



Clinical Toxicology

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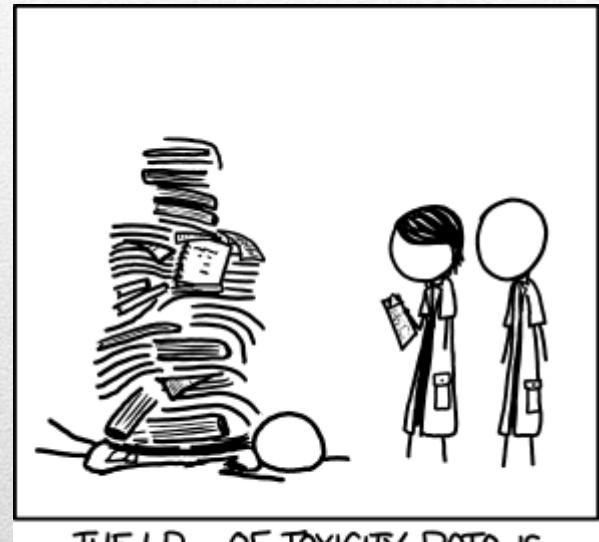
Toxicology

- Study of xenobiotics
 - Substances not normally found in or produced by the body
 - Poisons: animal, plant, mineral or gas
 - Snake venom, poison sumac, arsenic, or chlorine gas
 - Toxins: biologically synthesized
 - Botulinum toxin, cone snail venom



Toxicology

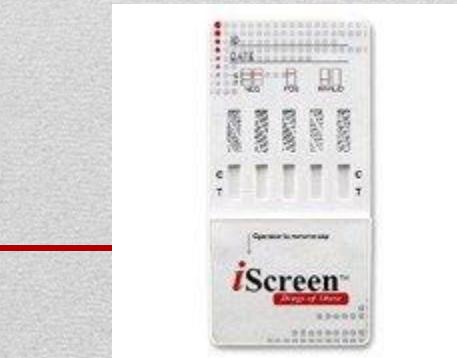
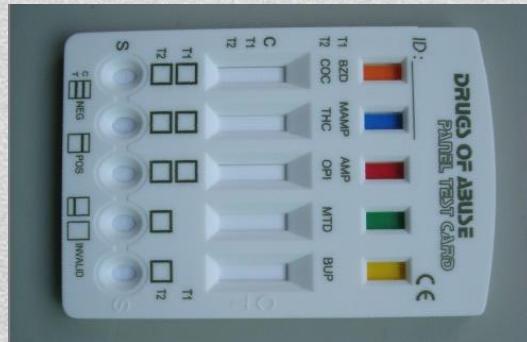
- Dose-Response Relationship
 - Too much of a good thing
 - “The dose makes the poison”
 - Relative toxicity
 - 70kg man
 - TD_{50} LD_{50}
 - Acute vs Chronic
 - Single exposure vs 3 months accumulation



THE LD_{50} OF TOXICITY DATA IS
2 KILOGRAMS PER KILOGRAM.

Laboratory Analysis

- Specimen must be carefully chosen (toxicokinetics)
 - Sample handled carefully (trace elements, volatility)
 - 2 Step analysis
 - Screening- rapid, sensitive, qualitative, non-specific, TLC
 - Confirmatory- More specific, GC, AAS, GC/MS



Alcohol



- Effects: Disorientation, confusion, euphoria, unconsciousness, paralysis, death
- CNS depressant, recovery is rapid and complete after cessation
 - Biotransformation of alcohols leads to specific toxic effects
 - Alcohol $\xrightarrow{\text{ADH}}$ Aldehyde $\xrightarrow{\text{ALDH}}$ Acid

Alcohol

- Ethanol-C₂H₅OH
 - Acetaldehyde reactive intermediate
- Methanol
 - Formaldehyde reactive intermediate, formic acid
- Isopropanol
 - Acetone reactive intermediate, much longer half-life than EtOH
- Ethylene Glycol
 - Oxalic acid, glycolic acid, calcium oxalate crystals



