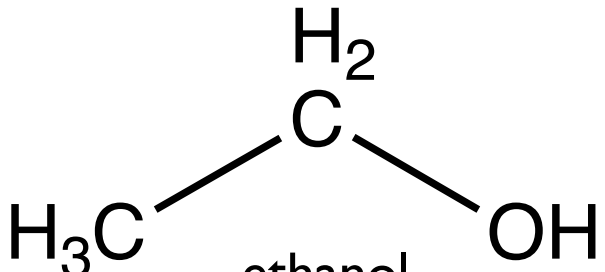
objectives

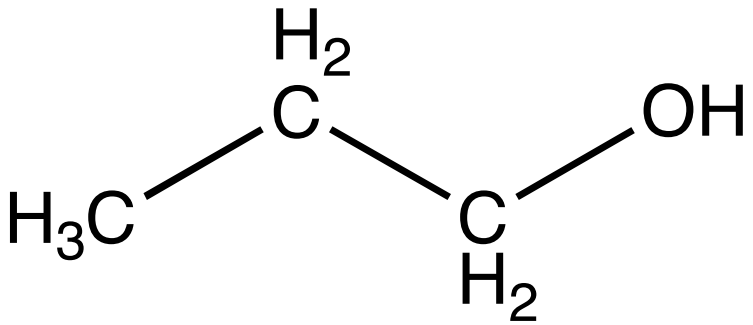
- learn how to classify alcohols
- Understand how ethanol is made
- Understand how ethanol enters the blood stream
- Describe some of the behavioural effects of ethanol
- understand how BAC is calculated
- understand the metabolism of alcohols

