

# Solvents

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# What is a Solvent?

For purposes of occupational toxicology:

- Liquid
- Organic compounds
- Dissolves other organic compounds
- Lipophilic
- Usually volatile
- Same compounds in other contexts

# Uses of Solvents

## As a Solvent

- Dissolution
- Extraction
- Degreasing
- Inks, dyes, paints, coatings
- Dilution, dispersal
- Dry cleaning

## As Something Else

- Fuels
- Feed stocks
- Drugs of abuse
- Beverages
- Antifreeze
- Explosives
- Pollutants

# Chemical Classes of Solvents - 1

Aliphatic hydrocarbons

*Gasoline*

Cyclic hydrocarbons

*Cyclohexane*

Aromatic hydrocarbons

*Benzene, toluene*

Ketones

*Cyclohexanone, acetone*

Aldehydes

*Acetaldehyde*

Alcohols

*Ethanol, methanol*

Ethers

*Glycol ethers*

Esters

*Ethyl acetate*

# Chemical Classes of Solvents - 2

Nitrohydrocarbons

*Ethyl nitrate, TNT*

Halogenated alkanes

*1,1,1-trichloroethane,  
carbon tetrachloride,  
chloroform*

Halogenated alkenes

*Trichloroethylene, vinyl  
chloride*

Mixtures

*Kerosene, "white spirit"*

# Toxicokinetics of Solvents - 1

- Rapid absorption
  - inhalation route (volatile solvents, by diffusion)
  - transdermal route
  - ingestion (uncommon)
- Distribution
  - by lipid content and vascularity
  - adipose and lipid-rich tissues are depots for storage

# Toxicokinetics of Solvents - 2

- Metabolism
  - generally hepatic, by MFO system
  - bioactivation to toxic metabolites for some
- Excretion
  - urine, conjugated products
  - feces, conjugated products
  - expired air, volatile solvents

# Common Features in Toxicity of Solvents

- Local dermal effects due to extraction of lipid from dermis
- CNS depressant effect
- Neurotoxicity
- Hepatotoxic effects
- Nephrotoxicity
- Variable cancer risk

# Hepatic Effects of Solvents - 1

- Chemical hepatitis, with ↑transaminases indicating hepatocellular injury
- Steatosis (fatty liver), occasionally progressing to hepatic necrosis
- Possible cirrhosis on recovery
- Reduced metabolism of other xenobiotics
- ?] Acetylcysteine

# Hepatic Effects of Solvents - 2

- Mechanisms of hepatotoxicity
  - dehalogenation
  - free radical formation
- Halogenated hydrocarbons have greatest toxicity
  - carbon tetrachloride, chloroform >>
  - 1,1,1-trichloroethane, trichlorethylene >>
  - nonhalogenated hydrocarbons

# Renal Toxicity of Solvents

- Acute tubular necrosis
  - acute heavy exposure
  - halogenated HCs, glycols, toluene, petroleum distillates
- Glomerulonephritis
  - chronic, long term exposure
  - gasoline implicated

# Acute Central Neurotoxicity of Solvents

General anesthesia-like activity or selective inhibition

- narcosis
- euphoria
- agitation (disinhibition)
- dyscoordination, ataxia, dysarthria

# Chronic Central Neurotoxicity of Solvents

- Controversial, difficult to attribute
- “Painter’s syndrome”
  - depression
  - retarded psychomotor performance
  - personality change
  - decline in short-term memory
- WHO Neurobehavioural Test Battery

# Problems in Assessing Neurotoxicity of Solvents

- Nonspecific case definition
- Replication of prevalence rates
- Variability in neurobehavioural tests
- Non-specificity of physiological measures
- Confounding with ethanol, trauma, other factors
- Mixed exposures

# Peripheral Neurotoxicity and Solvents - 1

- Distal axonal neuropathy
- Specific solvents known or suspected to cause PN:
  - *n*-hexane, methyl-*n*-butyl ketone (MnBK), carbon disulfide (known)
  - styrene, tetrachlorethylene (suspected)
- Generally presents first in lower extremities

# Peripheral Neurotoxicity and Solvents - 2

- Early sensory impairment paresthesias
  - numbness
  - loss of proprioception (later), e.g. Achilles tendon reflex, vibration
- Later motor impairment
  - motor weakness
  - denervation atrophy

