

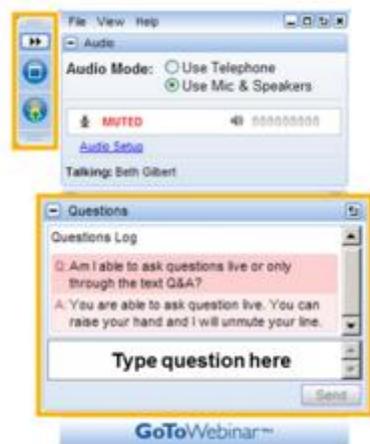
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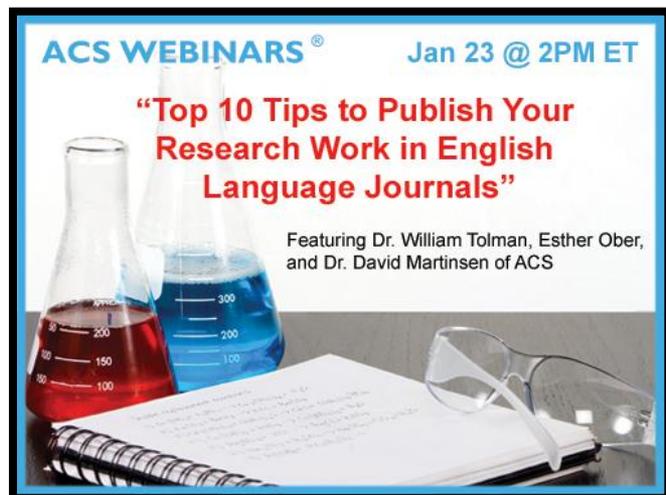
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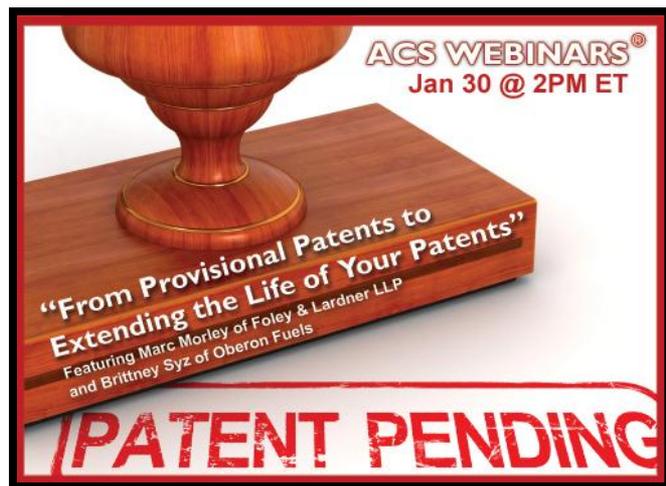
Thursday, January 23, 2014

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**Esther Ober**, ACS Journals Editing Manager, ACS

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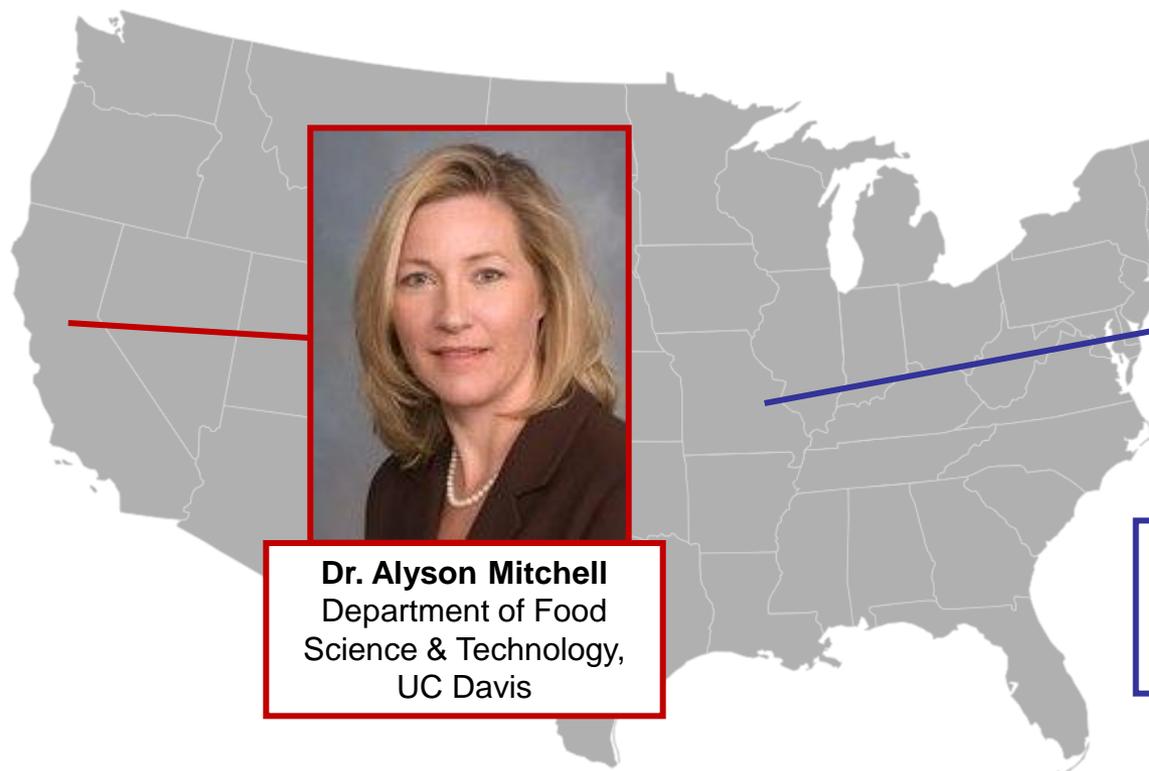
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## *The Chemistry and Anatomy of the Hangover*