alcohols

methanol

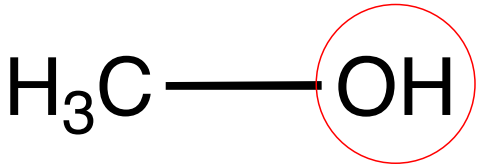


ethanol



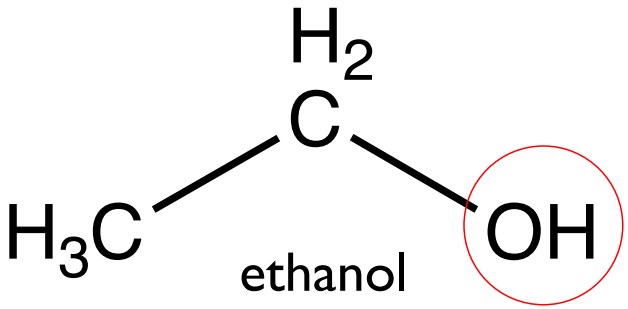
n-propanol

alcohols

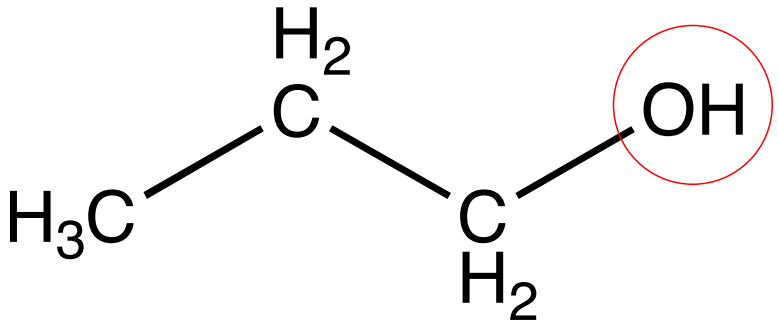


hydroxyl group

methanol



ethanol



n-propanol

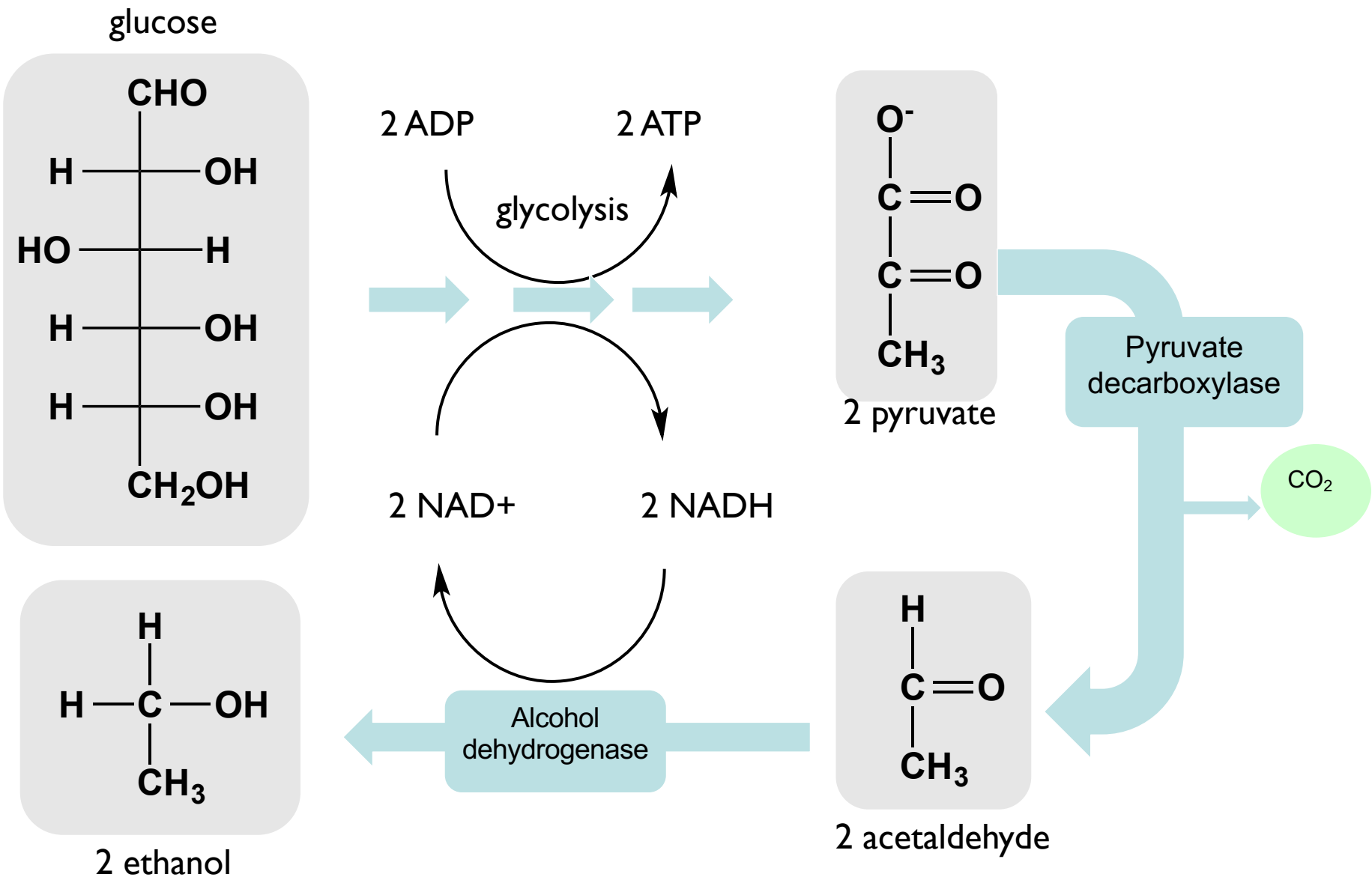
alcohol production

- still depends on yeast to ferment sugars (first converted into glucose, then pyruvate) into ethyl alcohol and carbon dioxide

$C_6H_{12}O_6 + 2ADP + 2Pi \rightarrow 2CH_3CH_2OH + 2CO_2 + 2ATP + 2\ H_2O$

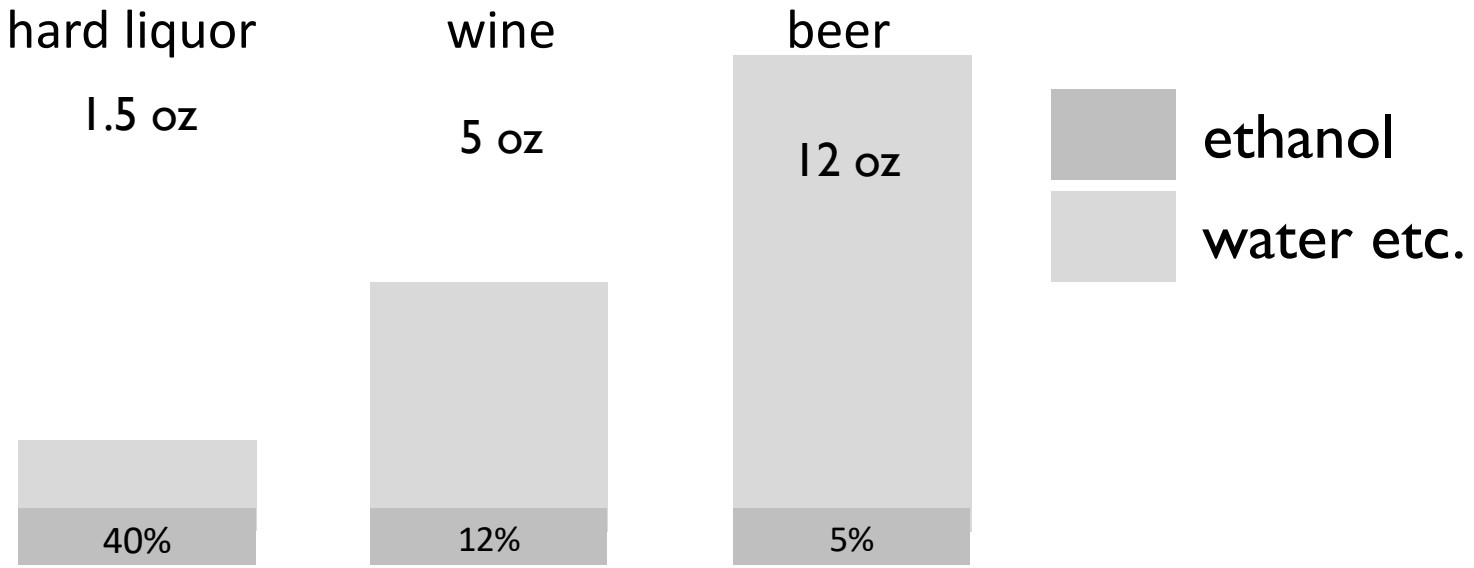
- Yeast are really using this pathway to generate NAD+, an enzyme cofactor used in glycolysis
- yeast can produce up to 15% ethanol before the ethanol kills it
- Drinks with higher alcohol percentage require a distillation process

