Systematic Approach to Solvent toxicity

Raj Puri, MD, MPH
Chief Resident Emeritus,
UCSF Occupational and Environmental Medicine

Disclosure

- I have no financial interests and nothing to disclose.
Chris Christie, Governor of New Jersey joins President of Bayer HealthCare Phil Blake, and Marijn Dekkers, Chairman, Bayer AG
What is a solvent?

- Any substance, usually a liquid at room temp., that dissolves another substance resulting in a solution.

- Classification
  - Aqueous (water based)
  - Organic (hydrocarbon based - most industrial solvents)

- Used for cleaning, degreasing, thinning, extraction

- More than 30,000 industrial solvents
Where are solvents?

- Everywhere

- Significant industrial use
  - Work environment typically where the highest exposures occur

- Most severe exposures seen in confined spaces with inadequate ventilation

History

- Organic solvents arose in the latter half of the 19th century from coal-tar industry

- Introduction of chlorinated solvents in the 1920s led to reports of toxicity
A 1912 postcard depicting harvesting pine resin for the *turpentine* industry.
Current demand

- US demand for solvents is expected to increase at a 1.5% annually through 2018 to 11 billion pounds (Transparency Market Research, 2012)
  - driven by a robust recovery in construction
  - Paint and coatings market will replace the transportation market as largest solvents consumer by 2018

- Global solvents market to reach an estimated value of ~US$30 billion by 2018

Solvents Market- Global Industry Analysis, Size, Share, Growth, Trends and Forecast 2012-2018; Transparency Market Research
Outline

- Physical & chemical properties
- Common solvents
- Pharmacokinetics
- Health effects
- Stepwise approach
- Cases

Physical properties

- Solubility
  - Lipophilic
  - Hydrophilic
- Flammability & Explosiveness
- Volatility
Chemical properties

- 3 Basic Structures
  - Aliphatic
  - Alicyclic
  - Aromatic

- Functional Groups
  - Halogens
  - Alcohols
  - Ketones
  - Glycols
  - Esters
  - Ethers
  - Carboxylic Acids
  - Amines
  - Amides

Classification of Solvents

- Inorganic solvents
  - water and aqueous solutions containing special additives (surfactants, detergents, PH buffers, inhibitors).
  - acids and bases e.g. liquid anhydrous ammonia (NH₃), concentrated sulfuric acid (H₂SO₄)

- Organic solvents
  - Oxygenated solvents
    - contain oxygen, e.g. alcohols, glycol ethers, methyl acetate, ethyl acetate, ketones, esters, and glycol ether/esters.
  - Hydrocarbon solvents
    - consist only of hydrogen and carbon atoms.
      - Aliphatic solvents: have straight-chain structure; e.g. hexane, gasoline, kerosene.
      - Aromatic solvents: have benzene ring structure; e.g. benzene, toluene and xylene.
  - Halogenated solvents
    - contain halogenic atoms (Cl, F, Br or I).
**Common Solvents & Uses**

<table>
<thead>
<tr>
<th>Category</th>
<th>Solvents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paints and lacquers</td>
<td>Toluene, xylene, methyl ethyl ketone</td>
</tr>
<tr>
<td>Adhesives</td>
<td>Cyclohexanes, acetones</td>
</tr>
<tr>
<td>Antifreeze</td>
<td>Ethylene glycol</td>
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<tr>
<td>Degreasing</td>
<td>Trichloroethylene (TCE), perchloroethylene, 1-Bromopropane</td>
</tr>
<tr>
<td>Dry cleaning</td>
<td>Perchloroethylene, 1-Bromopropane</td>
</tr>
<tr>
<td>Printing</td>
<td>Turpentine, white spirits, xylene</td>
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Routes of exposure

- **Pulmonary**
  - Inhalation—Primary Route for Occ Exposure
  - At Rest, pulm retention for most organic solvents is 40-80%
  - Physical Exercise at work
    - Increases pulm uptake of solvents by 2-3x at rest