**Dr. Alyson Mitchell**  
Department of Food  
Science & Technology,  
UC Davis



**Bill Courtney**  
Analytical Chemist and  
Chef, Cheese-ology  
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# The Chemistry of a Hangover

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JOHN KINSELLA CHAIR IN FOOD,  
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FOOD SAFETY AND MEASUREMENT  
FACILITY, UC DAVIS**



ACS Webinar  
The Chemistry of the Bar  
Jan 16, 2014



# When was the last time you experienced a Hangover?

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- **WITHIN A MONTH**
- **WITHIN THE LAST 6 MONTHS**
- **WITHIN THE LAST YEAR**
- **IT'S BEEN A FEW YEARS**
- **I'VE NEVER HAD ONE**

# Hangover is a Common Occurrence

13

**MOST ADULTS HAVE EXPERIENCED A HANGOVER AT LEAST ONCE IN THEIR LIFETIME**

**70% OF ALCOHOL CONSUMERS EXPERIENCE A HANGOVER AT LEAST ONCE PER YEAR, AND 15% EXPERIENCED THE SYNDROME IN THE PREVIOUS MONTH**

# What Exactly is a Hangover

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- Hangover, or Veisalgia occurs in response to the over-consumption of ethanol ( $\text{CH}_3\text{CH}_2\text{OH}$ )
- Hangover is characterized by numerous unpleasant mental and physical symptoms that occur in response to:
  - (1) the direct effects of ethanol
  - (2) the direct toxic effects of acetaldehyde and acetate
  - (3) alcohol withdrawal (not the same)
  - (4) the toxic effects of products in fermented or distilled beverages (congeners)
- Hangovers are not entirely understood and there is no clear theory about the pathology of alcohol hangover
  - Age, genetics, medications, diet, immune system competency, weight and gender influence the severity of a hangover

# Suite of Hangover Symptoms

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<b>Class of Symptoms</b>	<b>Type</b>
Constitutional	Fatigue, thirst, drowsiness, weakness, restlessness and dry mouth
Pain	Headache and muscle aches
Gastrointestinal	Nausea, vomiting, diarrhea, lose of appetite and stomach pain
Sleep and Biological Rhythms	Decreased sleep, decreased REM
Sensory	Dizziness, photo-, and audio-sensitivity
Cognitive	Decreased attention, memory and concentration; visiospatial impairment
Mood	Depression, anxiety and irritability Decrease in REM time
Sympathetic Hyperactivity	Tremor, sweating and increased pulse and systolic blood pressure

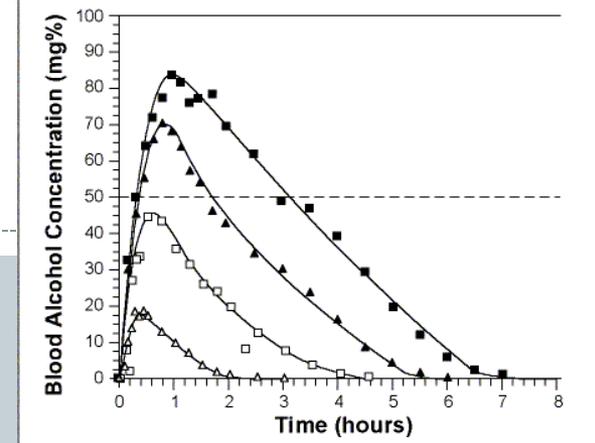
# The 10 Most Frequently Experienced Symptoms

16

	Presence (%)	Severity (0-10)
Tired	96.2	6.75
Thirst	90.7	6.38
Drowsiness	89.7	6.37
Sleepiness	88.3	6.37
Headache	88.2	5.77
Dry Mouth	84.4	5.92
Nausea	81.4	5.72
Weakness	80.0	5.48
Concentration Problems	78.7	5.03
Reduced Alertness	78.6	4.63

# Working Definition of Hangover

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- A general discomfort after drinking
- It is unclear how the presence and severity of hangover relate to blood alcohol content [BAC]
- A typical hangover begins several hours after the cessation of drinking when the BAC is decreasing
- Symptoms usually peak about the time the BAC is zero and may continue up to 24 hours thereafter (J. Verster, 2008)
  - Challenging as there is no consensus when to measure hangover or what symptoms to measure
- Puzzling phenomenon as it is unclear why symptoms are present after alcohol and its metabolites are eliminated from the body

# Hangover Characteristics

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- The particular hangover symptoms experienced and their intensity vary profoundly from person to person and from occasion to occasion
  - A BAC of 0.10% is usually need to produce hangover (L.F. Chapman 1970)
- Hangover characteristics depend on numerous factors such as:
  - The amount of alcohol consumed and time frame of consumption
  - The type of alcoholic beverage consumed
  - The individuals health and genetics
  - Time and type of last meal

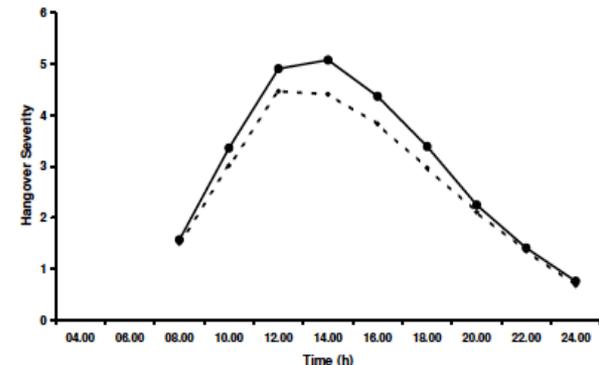


Fig. (1). Hangover severity and amount of alcohol consumed. Reported by women (N=1045) after consuming 5-10 alcoholic beverages (dashed line) and 10-15 alcoholic consumptions (uninterrupted line). Although the difference between hangover severity is significant ( $p < 0.003$ ), the clinical relevance on a 10-point scale is limited. Data from [4].