fermentation



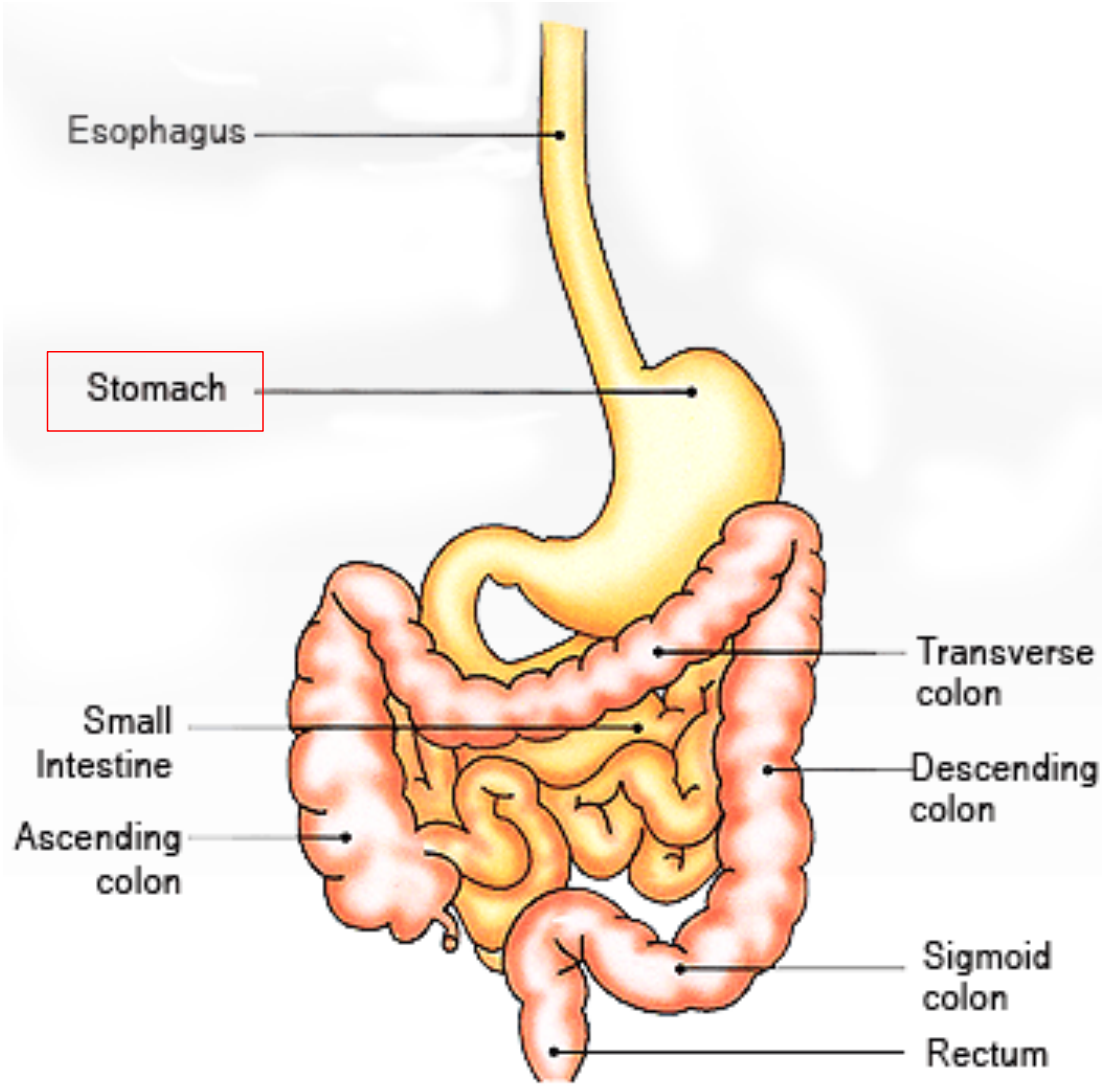
how much alcohol/drink?

- one shot of spirits , one glass of wine, one can of beer contain approximately 0.6 oz of ethanol (in Canada)
- Percentages below are vol/vol



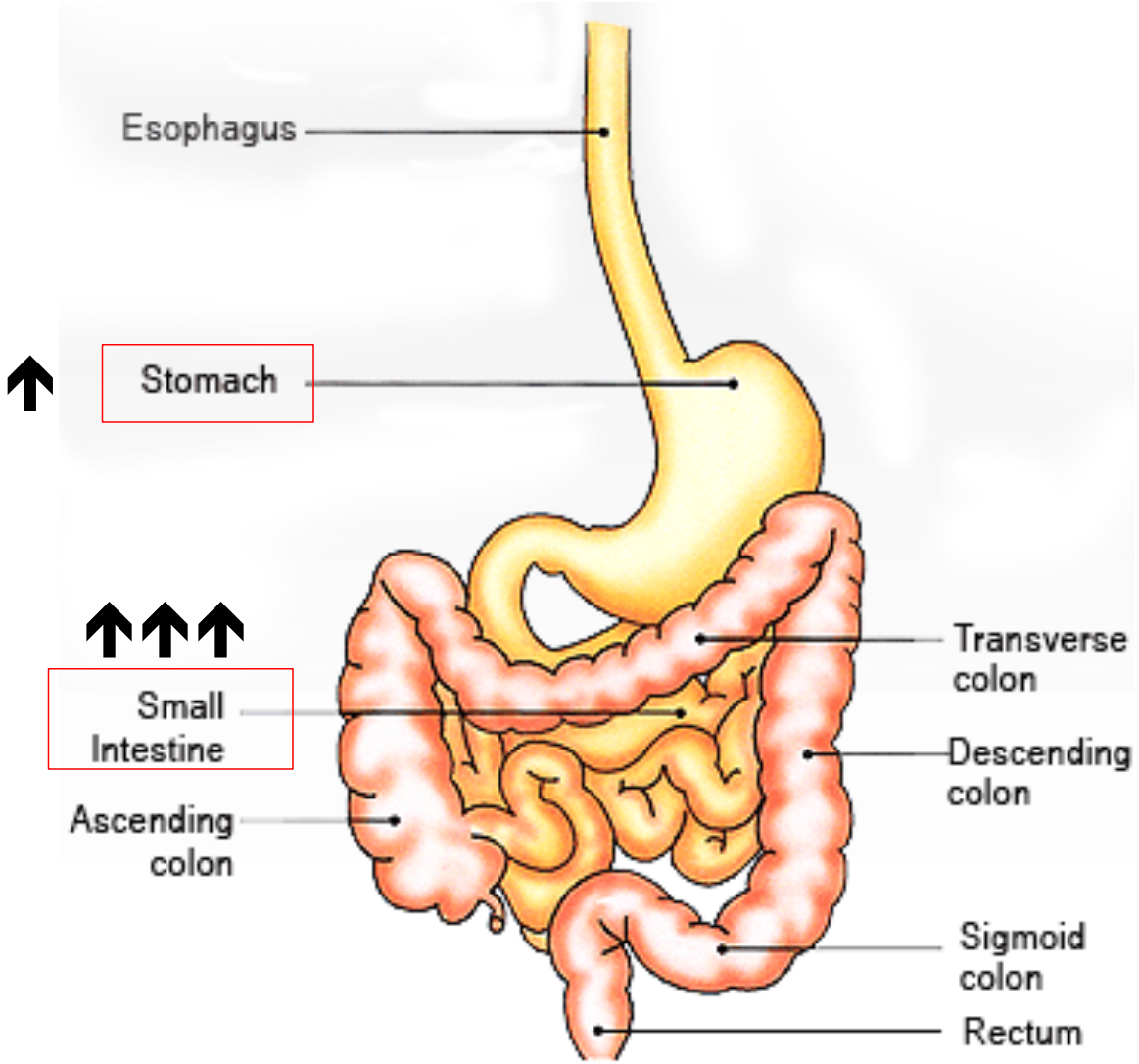
- there are 22.3 grams of ethanol in an ounce
- Standard drink = 22.3g/oz X 0.6oz = 13.38g