- **Dermal Exposure**
  - Solvents with both lipid & water solubility are most readily absorbed through skin
  - Skin absorption factors

Distribution

- Adipose tissue
- Nervous System
- Liver
- Cardiac
- Skeletal Muscle
- Breast Milk and Placenta
Metabolism

- Generally hepatic, by MFO (Mixed-function oxidase) system
- Some activated to toxic metabolites
- Many solvents including TCE (trichloroethylene) are metabolized by alcohol and aldehyde dehydrogenase

Excretion

- Exhalation of unchanged compound
  - i.e. Perchloroethylene, poorly metabolized
- Elimination of metabolites in urine
- Or, combination of both
Biological monitoring

- ACGIH has recommended BEIs (biologic exposure indices) for many solvents
  - i.e. acetone, benzene, phenol, TCE (trichloroethylene), toluene, and Xylene

- Measurements in exhaled air (most), and blood (slow excretion)

Health effects of solvents

- **Acute** exposures
  - generally refer to **single dose**
  - high concentration exposures over **short periods**

- **Subacute**
  - Repetitive exposures over workweek w/ reversible acute effects
    - i.e. CNS depression & mucous membrane irritation

- **Chronic** exposures
  - repeated or continuous exposures over **long periods**
**Health effects**

- **Skin**
  - **Occupational dermatitis**
    - 20% of cases, caused by solvents
    - Most common work practice via washing hands with solvents
    - **Occupations**: painting, dry cleaning, printing, and mechanics
    - Almost all organic solvents are skin irritants
    - Determinants: concentration, duration of exposure, and covering of exposed areas (i.e. clothes)
  - **Allergic contact dermatitis**
  - **Scleroderma**
**Acute irritant dermatitis**

- **Symptoms & signs**
  - Erythema and edema
  - Chronic dry, cracked eczema
  - Susceptible to sec. bacterial infection

- **Diagnosis**
  - Patch testing used rarely e.g. for turpentine, and formaldehyde
Acute Irritant Dermatitis

- **Treatment**
  - Topical corticosteroids
  - Emollients
  - Skin care

- **Prevention**
  - Education on properly handling of solvents
  - Use of engineering controls to minimize direct contact
  - Alternatives to washing
  - Solvent-resistant gloves, barrier cream and protective clothing

- **Prognosis**
  - Good with elimination of direct solvent contact
Acute CNS Effects

- **CNS depression**

- **Acute intoxication symptoms**
  - headache, nausea, vomiting, dizziness, vertigo, slurred speech, euphoria, sleepiness, weakness, irritability, depression, disorientation, confusion, LOC, death from resp. depression
  - lasts few minutes to <24hrs

- **Tolerance** to acute effects
  - morning “hangovers” and frank withdrawal on weekends

- **Secondary hazard**: increased risk of accidents
Acute CNS Effects

■ Treatment
  o Removal from exposure
  o Avoid use of alcohol or other CNS depressants

■ Prognosis
  o Good, if recognized early
  o Headaches can last for weeks

Chronic CNS Effects

■ Chronic solvent induced encephalopathy (CSE)
  o Historically, inhalant abuse, or “huffers” of glue
  o “Painter’s” disease
    ✦ Symptoms only (type 1)--- i.e. difficulty sleeping, dizziness, disorientation, depression, fatigue, gait disturbance, etc
    ✦ Sustained personality or mood swings (type 2A)
    ✦ Impairment of intellectual function (type 2B)
    ✦ Dementia (type 3)
Swedish Q16 questionnaire for long-term solvent-exposed workers

Questions – Yes or No answer

- Do you have a short memory?
- Have your relatives told you that you have a short memory?
- Do you often make notes about what you must remember?
- Do you often have to go back and check things you have done such as turned off the stove, locked the door, etc?
- Do you generally find it hard to get the meaning from reading newspapers and books?
- Do you often have problems with concentrating?
- Do you often feel irritated without any particular reason?
- Do you often feel depressed without any particular reason?