# Contributing Factors to Hangover

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- **Direct effects of ethanol**
  - Dehydration
  - Gastrointestinal disturbances
  - Low blood sugar (hypoglycemia)
  - Sleep and biological rhythm disturbances
  - Immune-related factors
- **Ethanol metabolites**
  - Acetaldehyde toxicity
  - Acetate toxicity
  - Redox imbalance
- **Congeners**
- **Non ethanol effects**
  - Food and hydration status
  - Genetics, gender, health status



Ever wonder why there is always such a long bathroom line at parties?

20

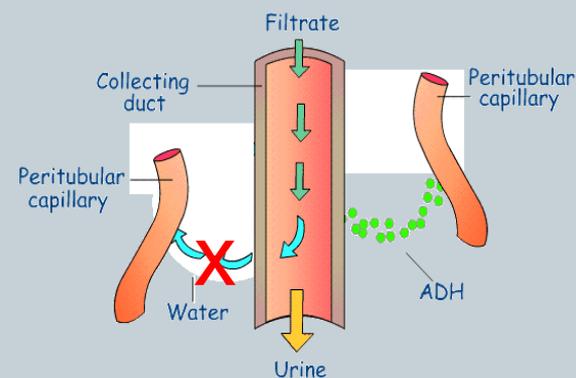


# Ethanol and Dehydration



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- Alcohol inhibits the pituitary secretion of anti-diuretic hormone (ADH; vasopressin)
- Reduced levels of ADH prevent the kidney from reabsorbing water and results in dehydration (symptoms of dry mouth, thirst, headache)
  - Drinking 50 g of alcohol in a 250 mL beverage causes the body to eliminate 600-1,000 mL of urine [up to 4x as much water is lost as gained]
  - Vomiting, sweating and diarrhea also contribute to water loss
- Dehydration = Headache
  - Electrolyte changes play only a minor role (if any) in the genesis of hangover (minor increases in serum  $\text{Na}^+$ )
  - Drinking water before going to bed may decrease dehydration symptoms (thirst, dizziness, dry mouth) but unlikely decreases the severity of alcohol hangover (Penning et al. 2010)



# Ethanol and Gastrointestinal Distress

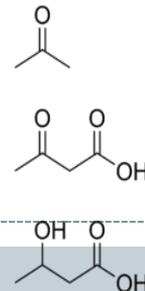
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- Ethanol directly irritates the lining of the stomach and intestines, causing gastritis and delayed stomach emptying times (Liber et al 1995)
- Ethanol also increases the production of gastric acid and pancreatic and intestinal secretions
- Result = Nausea and vomiting



# Ethanol and Metabolic Acidosis

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- Ethanol induced dehydration negatively affects gluconeogenesis
- Glucose levels in the blood drop (hypoglycemia)
- Free fatty acids are metabolized to compensate for this energy shortage producing ketone bodies
- Increased ketone bodies (acids), FFAs and lactate can decrease blood pH (metabolic acidosis) during the hangover phase
- Studies with sugar replacements (fructose and glucose) demonstrate that the correlation between MA and hangover severity are not significant (Ylikahri et al. 1976)
  - ✦ The sugars significantly reduced or prevented MA but did not result in a decrease in severity of hangover symptoms

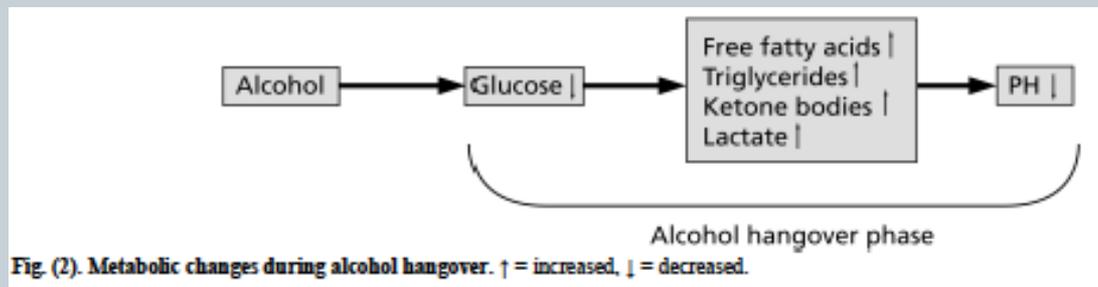


Fig. (2). Metabolic changes during alcohol hangover. ↑ = increased, ↓ = decreased.

