Polychlorinated Biphenyls

PCBs

PCBs

- 209 compounds in class, with varied toxicity profiles
- May have one to ten chlorines
- PCB formulations are mixtures
  - 20 PCBs generally present in forumalations
  - average 3 to 5 chlorines
- Hydrophobic, lipophilic
- Very stable chemically

Polychlorinated Biphenyls (PCBs)

- PCB's
  - Heat stable oils once used as transformer and hydraulic fluids
  - Non flammable transformer dielectric cooling oil
  - Mineral oil was used but PCB was more stable
  - Also used as a plasticizer and lubricant until banned in 1979
  - Basic unit aromatic hydrocarbon biphenyl, 10 possible Cl positions on two rings
  - 207 Congeners – compounds formed from the same process

Features in Common, esp. PCBs and Dioxins/Furans

- Highly lipophilic
  - bioaccumulation
  - bioconcentration
- Persistent organic pollutant
  - adsorbs onto clay particles
  - sorbs and desorbs on surface of vegetation
  - long-range seasonal transport
  - accumulation in Arctic of organochlorines

Features in Common, esp. PCBs and Dioxins/Furans

- Structural similarities lead to similar toxicity profiles among dioxins, furans and some "coplanar" PCBs
- Principal toxic outcome in human beings for the class is chloracne
  - acneiform skin rash, very persistent
  - preauricular distribution characteristic
  - refractory to treatment

Chloracne and polycyclic halogenated organics

- Chloracne is non-specific: may be cased by
  - polychlorinated dibenzofurans and dioxins
  - polybrominated dibenzofurans and dioxins
  - polychloronaphthalenes
  - polychlorobiphenyls
  - polybromobiphenyls
  - tetrachloroazobenzenes

Chloracne is an acne-like eruption of blackheads, cysts, and pustules associated with over-exposure to certain halogenic aromatic hydrocarbons, such as chlorinated dioxins and dibenzofurans. The lesions are most frequently found on the cheeks, behind the ears, in the armpits and groin region.

The condition was first described in German industrial workers in 1897 by Von Bettman, and was initially believed to be caused by exposure to toxic chlorine (hence the name "chloracne"). It was only in the mid-1950s that chloracne was associated with aromatic hydrocarbons. The substances that may cause chloracne are now collectively known as "chloracnegens". Chloracne is particularly linked to toxic exposure to dioxins (byproducts of many chemical processes, including the manufacture of herbicides such as Agent Orange) — so much so that it is considered a clinical sign of dioxin exposure. The severity and onset of chloracne may follow a typical asymptotic dose response curve.

PCBs

- Many desirable properties
  - low flammability
  - electrically nonconductive
  - good heat exchange
  - lubricating
  - solvent
- Ban on new manufacture
- Hazardous waste, old transformers

PCBs

- In addition to chlorine substitution, chlorine positioning plays a major role in toxicity:
  - para: resembles thyroxine
  - ortho: "non-co-planar" configuration
  - para, meta: "co-planar" configuration
- Co-planar PCBs resemble TCDD, bind to Ah receptor
- Co-planar $\rightarrow$ non-co-planar in environment

Toxicokinetics of PCBs

- Absorption by any route
  - low volatility but may be adsorbed on particles
  - heavy skin exposure common in past
  - transplacental, breast milk important routes
- Distribution
  - lipophilic, higher %Cl $\propto$ affinity for adipose
  - adipose depot
  - may mobilize with weight loss

Toxicokinetics of PCBs

- Metabolism
  - primarily hepatic metabolism
  - very slow
  - higher %Cl $\propto$ resistance to metabolism
  - induction of Phase I, II enzymes
- Excretion
  - bile, feces
  - breast milk

Toxicodynamics of PCBs

- Generalizations regarding toxicity:
  - much less potent than dioxins, furans, by factor of 10,000 or 100,000
  - higher chlorine content associated with greater toxicity
  - coplanar PCBs associated with higher TCDD-like toxicity, activity resembling dioxins and furans
  - non-coplanar associated with other toxicity

