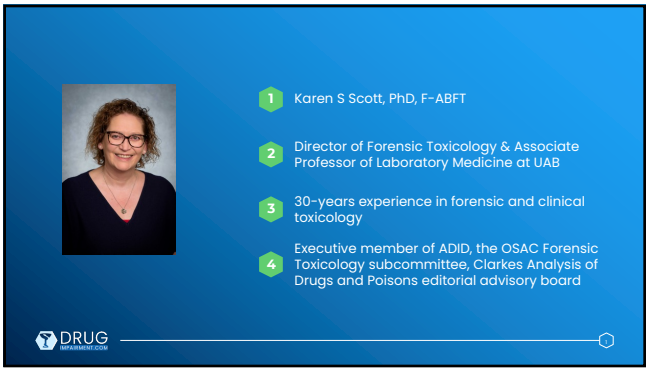
1 Karen S Scott, PhD, F-ABFT
2 Director of Forensic Toxicology & Associate Professor of Laboratory Medicine at UAB
3 30-years experience in forensic and clinical toxicology
4 Executive member of ADID, the OSAC Forensic Toxicology subcommittee, Clarkes Analysis of Drugs and Poisons editorial advisory board
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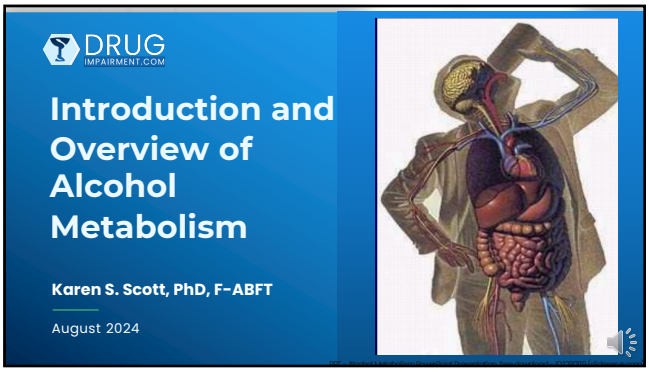
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Introduction and Overview of Alcohol Metabolism
Karen S. Scott, PhD, F-ABFT
August 2024

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Disclosures
The speaker has no disclosures.
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Learning Objectives

1. Understand the various metabolic pathways for alcohol in humans
2. Select appropriate elimination rates, based on individual circumstances
3. Appreciate which factors affect and do not affect the rate of elimination of alcohol from the body

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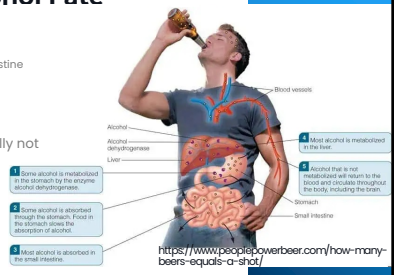
Summary of Alcohol Fate

- **Absorption**
  Stomach (~20%) and Small Intestine
- **Metabolism**
  By-products are essentially not detected
- **Elimination**
  Mainly via urine (15 mg/dL/hr)



https://www.peoplepowerbeer.com/how-many-beers-equals-a-shot/

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Ethanol Metabolism in the Stomach

- Some orally ingested alcohol does not enter systemic circulation ➡ metabolized prior to reaching bloodstream
- Modulates the toxicity of alcohol as it affects bioavailability
- In a fasted state ethanol rapidly passes to the duodenum from the stomach which minimizes this process (➡ higher peak concentrations)
- First pass metabolism is reportedly lower in alcoholics (especially females) due to decreased ADH activity
  - Decreases first pass effect and increases BAC
- The overall significance of 1st pass metabolism in the stomach is variable and controversial
  - Most enzymes are hepatic (greater role)
  - Effect of gastric emptying
  - Inhibition of enzymes by drugs

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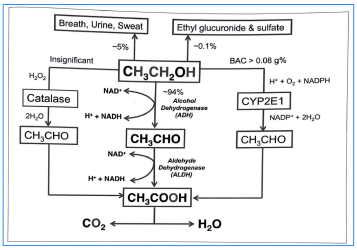
Metabolism of Ethanol



- **Three enzymatic pathways:**
  - **Alcohol dehydrogenase**
  - Catalase (H_2O_2 dependent)
  - CYP2E1

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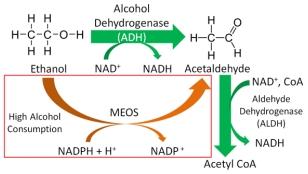
Alcohol Dehydrogenase – major pathway