# Ethanol and Fatigue

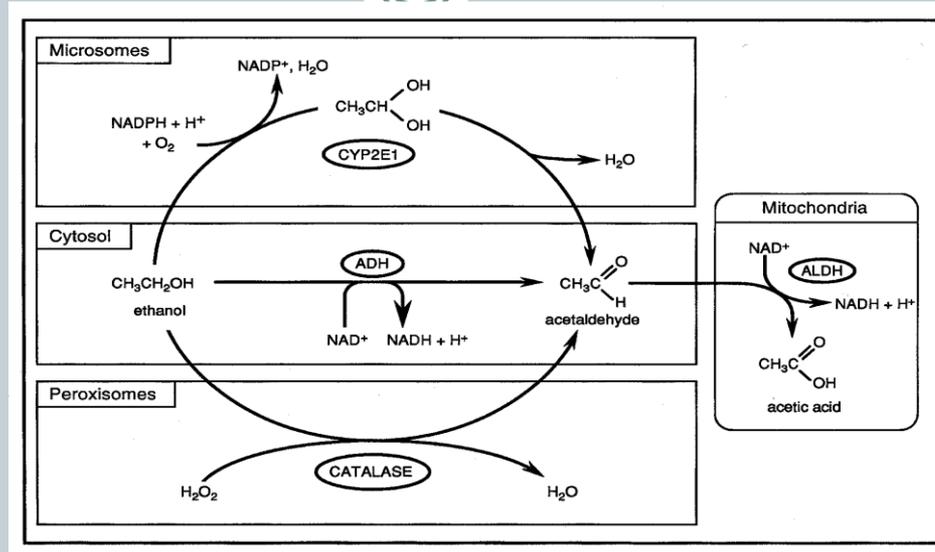
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- Ethanol induces hypoglycemia in individuals fasting and/or with deplete glycogen stores (e.g. chronic alcoholics, low carbohydrate dieters)
  - Hangover symptoms are most severe when glucose levels are at their lowest (Ylikahri et al 1977)
- Not eating and vomiting can also add to a reduction in the available carbohydrates
  - Decreases in blood glucose levels lead to the weakness, fatigue tiredness and changes in mood associated with hangover
- Ethanol disrupts normal sleep patterns decreasing the time spent in REM (rapid eye movement) which results in a less restful sleep and increases fatigue
  - REM sleep is necessary for memory, concentration and motor skills

# Ethanol Metabolism

25

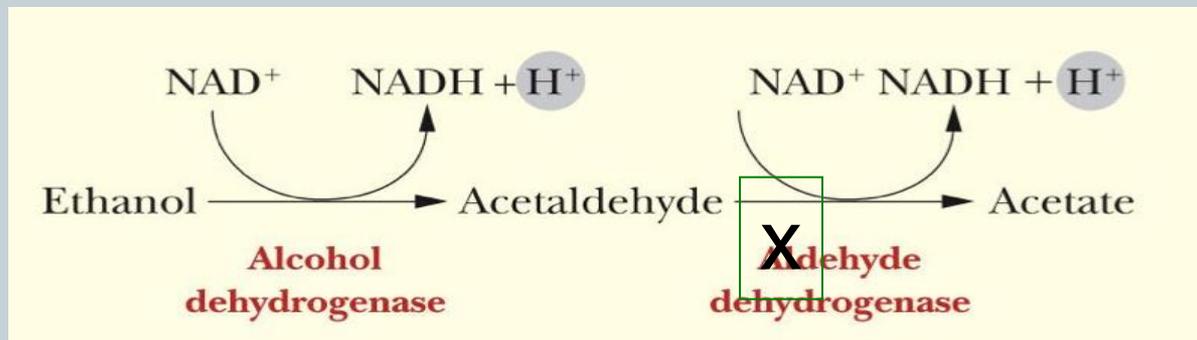


- 1. Ethanol (90%) is metabolized in the liver into acetaldehyde by alcohol dehydrogenase (ADH)
  - Microsomal CYP2E1 is induced with chronic ethanol consumption and helps to metabolize ethanol (10 %) at elevated ethanol concentrations
  - Acetaldehyde reacts with GSH resulting in GSH depletion creating a cytosolic environment vulnerable to free radicals
- 2. Aldehyde dehydrogenase [ALDH2] metabolizes the acetaldehyde to acetate which is further metabolized to acetyl CoA and  $\text{CO}_2$

# Ethanol Metabolism and Acetaldehyde

26

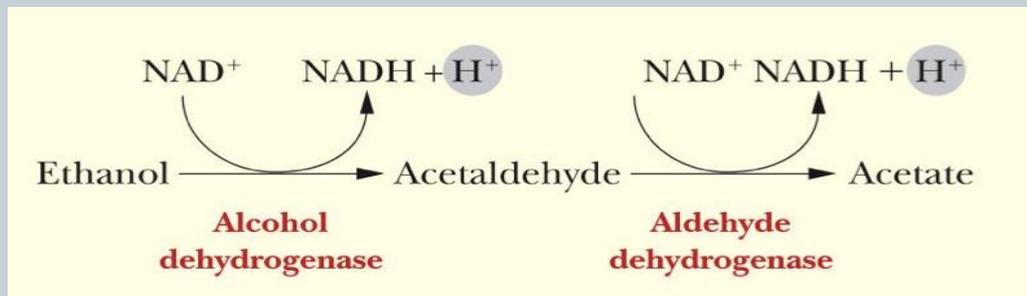
- Some hangover effects are attributed to increased blood levels of acetaldehyde
- Most people rapidly metabolize acetaldehyde and it is not present in the blood during hangover however it may due its damage prior to hangover
  - Acetaldehyde is directly toxic and can produce tissue damage, sponge up GSH, and lead to flushing, sweating, rapid pulse, nausea, vertigo and headache
- 50% Han Chinese, Taiwanese and Japanese populations have a form of ALDH2\*2 which is virtually inactive
  - Disulfuam (Antibuse); inhibits ALDH so acetaldehyde levels rise and produce these uncomfortable symptoms