Swedish Q16 questionnaire for long-term solvent-exposed workers

- Questions – Yes or No answer

- Are you abnormally tired?
- Are you less interested in sex that what you think is normal?
- Do you have palpitations of the heart even when you don’t exert yourself?
- Do you sometimes feel pressure in your chest?
- Do you perspire without any particular reason?
- Do you have a headache at least once a week?
- Do you often have painful tingling in some parts of your body?
- Do you have any problems with buttoning and unbuttoning?
Criteria for diagnosis of chronic CNS toxicity

- Verified quantitative (how much?) and qualitative (which one?) exposure known to be neurotoxic

- Clinical picture of organic CNS damage
  1. typical subjective symptoms i.e. headache, etc
  2. Pathologic findings in:
     • Clinical neuro status
     • EEG findings
     • Psychological tests i.e. Swedish Q16
  3. Exclude other organic diseases i.e. Alzheimers, CJD, etc
  4. Exclude psychiatric disorders

Treatment

- Removal from exposure
- Avoid alcohol and other CNS depressants
- Depression may respond to antidepressants and counseling
- Tx of chronic headaches w/ trials of meds, counseling, and biofeedback therapy
Effects on PNS & Cranial Nerves

- Many organic solvents cause peripheral neuropathies i.e. numbness, tingling
- Some specifically toxic to PNS causing central peripheral distal axonopathy (CPDA)
  - Carbon disulfide
  - Hexacarbons
    - n-hexane, Methyl n-butyl ketone (MBK)
  - 24 yr old male brake mechanic presented to OHS
    - Numbness, tingling developed in hands/feet spread proximally to his forearms and waist
    - Dx: Toxic Peripheral Neuropathy due to n-hexane solvent exposure (spray can degreaser)

Diagnosis

- History, PE
- Nerve Conduction Studies
- EMG’s
- Sural nerve biopsy (rare, for hexacarbons)
Treatment & prognosis

- Symptoms worsen initially, then improve up to a year.
- Permanent disability should not be judged until at least 1yr after exposure removal.
- Removal of exposure to all toxic agents.
- Physical therapy.

Respiratory Effects

- Upper respiratory tract irritation:
  - Sore nose, throat, cough, eye irritation.
- High overexposure leads to acute inhalational injury:
  - Tracheitis, bronchitis, chemical pneumonitis → non-cardiogenic pulmonary edema.
- Exacerbation of asthma.
- Chronic bronchitis.
Treatment and Prognosis-Resp

- Removal of exposure
- Treatment: oxygen and bronchodilators
- Prognosis
  - Depends on severity

Cardiac Effects

- Chlorinated hydrocarbon solvents
  - e.g. methylene chloride and trichloroethane
- Cardiac sensitization
  - increased predisposition to arrhythmias---trichloroethylene
  - Symptoms include dizziness, faintness, palpitations, LOC, low BP, irregular pulse
- Few have specific CVS effects
  - Carbon disulfide
    - Incr. risk of CAD
Dx, Treatment & Prognosis

- Cardiac monitoring helpful in dx.
- Removal of exposure
- Antiarrhythmic agents
- Prognosis
  - good, if exposure removed early

Liver Effects

- Hepatotoxic solvents
  - those with halogen or nitro groups
  - inversely proportional to chain length
- Halogenated hydrocarbons have greatest toxicity
  - carbon tetrachloride
  - dimethylformamide (DMF - ink, glues and fabric coatings)
  - dimethyl acetamide (DMAC - commonly used as a solvent for fibers e.g. spandex)
    - potent hepatotoxin and neurotoxin (hallucinations)
  - Alcohol consumption can enhance toxicity
Renal Effects

- Carbon tetrachloride, trichloroethane, petroleum distillates, among most toxic
  - gasoline, jet fuel and turpentine
- Acute renal failure: **acute tubular necrosis** from halogenated hydrocarbons
- Renal tubular acidosis (distal)--- Reported in toluene abusers, not in occ. workers
- Acute renal failure---Intrarenal deposition of oxalic acid from **ethylene glycol (antifreeze)** ingestion
- Chronic effects
  - Mild tubular dysfunction
  - Primary glomerulonephritis