Widely distributed in organs and tissues

- Encoded by five different genes.
- Exists in High and Low Km forms
- Present in the cytosol of cells in liver and stomach lining.
- Contains Zinc
- Oxidation of alcohol results in reduction of NAD+ to NADH

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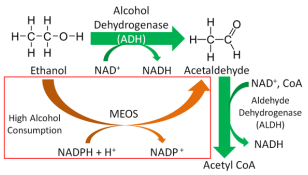
Microsomal Enzyme Oxidizing System (MEOS)



MEOS – Microsomal Ethanol Oxidizing System

- CYP2E1
- Km =~0.08 g/dL
- Oxidation of alcohol results in reduction of NADP+ to NADPH
- Higher Km than ADH
- Present in liver
- Major component of metabolic tolerance

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Km values for ADH

Ethanol Metabolism and Implications for Disease

Neuropathology of Drug Addictions and Substance Misuse, Volume 1, http://dx.doi.org/10.1016/B978-0-12-800213-1.00035-3

Roshanna Rajendram[1], Rajkumar Rajendram[2,3], Victor R. Preedy[3]
[1]Department of Emergency Medicine, The Royal Wolverhampton NHS Trust, New Cross Hospital, Wolverhampton, UK; [2]Department of Anaesthesia and Intensive Care, College of Medicine, King Khalid University Hospital, King Saud University Medical City, Riyadh, Saudi Arabia; [3]Diabetes and Nutritional Sciences Research Division, Faculty of Life Science and Medicine, King's College London, London, UK

Class	Subunit	Location	Km (mmol/l)[a]	Vmax
Class 1				
ADH1	α	Liver	4	54
ADH2	β	Liver, lung	0.05–34	
ADH3	γ	Liver, stomach	0.6–1.0	
Class 2				
ADH4	π	Liver, cornea	34	40
Class 3				
ADH5	χ	Most tissues	1000	
Class 4				
ADH7	σ	Stomach, esophagus, other mucosae	40	1510
	μ		20	
Class 5				
ADH6	–	Liver, stomach	30	

Low Km – active even at low concentrations – major role

High Km – more important at higher concentrations

ADH becomes saturated and the elimination process is **independent** of the ethanol concentration

When ADH is no longer saturated, ethanol elimination follows Michaelis-Menten kinetics (concentration dependent)
Typically below 0.015-0.020 g/dL

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Metabolic Enzymes (ADH) – Summary Points

- Thought to be mainly responsible for ethanol metabolism
- Class 1: located in cytosol fraction of hepatocytes, converts ethanol to more toxic acetaldehyde
  - Acetaldehyde is converted to acetate (acetic acid) by low km ALDH, located in the mitochondria
  - Acetate leaves the liver and enters Krebs cycle where it is converted to CO_2 and H_2O in peripheral organs and tissues
- Class IV: located in the gastric mucosa thought to contribute to first pass metabolism resulting in reduced bioavailability
  - Controversy if FPM is gastric or hepatic

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Metabolic Enzymes (CYP2E1) – Summary Points

- Final main enzyme is located in the smooth endoplasmic reticulum (microsomal fraction)
- CYP2E1 (Km 0.06-0.08 g/dL (cf 0.005-0.010 g/dL for Class 1 ADH)) ∴ involved in oxidation and clearance after heavy drinking
- After heavy binge drinking CYP2E1 activity increases
- This enzyme induction is the proposed mechanism for faster clearance in heavy drinkers and alcoholics
- Enhanced capacity rapidly declines with abstinence

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Elimination Rate Variations

ANSI/ASB Best Practice Recommendation 122, First Edition 2024

Best Practice Recommendation for Performing Alcohol Calculations in Forensic Toxicology

Elimination rate from blood, mg% per hour	Elimination rate from whole body, g/hr*	Conditions, treatment, or the special circumstances when such elimination rates are encountered
8–10	4–5	People with liver dysfunction (e.g., owing to cirrhosis or carcinoma) or who might be malnourished or eat low-protein diets. Treatment with enzyme inhibitor of alcohol dehydrogenase, fomepizole (4-methyl pyrazole).
10–12	5–6	Consumption of moderate doses of alcohol by healthy individuals after an overnight (10 hr) fast.
12–16	6–8	Consumption of moderate doses of ethanol under nonfasting conditions.
16–25	8–12	Healthy individuals who consumed alcohol to reach intoxicating BAC (>120 mg%) such as is the case with drunken drivers
25–35	12–17	Alcoholics during detoxification or periods of heavy drinking for days or weeks to reach high BAC (>200 mg%). People having a genetic predisposition for rapid disposal of ethanol. Factors leading to a hypermetabolic state (e.g., after burn trauma or hyperthyroidism or certain medicinal drugs).