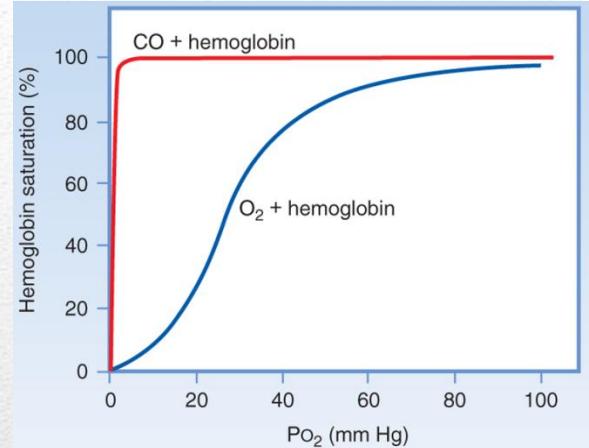
Alcohol Analysis

- Pre-analytic concerns: Iodine instead of alcohol wipe, specimen must remain capped
- Methods?
 - Osmolarity: osmolar gap due to EtOH
 - Not specific
 - Enzymatic Methods: Non-human ADH
 - $\text{EtOH} + \text{NAD}^+ \xrightarrow{\text{ADH}} \text{Acetaldehyde} + \text{NADH}$
 - SPECIFIC FOR EtOH
 - GC: Headspace chromatography can do multiple alcohols at once

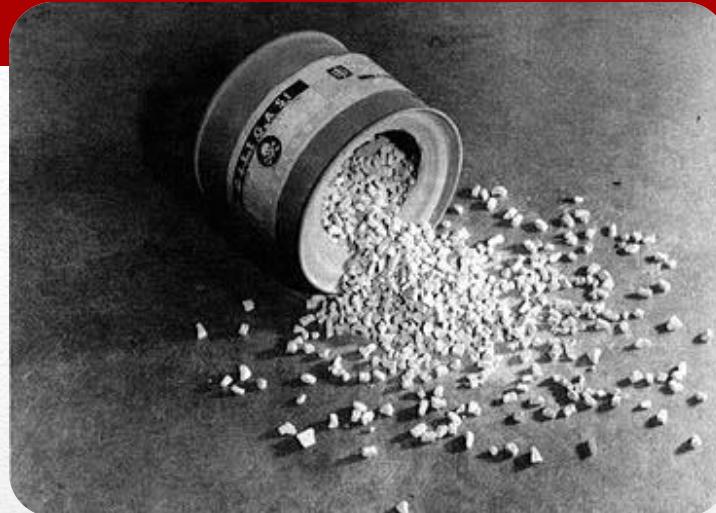


Carbon Monoxide

- Colorless, odorless, tasteless gas
 - Carboxyhemoglobin, 200-225x greater affinity than O₂
 - Leftward shifted hemoglobin saturation curve
 - Decreased Oxygen delivery to tissue
 - Methods: Spot test, GC, Co-oximetry,



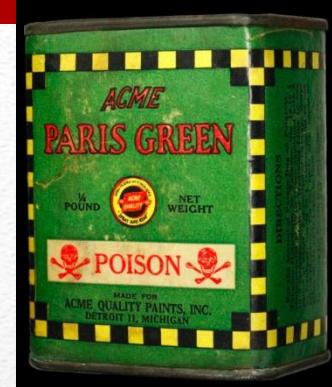
Cyanide



- “Supertoxic” substance in gas, solid, or in solution
- Industrially useful, insecticides, burning of plastics
 - Binds heme iron, cytochrome oxidase
- Elimination is mediated by enzymatic conversion to thiocyanate which is cleared renally
- ISE and Photometric assay for analysis
 - Chronic exposure: Urinary thiocyanate