Toxicity of PCBs - 1

Animal Models

- Hepatotoxicity
- Neuropathy
- Repro effects
- ↓Ab response
- Cancer (hepatic, GI, leukemia, lymphoma)
- Xenoestrogen effects

Humans and Primates

- Chloracne
- Hepatotoxicity
  - hepatocellular injury, possibly jaundice
  - porphyrin metabolism
- ?Otitis media
- Reduced neuro development

Toxicity of PCBs - 2

- Coplanar PCBs interact with Ah receptor
- Biotransformation enriches non-co-planar
- Non-coplanar PCBs may show different patterns of toxicity:
  - neurotoxicity
  - stimulation of insulin release, ↓biosynthesis
  - xenoestrogen effects
  - neutrophil inactivation

Toxicity of PCBs - 3

- "Fish-Eaters"
  - Great Lakes - Jacobson studies
  - Sweden, east v. west coast
  - Netherlands, North Sea
- Consistent and strongly suggestive
  - depressed neurocognitive function
  - associated with PCB-contaminated fish consumption at reasonable amounts

Toxicity of PCBs - 4

- Organochlorine ecosystem contamination
  - northern latitudes
  - susceptible population - Inuit
    - contaminated fish
    - marine mammals
    - breast feeding
  - elevated rate of otitis media, meningitis
    - immunsuppression
    - associated with PCB 77, 126, 169

Toxicity of PCBs - 5

- Great controversy
- Ecotoxicity?
  - marine mammals
  - zooplankton and filter feeders
- Issues arising:
  - breast feeding
  - breast cancer
  - fish advisories

Carcinogenesis of PCBs

- Highly controversial
- IARC classifies 2A: "probable"
- EPA, ATSDR treat as human carcinogens
- Evidence suggests certain types:
  - hepatocellular Ca
  - ?cholangiosarcoma and biliary tract
  - ?leukemia
  - ?non-Hodgkins lymphoma

Problems in studying PCBs

- Most human toxicity information comes from Yusho incident
  - very high level of exposure
  - contamination by furans
- Susceptible populations are confounded
- PCBs track with other organochlorines
- Ubiquitous distribution in industrial society
- Analytical methods difficult, expensive

Toxic Equivalency Factors

- Most common system is WHO/IPCS
- TEFs are based on potency compared to 2,3,7,8-TCDD = 1
- Applied to PCBs, dioxins, furans, other
- Database incomplete, not systematic
- Most TEFs derive from potency for enzyme induction (CYP1A1)

The Xenoestrogen Hypothesis

- Many POPs have weak estrogenic properties, inc. D&Fs, PCBs, pesticides
- Concern over:
  - breast Ca
  - endometriosis
  - ↓sperm counts, ↑hypospadias
- Phytoestrogens in diet
- Increased number of menstrual cycles

TRACE ORGANICS TESTING LABORATORY

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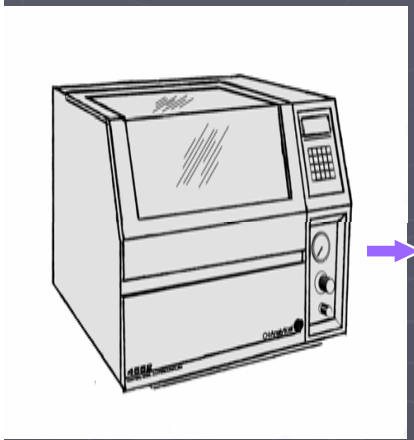
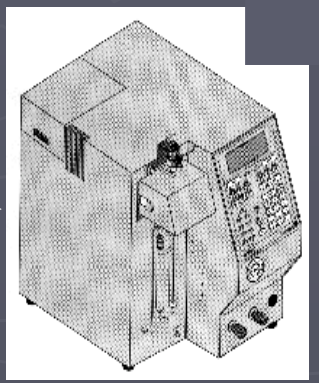
INSTRUMENTATION I

Sampling → Purge, Trap & Desorption → Analysis → Process Control, Data Process & Report



O.I.Analytical
4552 Water/Soil Autosampler



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Sampler Concentrator

Shimadzu QP-5000
GC/MS

Micron
Computer

HP Laser
Printer