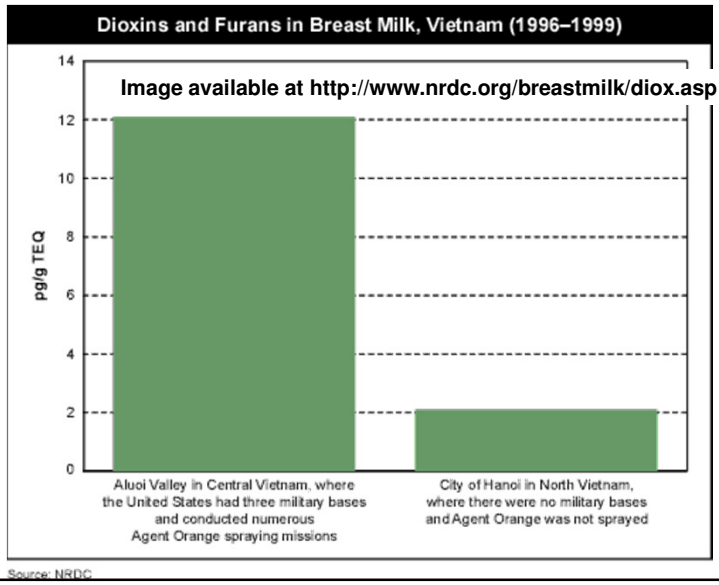
Figure 7 shows that dioxin and furan levels in breast milk collected between 1996 and 1999 from women in the Aluoi Valley in central Vietnam were about ***six times higher*** than those in breast milk collected in 1988 in the city of Hanoi in northern Vietnam, where no **Agent Orange** was sprayed



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Polychlorinated Biphenyls (PCBs)

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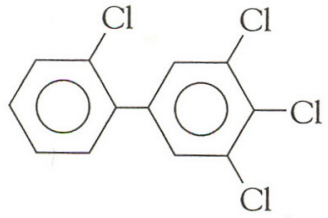
Structure and Properties of PCBs

Structure

- An example of a PCB molecule is:
- Ring C #ing similar to dioxins



2,3′,4′,5′-tetrachlorobiphenyl

Properties

- High chemical, thermal and biological stability
- Low vapor pressure
- Insoluble in water; Soluble in fatty/oily substances
- Inexpensive, yet excellent electrical insulators

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Uses of PCBs

- ***Coolant-insulation fluids*** in transformers and capacitors
- ***Plasticizers*** = agents used to make other materials more flexible
- ***Deinking solvent*** for recycling newsprints
- ***Heat-transfer fluid*** in machinery

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Environmental Contamination of PCBs

- From PCB-containing **discarded electrical equipment**
- **Incineration** plants --- since PCBs escape as vapors
- **Waste discharges** from capacitor manufacturing plants
  - Source of PCB contamination in the sediments of **Hudson River**
    - ***Bioaccumulated*** in fish and other aquatic organisms

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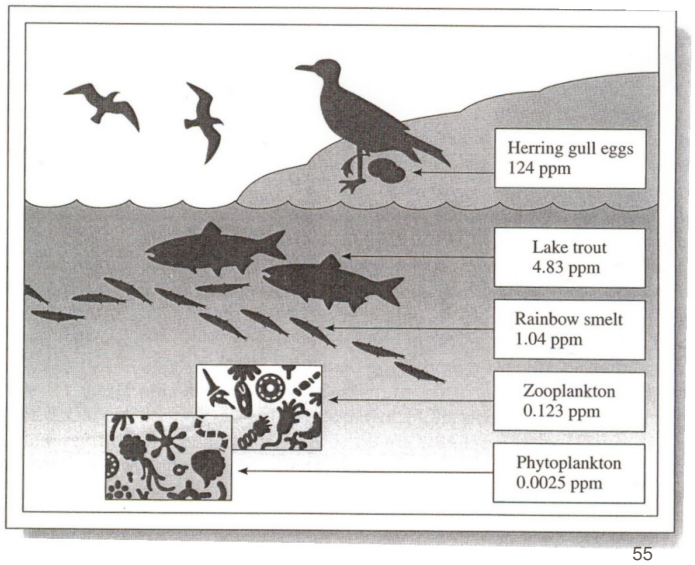
Environmental Contamination of PCBs

Figure 6-7
The bioaccumulation and biomagnification of PCBs in the Great Lakes aquatic food chain. (Source: *The State of Canada's Environment*. 1991. Ottawa: Government of Canada.)



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Environmental Contamination of PCBs

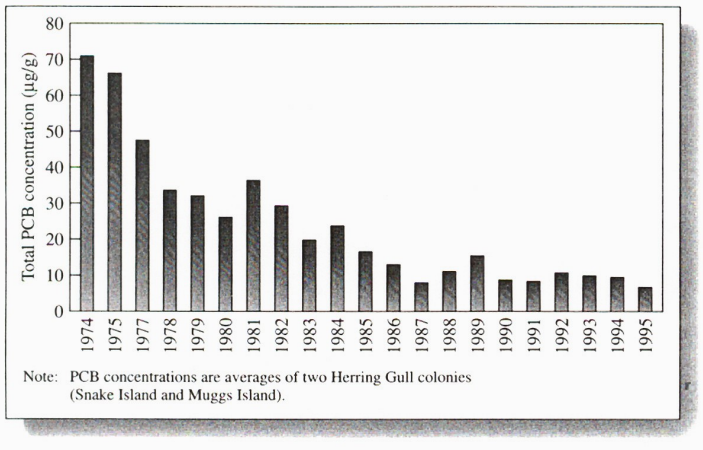

Figure 6-8
Trends in total PCB concentrations in herring gull eggs in Lake Ontario, 1974–95. (Source: *The State of Canada's Environment 1996*. 1996. Ottawa: Government of Canada.)

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Aside: Toxic Alkaloids

Alkaloids are naturally-occurring complex amines, usually isolated from plants

Medical uses of alkaloids

- ***Stimulants*** – Ex. Caffeine, Nicotine
- ***Analgesic*** – Ex. Morphine, Codeine
- ***Tranquilizers***

Other properties

- ***Addictive***
- ***Narcotics*** – Ex. Morphine; Heroin
- ***Some are toxic*** – Coniine (cup of hemlock); Nicotine

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Alkaloids (Cont.)

Some alkaloids from nature: The opium ***poppy***

"Incisions in the seed capsules of this plant yield a milky sap. When air-dried and kneaded, the sap forms a soft material known as opium, which contains ***opioids***, a class of alkaloids known for their pain-killing and tranquilizing effects."

Source: J. Suchocki. "Conceptual Chemistry," Addison Wesley, San Francisco: 2001. Chapter 14 opening photograph, p. 436

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