# Acetaldehyde?

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- Acetaldehyde concentrations do not significantly correlate with hangover severity (Ylikahri et al 1974)
- Most people metabolize acetaldehyde rapidly and therefore it is in the blood in very low concentrations and is eliminated before the hangover phase even begins
- Possible: Acetaldehyde acts during the intoxication phase (tissue damage) and promotes delayed or persistent effects that promote the subsequent hangover



# Ethanol Metabolism and Acetate

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- More recent research indicates acetate may be involved in hangover symptoms
  - Acetaldehyde levels do not correlate directly with hangover severity
  - Serum levels of acetate are in the mM range whereas acetaldehyde levels are in the  $\mu$ M range
  - Blood acetate levels are elevated for 6 hours whereas acetaldehyde is rapidly cleared
  - Kidney patients undergoing dialysis that receive acetate report headache
- Recent studies (in drunk rats) demonstrate that acetate contributes to hangover headache (Maxwell et al., 2010)

# Ethanol Effects on Immune Function

- Alcohol produces changes in the immune function of cells 13 h after alcohol consumption (Kim et al., 2003)
  - Increases concentrations of cytokines [IL-10], [IL-12] and interferon-gamma [IFN])
  - Increases in [IL-12] and IFN correlate with hangover severity
  - Injections of IL-10 or IL-12 produce flu-like symptoms including: headache, chills, nausea, vomiting and fatigue
- Inhibitors of prostaglandin and cyclooxygenase synthesis (Tolfenamic acid) decrease hangover symptoms (Kaivola et al 1983)
- During hangover CRP is increased 50%
  - *Opuntia ficus indica* (OFI) attenuated this response (Wiese et al., 2004)

# Alcohol Congeners

30

- Alcohol congeners are produced during the fermentation of alcoholic beverages
  - Low molecular weight alcohols, aldehydes and esters; histamines, tannins, and phenols
    - ✦ Methanol, propanol butyl and amyl alcohol, ethyl acetate and ethyl formate
- Congeners contribute to the distinct taste, smell, and appearance of individual liquors
- It is thought that the congeners have direct toxic effects themselves
  - Methanol is metabolized into formaldehyde and formic acid by the same enzymes that metabolize ethanol into acetaldehyde and acetate
  - Formaldehyde is more toxic than acetaldehyde and may play a role in the symptoms of hangover

# Do you have any Homemade “Hangover Cures”?

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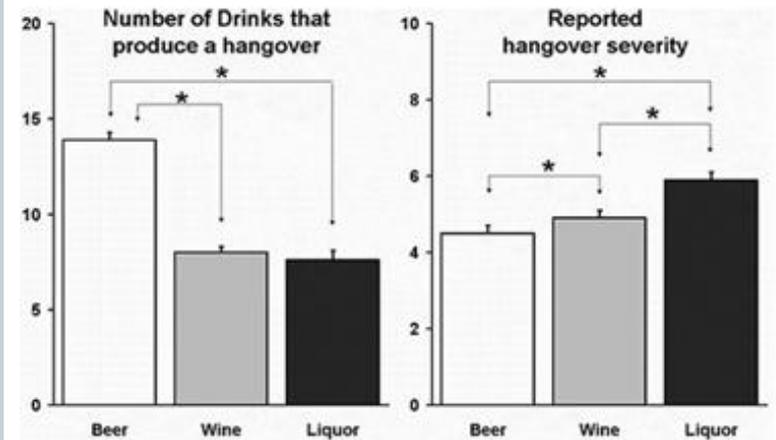
- **YES**
- **NO**

**LET US KNOW WHAT THEY ARE IN THE COMMENTS SECTION.**

# Folklore: Does The Type of Alcohol Matter?

32

- Congeners are found in highest concentrations in dark liquors such as brandy, tequila, whiskey, and red wine
- Hangover severity increases with congener content (Rohsenow and Howland, 2010)
- Clear liquors, such as vodka, rum, and gin, have fewer congeners
- Mixing drinks can increase congeners