Absorption



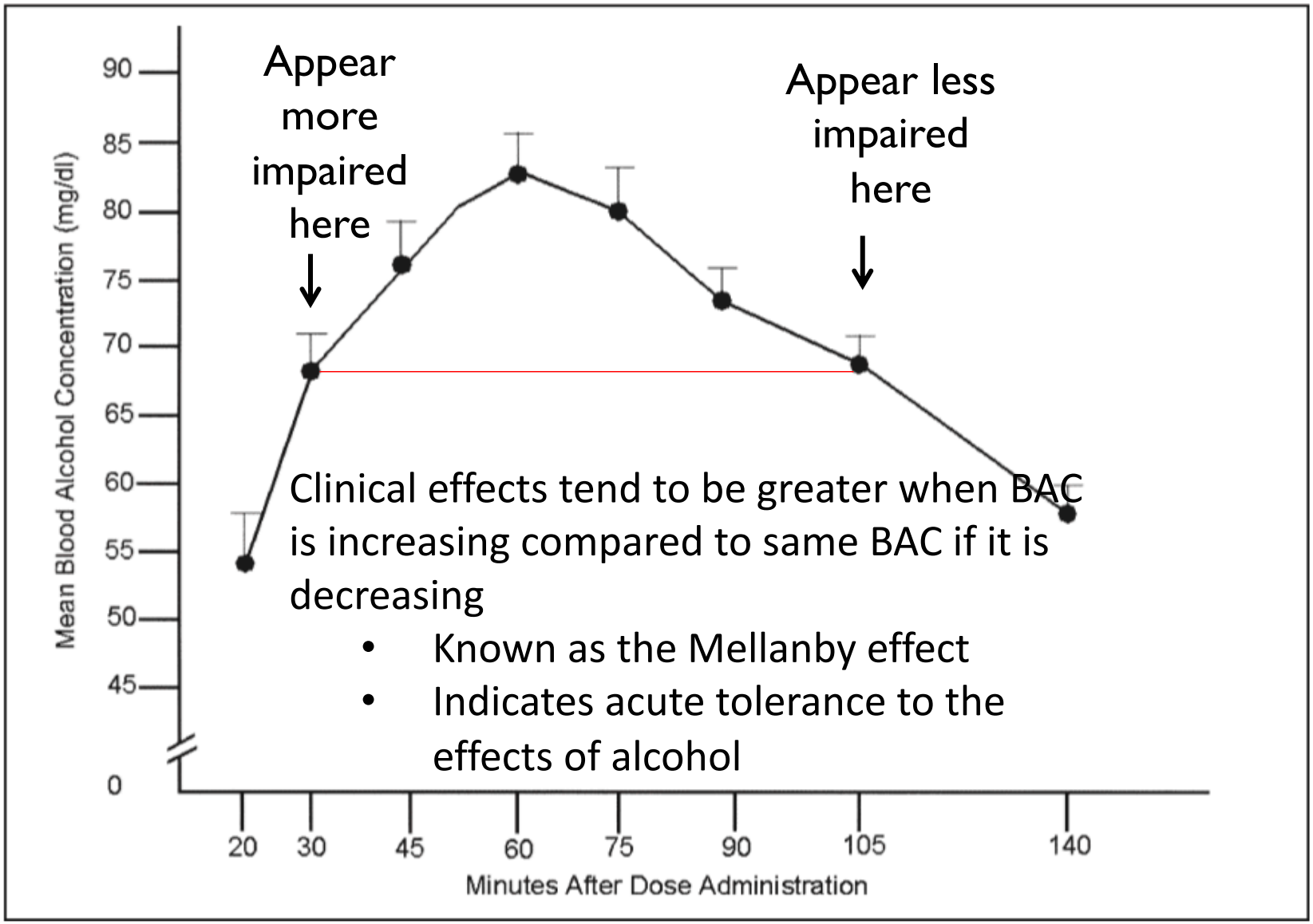
- food slows emptying of stomach where absorption is slow
- Ethanol does not “bind” to food
- Also stomach contains aldehyde dehydrogenase
- pH of stomach does not alter charge on ethanol so has no effect on absorption