Arsenic



- Present in many organic molecules, toxicity dependent on valence state
 - Inhalation of gas is most toxic
- Non-specific symptoms anorexia, GI distress, hematopoetic effects, renal impairment
- Mostly cleared by renal filtration of ionic arsenic
- Persistent exposure leads to bioaccumulation
 - Hair and fingernails for long-term testing
- Urine is specimen of choice 6 days vs couple hours

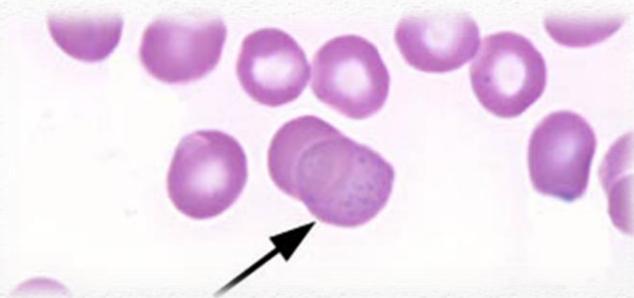


Cadmium

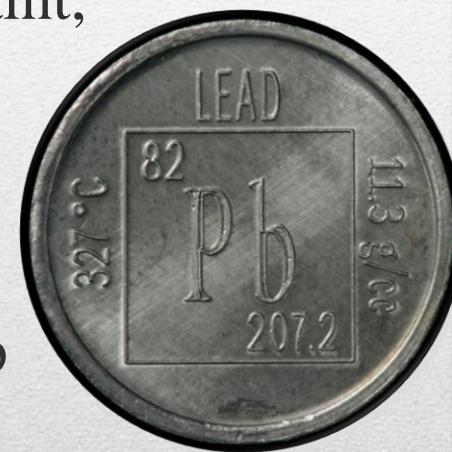


- Frequently used in industry, paints, plastics, batteries
- Environmental contaminant, builds up in tobacco
- Primarily binds to proteins, causing toxic effects on the kidneys. Also affects parathyroid
 - Proteinuria, glucosuria, aminoaciduria seen
 - Itai itai disease due to osteomalacia and osteoporosis from Cd-contaminated rice

Lead

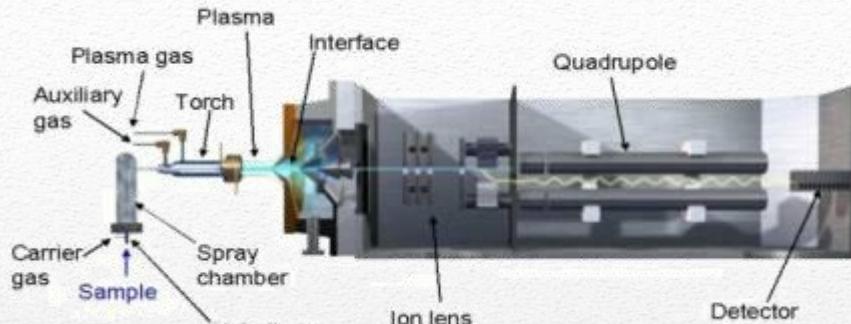


- Widespread environmental contaminant (gas, paint, plumbing)
- Toxicity largely age dependent (adults resistant)
- Elimination largely renal
- Subclinical toxicity: behavior disorders, IQ drop
 - Enzyme inhibition leads to heme synthesis issues
 - Increase in intermediate compounds like aminolevulinic acid and zinc protoporphyrin (ZPP). Both testable
 - Basophilic stippling in erythrocytes (residual nucleus)



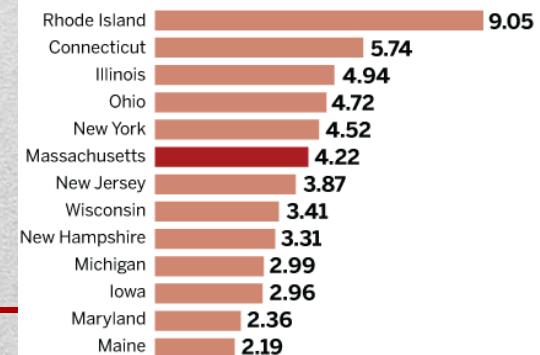
Lead

- Treatment: chelation with EDTA or dimercaptosuccic acid
 - Low molecular weight complexes that are cleared by kidney
- Assessment: Whole blood in lead-free tube
 - Reference Method: graphite furnace AAS
 - ICP-MS inductively coupled plasma mass spectrometry
 - Detection of levels as low as 1 ppq
(that's quadrillion!)