Hangover Severity



Brandy  
Red Wine  
Rum  
Whisky  
White Wine  
Gin  
Vodka  
Beer

Congener Content

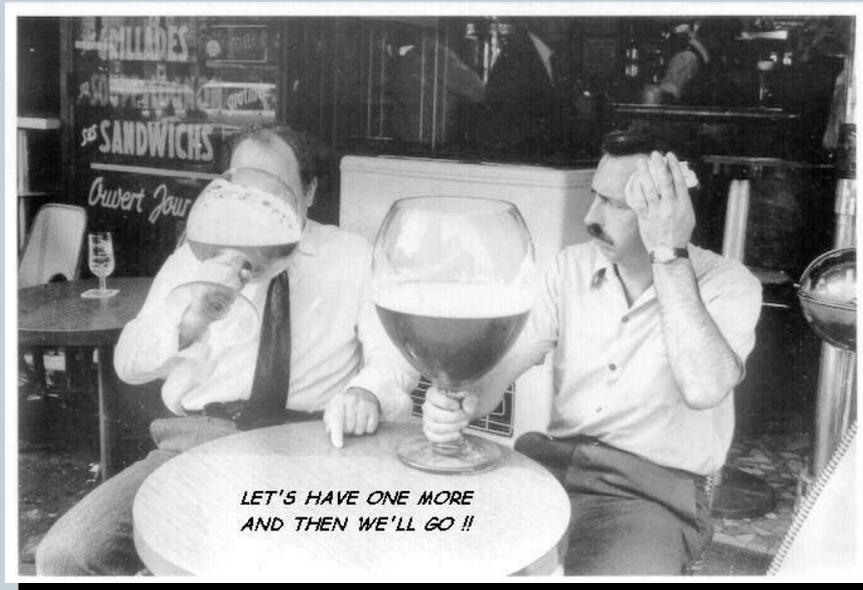


Ethanol diluted in orange juice

# Folklore: Can Men Drink More?

33

- When you compare men and women of the same height, weight and build, men tend to have more muscle and less fat than women
- Because muscle tissue has more water than fat tissue, a given dose or amount of alcohol will be diluted more in a man than in a woman
- Males have higher stomach metabolism of ethanol (ADH) than females



# Folklore: Hair of the Dog?

34



- Can drinking additional alcohol during a hangover alleviate hangover?
- Prat et al., (2009) considered the possibility that the hangover is an early stage of alcohol withdrawal (Swift and Davidson, 1998; Weise et al 2000)
  - However, Prat et al., (2009) concluded that the symptoms of alcohol withdrawal and hangover are significantly different in non-heavy drinkers
  - In heavy drinkers hangover and withdrawal symptoms may occur at the same time
    - ✦ If this is the case, then consuming more alcohol would alleviate withdrawal symptoms
- Methanol congeners are metabolized into formic acid and formaldehyde (both are toxic)
  - Ethanol blocks the metabolism of methanol; consequently methanol build up during drinking and only begins to be metabolized when ethanol clears
  - Consuming more alcohol during hangover would delay the metabolism of methanol

# Folklore: Beer before liquor never sicker...

35

- Beer before liquor, never sicker, liquor before beer, never fear?
  - Carbonated drinks like beer and sparkling wines tend to irritate the lining of the stomach, which may increase the rate of alcohol absorption
  - Starting with beer and then drinking liquor may conceivably lead to intoxication more quickly...
- However, there is no study to show this and most experts agree that it is the amount of alcohol consumed per unit time and not the order in which it is consumed that matters
  - The myth was likely started because most people don't drink a lot of beer after they have drunk liquor
  - It is more typical for people to consume beer and then move on to liquor as the night progresses, and so they think it's the order of consumption that made them sick

# Minimizing Hangover

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- Eat fatty or fried foods prior to drinking
  - Eating fatty or greasy foods will help coat the lining of the stomach and slow alcohol absorption
- Hydrate while drinking
  - Ethanol is a diuretic. Drink plenty of fluids, water or fruit juices along with ethanol. Do not drink coffee, or caffeinated energy drinks (caffeine is a diuretic), as they will compound the diuretic effect of alcohol
  - Fruit juice may help replace the glucose lost during a hangover
- Avoid consuming congeners and don't mix drinks
  - Drink lighter colored beverages
- Avoid over consumption of alcohol
  - The best way to avoid a hangover is to not over-drink!



# Treating Hangover

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- Rehydrate:
  - The dehydration effects of alcohol cause some of the most discomfort associated with hangovers (e.g. headache). Sports drinks may be better than water as they relieve dehydration, and also replace electrolytes (minor effect).
- Take aspirin or ibuprofen (Advil or Motrin), or buffered aspirin (alka Seltzer)
  - Do not take Acetaminophen (Tylenol) during a hangover because ethanol metabolism enhances acetaminophen's toxicity
- Exercise:
  - Exercise raises your metabolic rate and increases delivery of oxygen to tissues facilitating the rate of metabolism of toxins associated with drinking
- The following foods MAY also help:
  - Eggs contain cysteine, which helps to remove acetaldehyde from the body
  - Broth (Bullion) can help replace fluid and salts lost due to the diuretic effect of alcohol (minor)
  - Fruit Juice - glucose (energy – minor effect)
  - Vitamin B Complex: B vitamins are depleted when you drink (energy)

# Summary: More Research is Needed

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- Hangover is a common occurrence, effecting ~70% of individuals that drink
  - Most prevalent adverse phenomenon associated with drinking
  - Chronic alcoholism is responsible for only a small proportion of the total societal cost of alcohol use
- Substantial economic costs associate with hangover including worker absenteeism, reduced cognitive and technical performance, and decreased productivity
  - Australia, \$3.8 billion; Canada 8.9 billion; United States, \$148 billion
- Long term health impact of repeated hangovers are not known

Number of Google Hits (6/24/2010) versus number of scientific publications over the past 50 years, as indexed by Pubmed