Absorption



- Most of the absorption takes place in the small intestine

Ethanol absorption and effects in humans



Fillmore et al. (2005) J.Stud.Alcohol 66:663-672

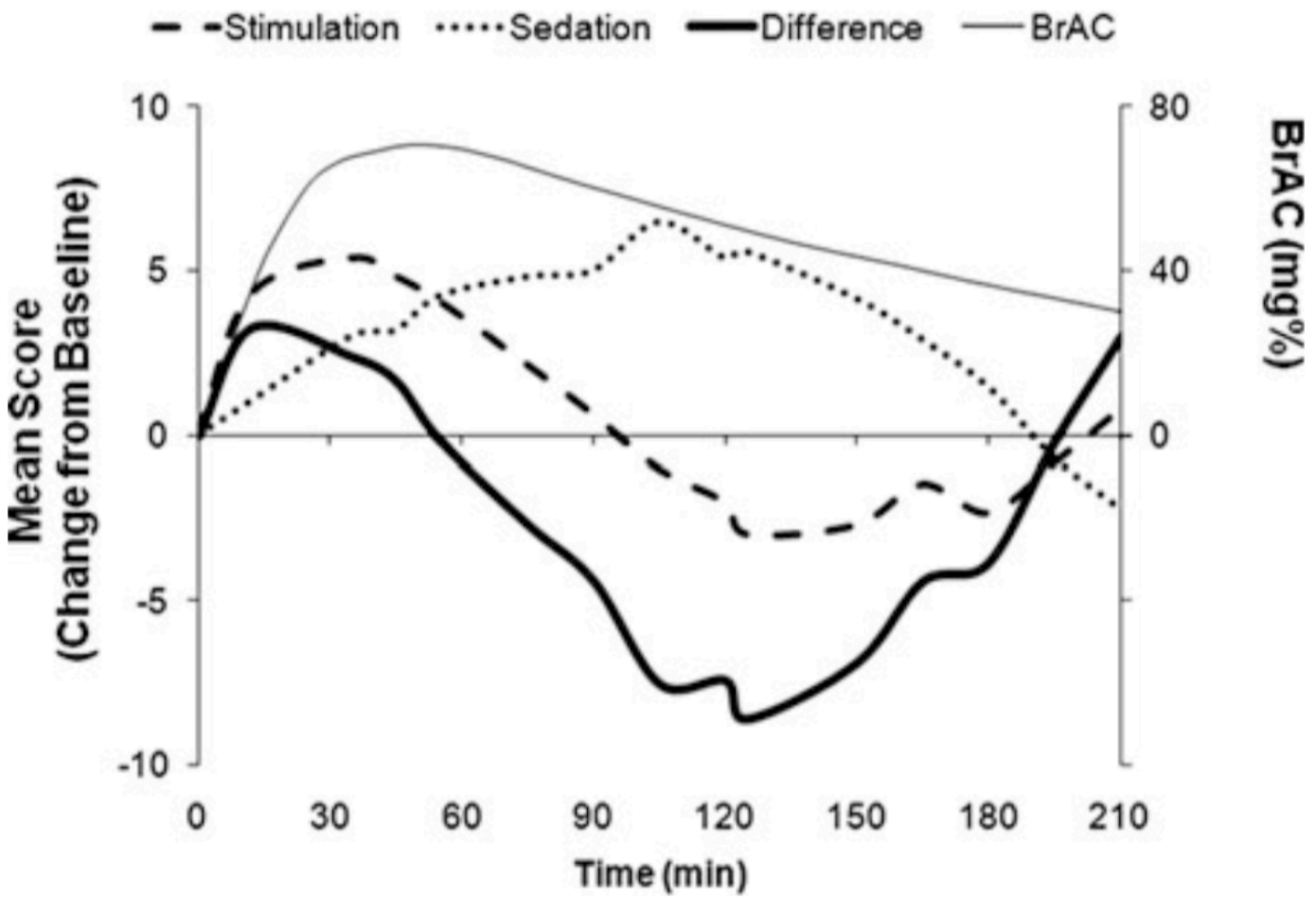
Effects are biphasic

Ethanol has a biphasic effect in most animal models

- At low doses it can increase locomotion – it acts as a motor stimulant – this always peaks first
  - This effect is likely due to increased dopamine levels in ventral striatum
  - Thought to be more rewarding than the depressant effect
  - Thought to motivate wanting to ingest more

Effects are biphasic

- At higher doses it is a sedative/depressant – these effects seem to be mediated via effects on receptors for GABA (an inhibitory neurotransmitter) and glutamate (an excitatory neurotransmitter)
  - This always peaks after the stimulant effect
  - Most often reported as unpleasant
  - Not thought to be the rewarding component of alcohol
  - Likely independent of the reward pathway



In this experiment, Difference = (stimulation score – sedation score)
Note how sedation continues to increase even as BAC is decreases

Stimulatory effects – dopamine mediating

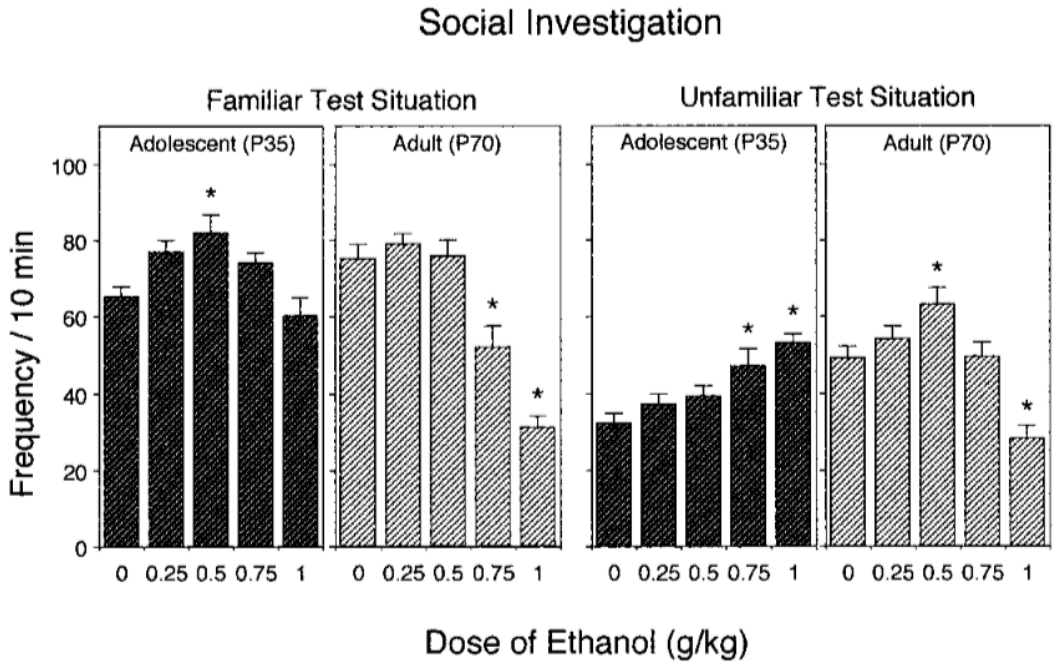
- Those who experience more of the stimulant effects than sedative effects are at greater risk for addiction – they like alcohol more and report more positive effects
- Can also reliably measure increased heart rate as a marker of physiological stimulation
- Stimulatory effects seem to be most rewarding
- Nucleus accumbens activation is crucial and correlates with self-reported intoxication