Diagnosis & Treatment - Renal

- **Symptoms**
  - fatigue and weakness from electrolyte abnormalities
- **Signs:** polyuria, glycosuria, proteinuria, acidosis; exclude DM
- **Electrolyte disorders**
  - Hypokalemia, hypophosphatemia, hyperchloremia
- **Routine monitoring**
  - **Not recommended** for workers exposed to solvents
- **Treatment**
  - Removal of exposure
**Hematologic Effects**

- **Benzene**
  - Aplastic anemia after months to years of exposure
  - Could lead to leukemias including AML, CLL, NHL, and MM

- Glycol Ethers
  - Hemolytic anemia

- Monitoring
  - Recommended blood count monitoring for benzene and glycol ether exposure

- Treatment
  - Removal of agent and transfusion, if needed

**Carcinogenic Potential**

- Benzene
  - Only commonly used solvent w/ established evidence of carcinogenicity

- Halogenated hydrocarbons
  - Limited evidence of hepatocellular CA in mice

- Trichloroethylene (TCE)
  - Increased risk of NHL & renal cancer
**Reproductive Effects**

- Decreased fertility
- Increased risk for spontaneous abortion
- Visual deficiencies in offspring
- Teratogenicity
  - Glycol ethers, toluene, and ethyl alcohol (i.e. FAS-fetal alcohol syndrome)
- Toluene
  - Causes increased time to get pregnant
- Glycol ethers
  - Causes decreased sperm count
- Recommendation
  - Avoid exposure in pregnancy

**Prevention & control measures**

- Evaluation
  - Environmental sampling and analysis should be undertaken at regular intervals
  - Monitoring work environment involves measuring atmospheric contaminants at selected locations in the workplace
  - Personal monitoring
  - Biological monitoring
Control measures

- Control measures are ranked in priority of their effectiveness
  - Elimination/substitution
    - use of water solvents i.e. water-based paints, “green” dry cleaning
  - Engineering controls
    - Administrative controls
    - Use of personal protective equipment (PPE)

Engineering controls

- Process enclosure (closed-system): to control vapors
  - i.e. paint spray booths, trichlorofluoroethane for dry cleaning

- Ventilation systems
  - Hood capturing contaminant at point of generation
  - Duct system with appropriate airflow
  - Air cleaning system to prevent pollution of the general atmosphere
  - Exhaust fan
**Personal Protective Equipment**

- Used **only when engineering controls not feasible** i.e. in confined space, construction, etc
- Comprehensive respiratory protection program
- Respirators
  - air purifying devices with gas absorbers (canister or cartridge types)
  - supplied air devices – self-contained breathing apparatus supplying **half or full-face masks**
- Protective clothing
  - **Proper glove** & eye protection
- Barrier creams are not recommended as substitute for gloves

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**Stepwise approach to solvent exposure**

- **5 key elements**
- **Suspicious symptoms/ signs**
  - Liver dysfunction, peripheral neuropathy, chronic headache
  - cognitive impairment, and respiratory symptoms (irritation/bronchitis)
Step 1 – History & Physical Exam

- Symptoms & exposure history
- Past Medical history: Asthma, Blood dyscrasias, psych.
- Physical examination, Labs, EKG, CXR, Spirometry
- Specific job duties, solvent exposures
- Frequency of acute solvent intoxication episodes
- Industrial Hygiene data
- Labels, Safety Data Sheets (SDS), Chemical Inventory Lists
- OSHA log reports

Physical examination

Focus on:
- Skin
- Eyes
- Gastrointestinal
- Neurologic system
- Psych.
**Laboratory tests**

- Screening
- Biological indices
- Pathologic indices

NIOSH Database of Medical Tests for OSHA Regulated Substances: http://www.cdc.gov/niosh/nmed/medstart.htm

**Other tests**

- Nerve Conduction Studies
- Color Vision
- Hearing
- Peak flow
Step 2: Site visit

“Walk through” of patient’s workplace

- Assess workplace and potential exposures
  - Industrial hygiene sampling
  - Ventilation of worksite
  - Potential exposure routes
  - PPE

- Obtain prior environmental test results, if available

Step 3: Establishing temporal relationship

- Decide whether patient’s symptoms is more likely than not work-related

- Is the latency period adequate?