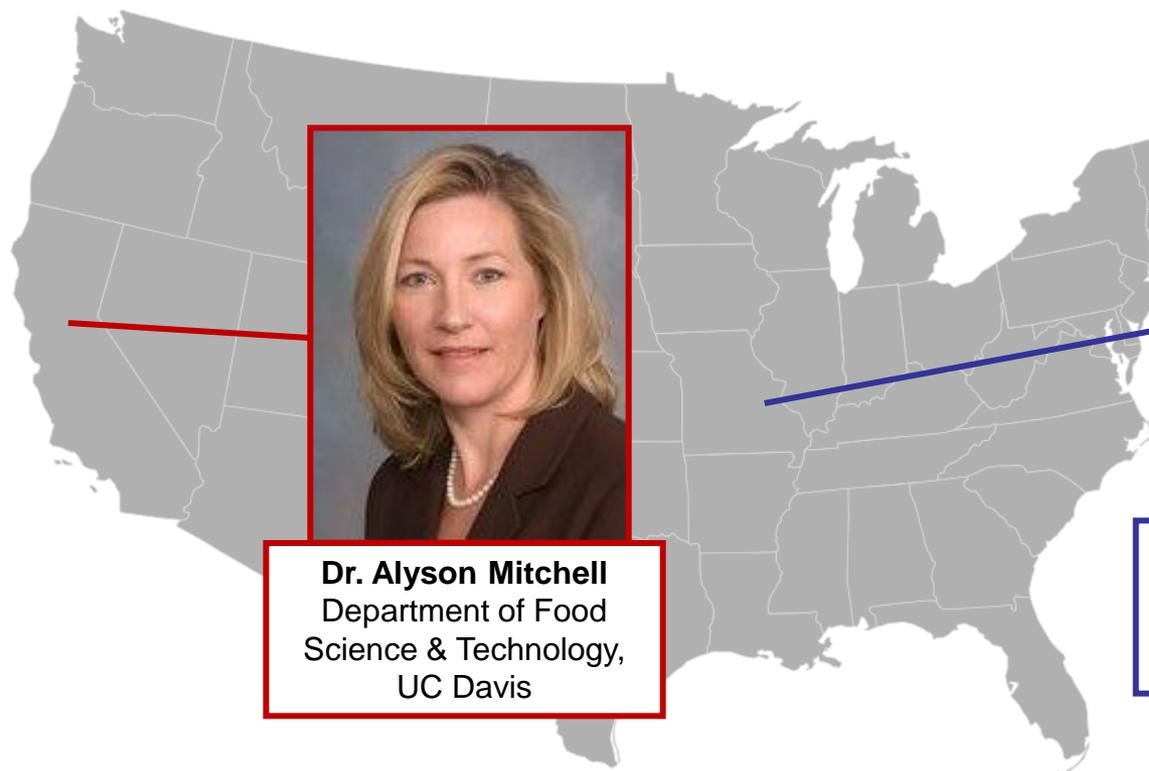
	Google	Pubmed
Alcohol	131,000,000	658,610
Hangover	15,000,000	406
Dementia	12,400,000	113,677
Schizophrenia	8,750,000	88,679
Hay Fever	5,760,000	12,161
Deafness	3,770,000	29,449

# Questions to Consider

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- Why do 28% of drinkers not experience hangover?
- What is the role of individual congeners in hangover development or additional symptoms that complicate hangover?
- Are there synergistic effects between congeners?
- Does acetate contribute to hangover symptoms in humans?
- Are there any health consequences related to hangover (good or bad)?
  - Individuals prone to hangover are more likely to be alcoholics
- What is the chemistry of recovery and can it be facilitated?
  - Should it be facilitated?
- Others?