Anxiolytic effects of alcohol

- Likely due to effects on amygdala
- Amygdala involved not only in memory but also in fear
- Normally, amygdala becomes more active when confronted with threatening imagery
- Alcohol decreases difference in amygdala activation when viewing threatening vs non-threatening images
- Therefore, alcohol may disrupt threat detection circuitry

Ethanol can increase sociability and decrease anxiety in animal models

- At low doses, ethanol increases social interaction
  - Bigger effect in adolescent animals
- Ethanol relieves anxiety
  - Can be seen as overcoming the inhibitory effects of an unfamiliar environment on social interaction



What is BAC (Blood Alcohol Concentration)?

- BAC is g of ethanol per 100 ml of blood
- so a BAC of .08 is .08 g of ethanol in 100 ml of blood
- Lethality around 0.4 to 0.5
- to calculate
  - divide the number of grams of ethanol ingested by the volume in which it can distribute (simplest)
  - can also take into account clearance from blood over time

how do you estimate Blood Alcohol Concentrations (BACs)?

one standard drink = 13.4 grams of pure ethanol

Average man is 58.3% water

Average woman is 48.5 % water

One litre of water weighs 1 kg, so:

- 90.7 kg (200 pound) woman X 0.485 = 44 L
- 90.7 kg (200 pound man) X 0.583 = 52.9 L

note that this is for estimates - a blood test will remove any doubt

BAC

13.4g/44L = 0.30g/L = .030g/100mL = .030%

13.4g/52.9L = 0.25g/L = .025g/100mL = .025%

- these are the water-alcohol concentrations
- how does this relate to BAC?

- blood is 80.6% water so multiply water values by this number
  - .03 X .806 = .024 (Female)
  - .025 X .806 = .020 (Male)
  - these are the blood alcohol concentrations

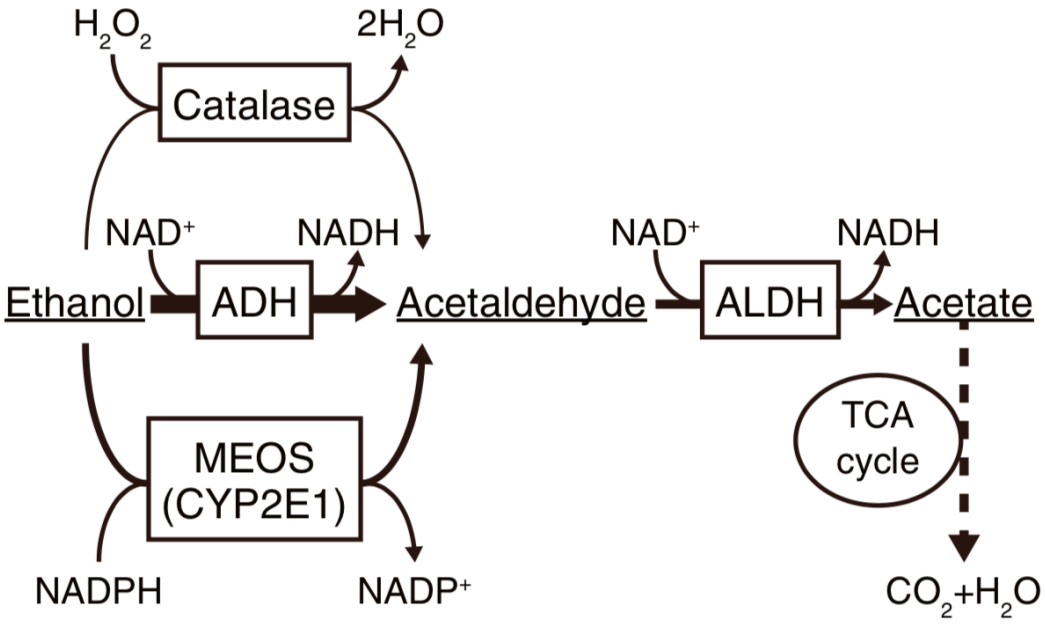
metabolism

2 % excreted unchanged in breath, skin, urine

90 % metabolized in liver

Some metabolism in stomach

metabolism



ADH - alcohol dehydrogenase, ALDH aldehyde dehydrogenase, H_2O_2 hydrogen peroxide, NAD and NADP - enzyme cofactors

MEOS – microsomal ethanol oxidizing system

- alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are the major enzymes
- Most metabolism occurs in liver but small amounts are metabolized elsewhere
- the enzyme CYP2E1 normally metabolizes less than 20% usually but percentage increases with heavy drinking
- catalase - minor role overall. May produce acetaldehyde in brain, may induce acute increase in alcohol metabolism

Ethanol metabolism

- Hepatic metabolism shows saturation/zero order kinetics
- The ability for enzymes to metabolize ethanol is quickly overwhelmed before a single drink is finished