Lead poisoning cases

Per 10,000 residents



SOURCE: Childhood Lead Poisoning Prevention Program

GLOBE STAFF

Mercury



- Exposure primarily through inhalation or ingestion
- Mostly contaminated foods now. Mad Hatter?
- Attracted to hydrophobic compartments
 - Brain and nerves, binds to protein
- Elimination via kidneys
 - Ionized or low molecular weight
 - Proteins are not low weight, accumulation
- AAS on whole blood, Hg is volatile!



Pesticides

- Acute exposure most problematic
 - Renal disease, death
- Organophosphates
 - Inhibit acetylcholinesterase present in both humans and insects
 - Protein binding prevents analysis
 - SChE more present in serum, but not as specific
 - 4k-12k U/L 40% reduction for symptoms



Salicylates

- Aspirin
 - Analgesic, antipyretic, anti-inflammatory, antiplatelet
 - Inhibition of cyclooxygenase production of prostaglandins
 - Direct stimulation of respiratory center
 - Respiratory alkalosis
 - Increased organic acids (salicylic acid)
 - Metabolic acidosis
 - Inhibition of Kreb's Cycle → More acid!
 - Mixed acid-base status



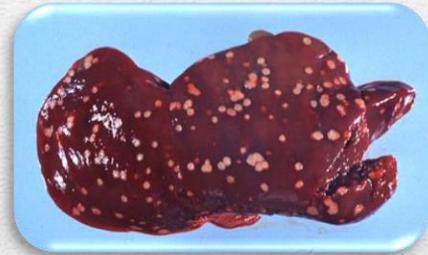
Salicylates

- Reye's Syndrome: Childhood viral infection + Aspirin
- Toxic effects: metabolic acidosis, headache, tinnitus, hyperventilation, decreased platelet function, irrationality, disorientation
- Analysis: GC or LC provide high sensitivity and specificity
 - Immunoassay methods, Trinder reactions, enzymatic assay



Acetaminophen/paracetamol

- Analgesic with SEVERE hepatotoxicity above therapeutic doses
 - Low free fraction due to protein binding
 - Detoxed by conjugation with glutathione
 - If glutathione is depleted reactive intermediates will lead to liver necrosis
 - Serum indications 3-5 days after dose, symptoms vague and do not indicate liver involvement
 - Alcoholics will metabolize acetaminophen faster



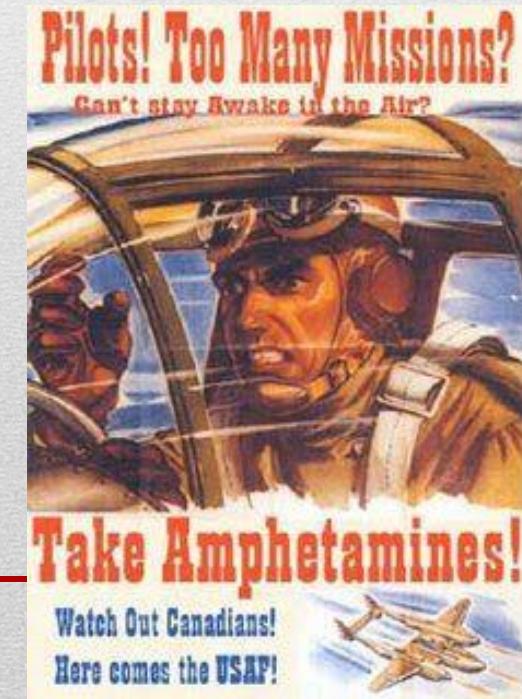
Drugs of Abuse (DAT)