*This calculation assumes a nonobese male person with body weight 70 kg and volume of distribution (rho-factor) of ethanol of 0.70 L/kg.

ASB Range (g/dL)

Low 0.010

Average 0.015

Fast 0.025

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Factors Affecting Elimination

Factor	Affect
Sex	Faster rates in ♀ versus ♂ when corrected for lean body mass
Age	Low elimination rates in younger subjects. Small decline with aging if liver compromised
Race	Elimination ↑ in subjects expressing β3 class 1 ADH isoforms compared to β1 class isoform Some studies indicate native Americans show increased rates *cf* Caucasians (In Asians the ALDH gene is affected not ADH)
Food	Fasting lowers ethanol metabolism due to decreased ADH levels
Exercise	Most studies report small rate increase with exercise, possibly due to increased temperature of catecholamine release
Alcoholism*	Heavy drinking increases ethanol metabolism Advanced liver disease will decrease metabolic rate
Drugs	Some drugs can inhibit (e.g. pyrazoles) or compete with ethanol (e.g. methanol) for ADH, others inhibit mitochondrial respiratory chain → decreased elimination Antabuse inhibits elimination of acetaldehyde to slow ethanol metabolism

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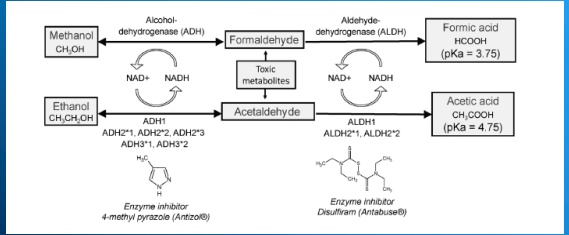
Alcohol, its absorption, distribution, metabolism, and excretion in the body and pharmacokinetic calculations



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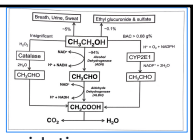
Non-oxidative metabolism



- <0.1% of ethanol dose metabolize via non-oxidative pathways
- Produces:
  - Ethyl glucuronide (EtG)
  - Ethyl sulfate (EtS)
  - Phosphatidylethanol (PEth)
  - Fatty acid ethyl esters (FAEEs)
- Useful biomarkers for chronic markers of alcohol consumption

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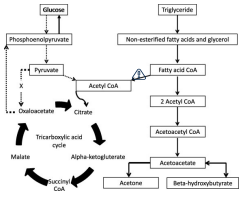
Alcoholic Ketoacidosis

Alcohol and hypoglycemia

- Wide anion gap metabolic acidosis associate with acute cessation of alcohol consumption after chronic alcohol abuse
- Typically associate with nausea vomiting and vague GI complaints
- Metabolism of ethanol combined with little or no glycogen reserves
- Can result in death



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Markers of Alcoholism

Methanol and Ethanol Contents of Alcoholic Beverages

Beverage	Methanol (mg/l)	Ethanol (g/l)
Beer	1 - 10	30 - 50
White Wine	20 - 40	60 - 100
Red Wine	60 - 100	70 - 110
Brandy	200 - 300	300
Vodka	1 - 100	300 - 400
Whisky	80 - 200	300 - 320
Fruiterer	1000 - 4000	300 - 350

- Methanol
  - Contained in drinks
  - Extremely toxic
- Acetone
  - Linked to ketoacidosis
    - Formed by decarboxylation of aceto-acetic acid
- Isopropanol
  - Potentially formed through metabolism of acetone
  - Levels typically low in comparison to poisoning cases

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Overall Summary

- Ethanol metabolism is reasonably simplistic compared to many drugs
- For the most part it follows zero order kinetics with Low Km
- Three major enzymes ADH, ALDH and CYP2E1
- Up regulation of CYP2E1 during binge drinking/alcoholism
- Wide variation in elimination rates within population
- Metabolic biomarkers can be useful in determining drinking and or health status of individuals

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CONTACT ME

Karen S. Scott, PhD, F-ABFT

karenscott@uabmc.edu

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