Therefore, not all of it gets metabolized the first time through the liver (or else no one would ever get drunk)

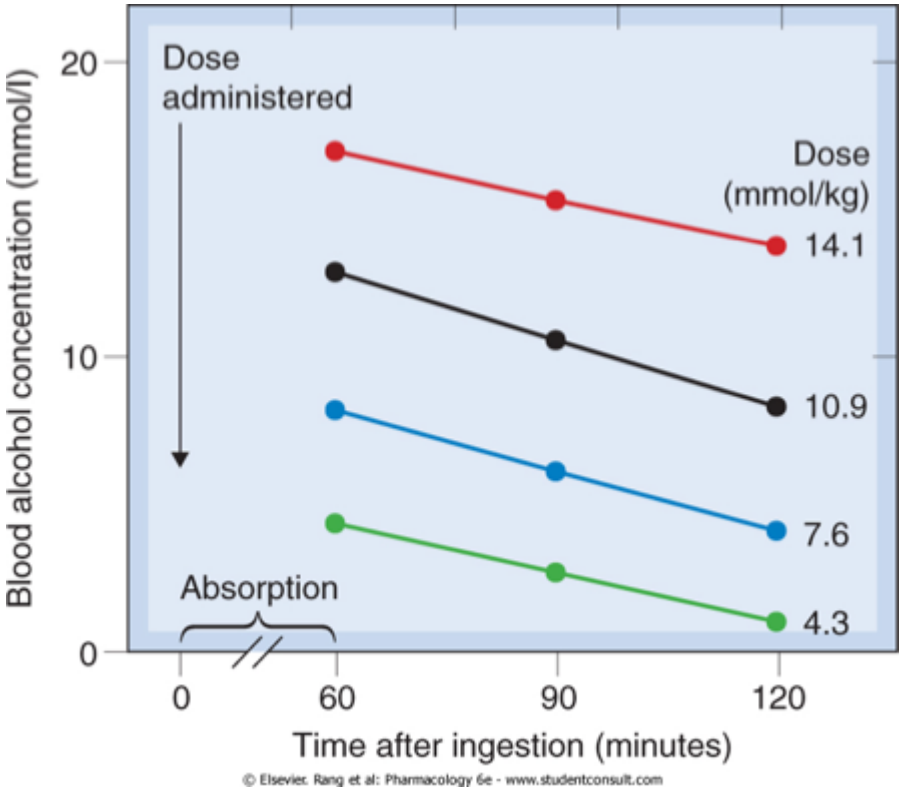
Reason – enzymes need the cofactor NAD^+ to work

Metabolizing 1 standard drink requires a large quantity of NAD^+

NAD^+ availability limits metabolism to about 8 g/h (one standard drink = 13.38 g of ethanol)

kinetics of metabolism

- with most drugs, a constant proportion is removed in a given amount of time, regardless of dose
- with alcohol, a constant amount is removed in a given amount of time regardless of dose
- There is so much ethanol that all enzymes involved in its metabolism are completely occupied – there is no excess capacity in the system
- The metabolic pathway operates at a maximum level with a modest amount of alcohol in the system



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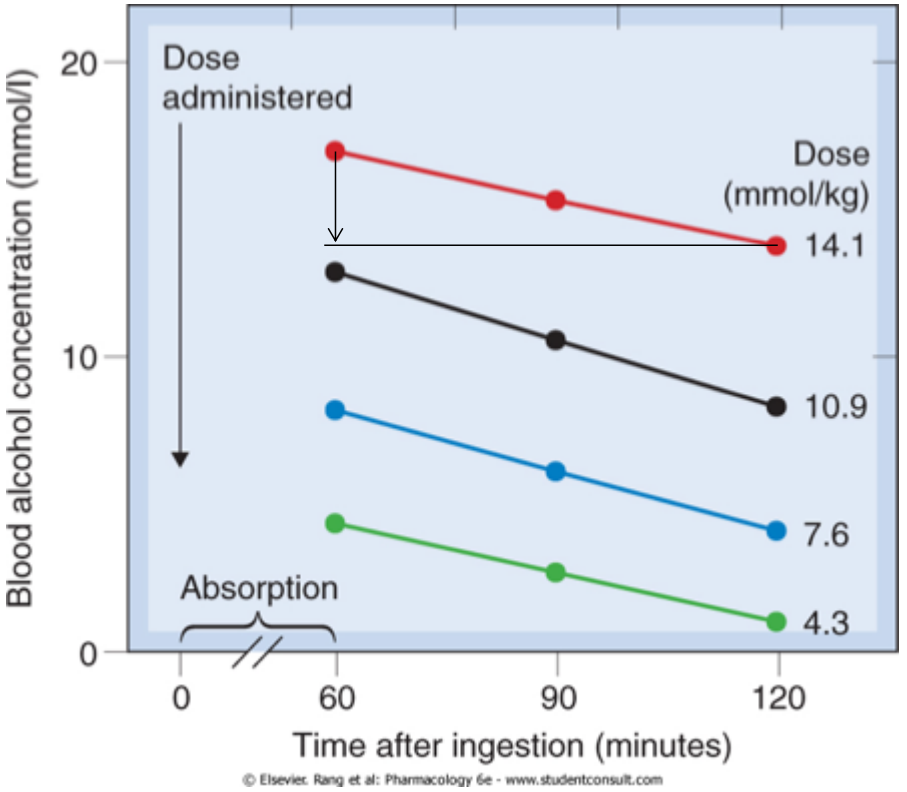


Metabolism and BAC

- metabolism will depend on alcohol experience – experienced drinkers tend to metabolize more quickly due to metabolic tolerance
- average drinker metabolism rate is such that we expect a 0.017 BAC decline per hour
- a more conservative value of 0.015 BAC per hour has been widely accepted as average in Canada

Metabolism and BAC?