- Exposure data consistent?

- Was the dose of the solvent exposure adequate to cause the problem?

- Or is the patient particularly sensitive to the effects of solvents
  - Increased individual susceptibility or acquired intolerance?
Step 4: Establishing diagnosis

- Rule out differential diagnoses
  - Psych, DM
- Decide if pre-existing condition has been exacerbated
  - asthma
- File Doctor’s first report (DFR)

Step 5 - Disposition

- Return to work
- Modified duty
- Factors of disability
  - Objective/subjective
- Vocational rehabilitation
- Permanent & Stationary (P&S)
Case #1

- **Chief Complaint:** 50-year-old diesel mechanic with recurring nosebleeds, fatigue, and weight loss

- **HPI:** Nosebleed recurring x 6 months
  - Easy fatigability at work, 2 months ago noticed bruising on arms and legs
  - Lost >12 pounds in last 2 years

- **PE:** Conjunctivae are pale
  - Numerous ecchymoses, petechiae noted on arms/ legs
  - Many seem to be old w/ incomplete healing
**Case #1 contd**

**Labs:**
- Hgb 10.2 g/dL (normal 14.0–18.0)
- WBC 1.5 (5–10)
- Platelets 50,000/mm$^3$ (150,000–400,000)
- MCV 98 fl (80–100)
- Remainder of labs are normal including Cr, LFT’s

**Dx:** Aplastic Anemia sec. to Benzene Exposure from unleaded fuels

**Case #2**

- **Chief complaint:** A pregnant 28-year-old with cough and dyspnea
- **HPI:** coughing spasms, chest tightness, symptoms began ~ 6 hours earlier
  - while repainting a disassembled bicycle with an acrylic lacquer spray paint in a small, poorly ventilated basement area x 2 hrs
  - nausea, headache, and dizziness cleared w/in 1 hour upon finishing
Case #2 contd.

**PE:** Vital signs--- normal

**Resp:** Mild expiratory wheezes throughout, no rales
- Moderately decreased peak expiratory flow rate

**Dx:** Toluene exposure from the paint causing resp irritation and CNS depression

Case #3

- **Chief complaint:** 67-year-old paint stripper w/ confusion and chest pain

- **HPI:** unable to provide additional information due to confusion and disorientation
  - Over past 2 weeks, wife noted progressive loss of mental alertness and increasing fatigue and lethargy, much worse in the evening
  - usually sleeps 8 hrs/night, but past 2 days slow to rise even after 10 hours of sleep
  - increasingly slow to respond, slurred speech, mood swings
Case #3 Contd.

- **HPI:** working ~2-hour intervals, removing paint from furniture

- **PE:** Anxious and disheveled man
  - mildly diaphoretic
  - BP 145/80, pulse is 110 and regular, temp is normal
  - slurred speech and 15- to 20-second delays in responding to questions
  - oriented only to person
  - remainder of exam including labs, ekg, and PE are normal

**DX:** Methylene chloride exposure sec. paint stripping  
primary effect from CNS depression

Question #1

Which organic solvent is a proven human carcinogen?

A) Acetone  
B) Toluene  
C) Xylene  
D) Benzene
**Question #2**

Which of the following statements about gloves are true?

A) gloves are always protective  
B) gloves are protective based on brand name and money spent  
C) gloves can act as an occlusive dressing and increase exposure  
D) barrier creams can be used as alternative to gloves

**Question #3**

Which of the following tests can help to assess chronic CNS effects from solvent exposure?

A) Wechsler Adult Intelligence Scale (WAIS)  
B) Mini-mental state exam (MMSE)  
C) Physical activity readiness questionnaire  
D) Swedish Q16 questionnaire
Thank you!!