## *The Chemistry and Anatomy of the Hangover*



**Dr. Alyson Mitchell**  
Department of Food  
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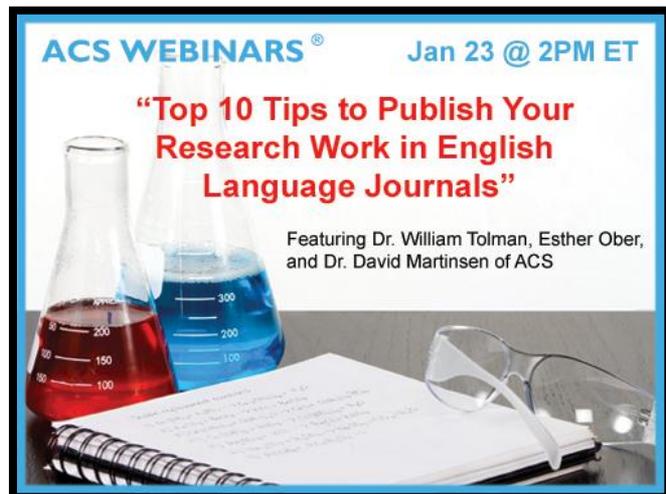
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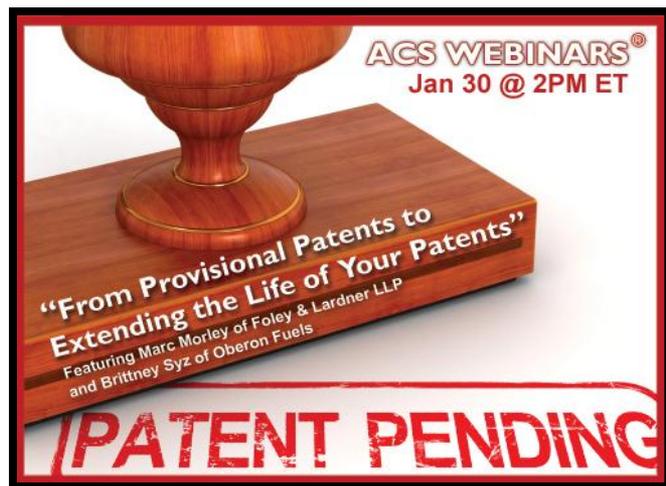
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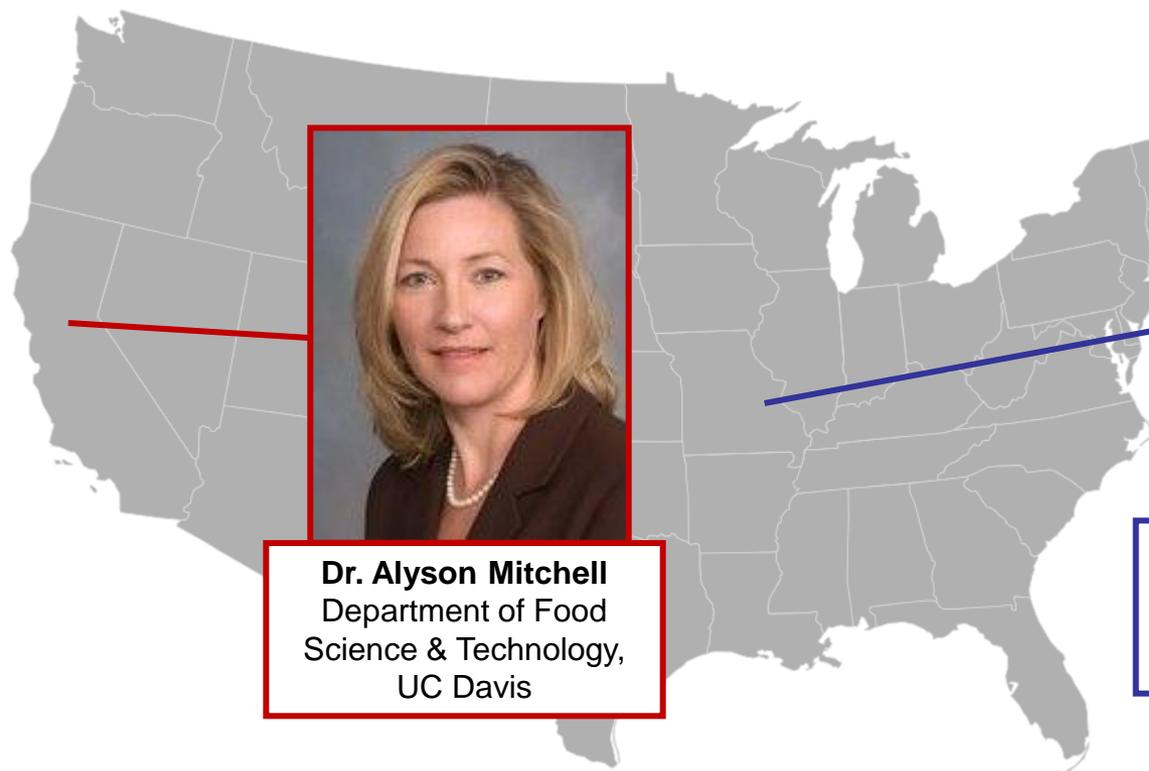
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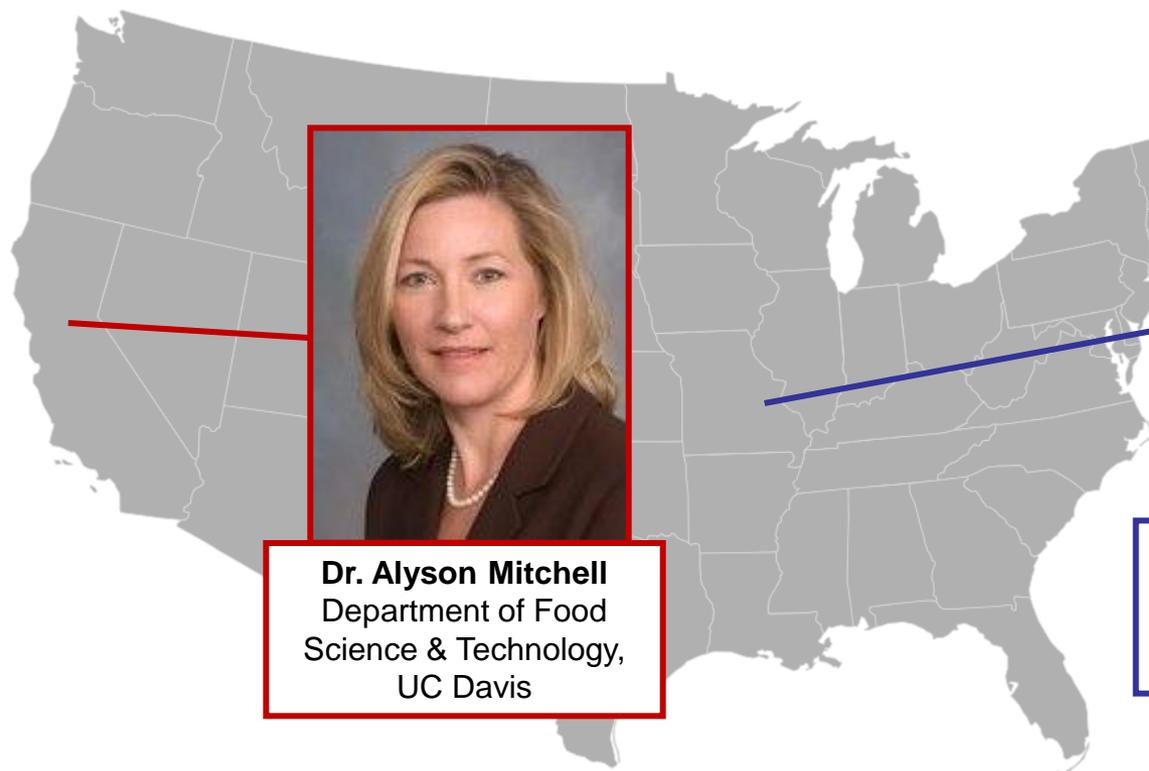
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