- Legally admissible and defendable
- Specimen security (chain of custody)
- Tests for adulteration
- Two-tiered, screen and confirmation
 - Spot tests
 - GC/MS



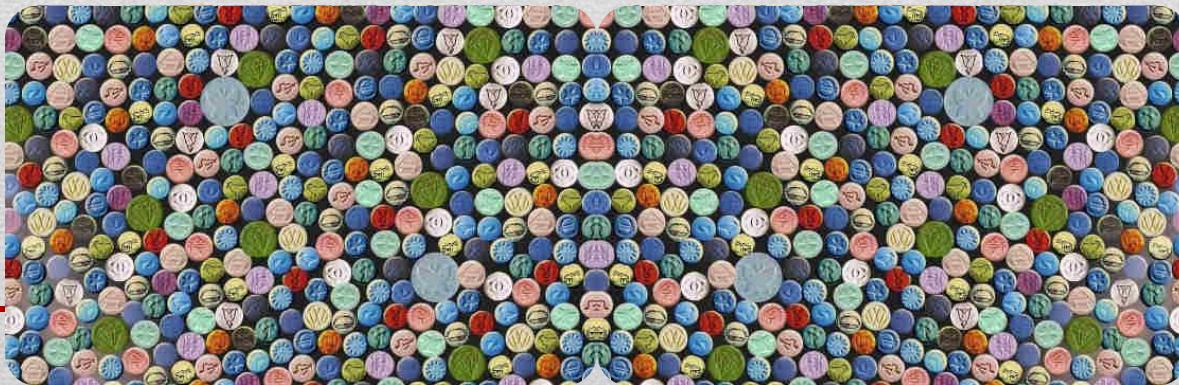
Amphetamines

- Stimulants with high abuse potential
- Overdose results in hypertension, arrhythmia, convulsions, death
 - Chemically related: ephedrine, pseudoephedrine, and phenylpropanolamine
 - OTC drugs may give false positives on immunoassay



Methylenedioxymethamphetamine

- MDMA, ecstasy, molly, mandy in UK
- 200+ designer analogues
 - Side effects: anxiety, impaired memory, violence, hypertension, hyperthermia, cardiac, liver, and renal toxicity



Cannabinoids



- Major metabolite: 11-nor-tetrahydrocannabinol-9-carboxylic acid (THC-COOH)
 - After single use detectable for 3-5 days
 - After *chronic* use detectable for 4 weeks after cessation
- Immunoassay for THC-COOH is screen with GC/MS to confirm



Cocaine



- Local anesthetic at low dose, CNS stimulant at high dose
- Acute toxic effects: hypertension, arrhythmia, seizure, MI
- Rapidly metabolized to inactive compounds
 - Largest metabolite benzoylecognine: detectable 3 days single use, 20 days in chronic use
- Immunoassay screen and GC/MS confirmation



Opiates



- Analgesia, sedation, anesthesia
- Derived from *Papaver somniferum*
- Synthetic and natural forms all metabolized to morphine
- Immunoassays detect morphine, codeine but leverage cross-reactivity
- GC/MS confirms, narrows down
- Epidemic



Phencyclidine (PCP)



- Stimulant, depressant, anesthetic, hallucinogen all in one
 - At recreational doses: Agitation, hostility, paranoia
 - At overdoses: Stupor, coma
- Lipophilic, slow elimination
- Immunoassay screen with GC/MS confirmation



Sedatives-Hypnotics



- CNS depressants with wide therapeutic uses
 - Barbiturates- Higher abuse potential, less commonly abused
 - Secobarbital, phenobarbital, pentobarbital
 - Benzodiazepines- Lower abuse potential, more commonly abused
 - Diazepam (Valium), lorazepam (Ativan), alprazolam (Xanax)
- O.D. presents with lethargy, slurred speech, rapidly progresses to coma
 - Respiratory depression
 - Accentuated with alcohol
 - Broad Cross-reactivity allows for immunoassay screen
 - GC or LC to confirm



The End