# Peripheral Neurotoxicity and Solvents - 3

- Electrophysiology
  - denervation pattern
  - slowed conduction
- Differential diagnosis
  - other toxic (e.g. ethanol- induced) neuropathy
  - mechanical (e.g. compression) trauma
  - nutritional deficiencies, metabolic, hereditary SSxs
  - demyelinating conditions, paraneoplastic SSxs

# Peripheral Neurotoxicity Due to Hexanedione Product

## A Classic Toxicity Syndrome in OccMed

- Recognized in 1964 in Japan, sandal mfg.
- Later found to be prevalent
- Onset rapid (months)
- MEK may potentiate
- Control by substitution

## Common Mechanism of *n*-Hexane, MnBK

- Both metabolized to 2,5-hexanedione
- Axonal die-off
- Denervation
- Distal degeneration of axon
- Tri-*o*-cresyl phosphate

# Specific Toxicology of Aliphatic Solvents

- Gasoline
  - ?glomerulonephritis,
  - aspiration pneumonitis,
  - ?Pb content
- Aliphatic nitrates (inc. TNT)
  - methemoglobin
  - hypotension
  - severe hepatotoxicity

# General Toxicology of Halogenated Aliphatic Solvents

- May be significant water disinfection byproducts
- Severe hepatotoxicity ( $\text{CCl}_4$ ,  $\text{CHCl}_3$ )
- Nephrotoxicity
- Cardiac arrhythmias
- Carcinogenicity
  - alkanes: polyhalides, chlorides
  - alkenes: monohalides, chlorides

# Specific Toxicology of Halogenated Aliphatic Solvents

- Trichlorethylene (Ca)
  - “degreaser’s flush”
- Carbon tetrachloride, chloroform - (Ca)
  - severe hepatotoxicity
- Dichloromethane (methylene chloride,  $\text{CH}_2\text{Cl}_2$ ) (Ca)
  - metabolized to CO

# Ethanol - 1

- Ethanol is the relevant example for alcohols
  - $\rightarrow$ acetaldehyde ( $\text{CH}_3\text{CHO}$ ) $\rightarrow$ acetate ( $\text{CH}_3\text{COO}^-$ )
- Alcohol dehydrogenase
  - zero-order kinetics
  - inhibited by disulfiram, metranidazole
- Catalase (limited by  $\text{H}_2\text{O}_2$ )
- Inducible MEOS

# Ethanol - 2

- Adverse effects - numerous and protean!
  - Acute alcohol intoxication
  - inebriation
  - chronic alcohol abuse, dependency
  - fetal alcohol syndrome
- Withdrawal syndrome
  - delirium tremens
  - seizure disorder

# Other Alcohols

- Methanol
  - $\rightarrow$ formaldehyde  $\text{CH}_2\text{O}$  (by AD)  $\rightarrow$ formic acid  $\text{CHOO}^-$  (by aldehyde deHase)
  - metabolism from formate very slow in primates
  - retinal toxicity  $\Rightarrow$ visual  $\Delta \Rightarrow$ blindness
  - delayed metabolic acidosis (not lactic acidosis)
  - ] ethanol, hemodialysis with indications
  - Ethanol competitively inhibits AD

# Glycols

- Ethylene glycol (ethanediol) → →oxalate
  - oxalate stones,
  - nephrotoxicity, tubal deposition of oxalate
  - hypocalcemia (by chelation)
  - acidosis with large anion gap
  - ] ethanol, hemodialysis
- Glycol ethers
  - reproductive toxicity

# Benzene

- →epoxide (“NIH shift”)→phenol  
→catechol, →→*t*, *t*-muconic acid
- ?Nongenotoxic carcinogen
- Aplastic anemia, acute myelogenous leukemia
- Muconaldehyde, quinones in bone marrow
- Monitor urinary phenol, urinary benzene, CBC (PMNs)

# Specific Toxicology of Aromatic Solvents

- BTEX (benzene, toluene, ethylbenzene, xylene) - common contaminants in soil and water. Risk driven by benzene
- Toluene - potent CNS toxicity, chronic cognitive impairment
- Xylene - irritant to mucous membranes, esp. eye