- So consider the values for one standard drink calculated above – after one hour, BAC drops by 0.015
- Male
  - .020 -.015 = .005 = 25% of ethanol left (.005/.020 = 25)
- Female
  - .024 – 0.15 = .009 = 37.5% of ethanol left (.009/.024 = 37.5)

- after one hour, the male has metabolized 75% (100-25) of the single drink, the female has metabolized 62% (100-37.5)

Exhaled ethanol - breathalyzers

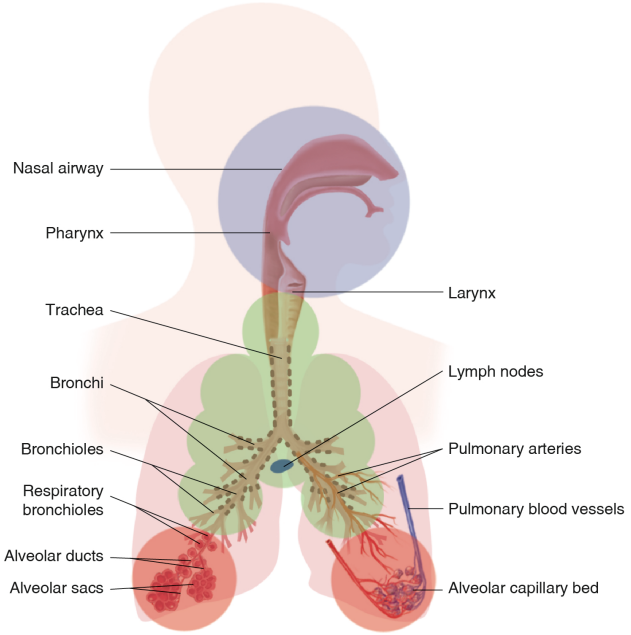


Figure 15-1. *Major regions of the respiratory tract and predicted fractional dep inhaled particles in the extrathoracic, bronchial, and alveolar region of th respiratory tract during (solid line) oral or (dashed) nasal breathing.* (Adapted f in Oberdörster *et al.* (2005) with drawing courtesy of J. Harkema and data from ICRP

Blood vessels (2100 parts)

↓

Lungs (1part)

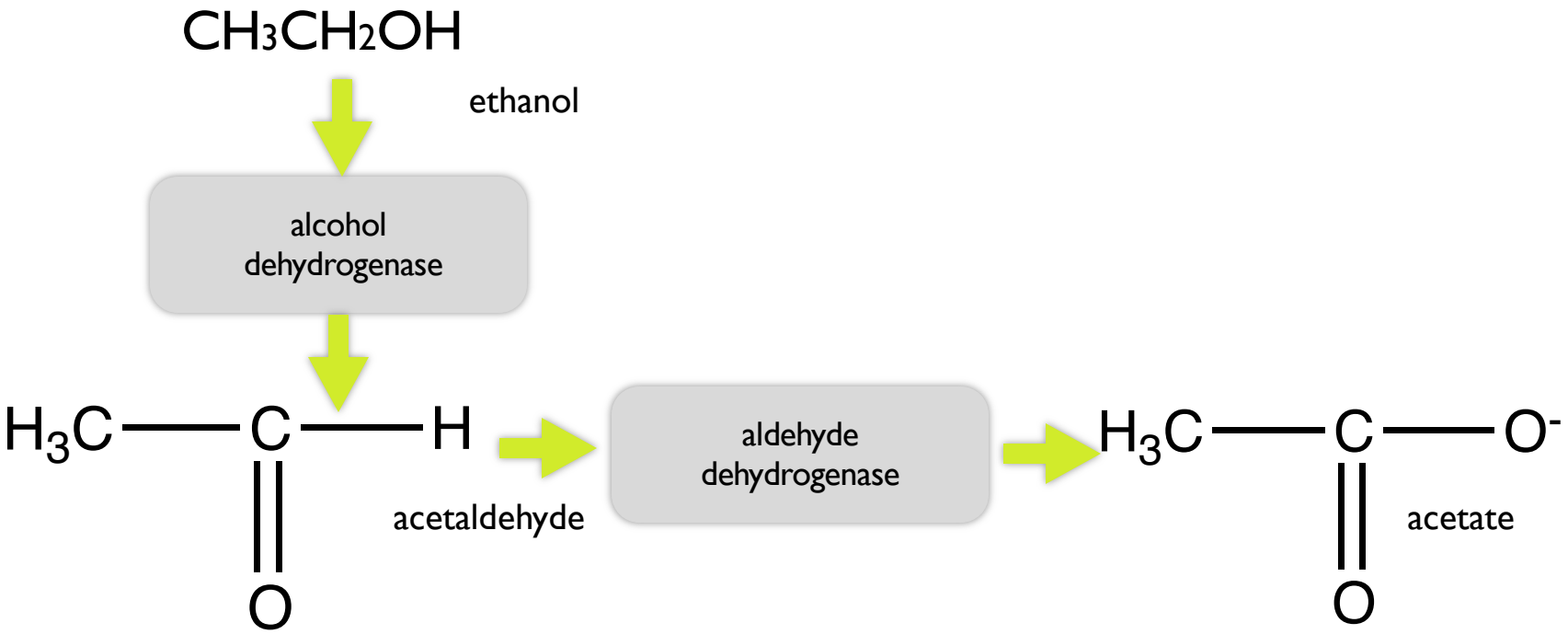
↓

Exhaled and measured

$[alcohol]_{blood} : [alcohol]_{exhaled\ breath} = 2100:1$

- So the breathalyzer records the amount of non-metabolized ethanol expired from the lungs
- Mouthwash will not cause positive result
- Ethanol-based hand sanitizer (70% ethanol) linked to positive tests in 6% of users in one study, even though actual BAC was zero
  - Due to inhalation of ethanol vapour, but effect was short lasting (one – two minutes after use)

Major metabolic enzymes

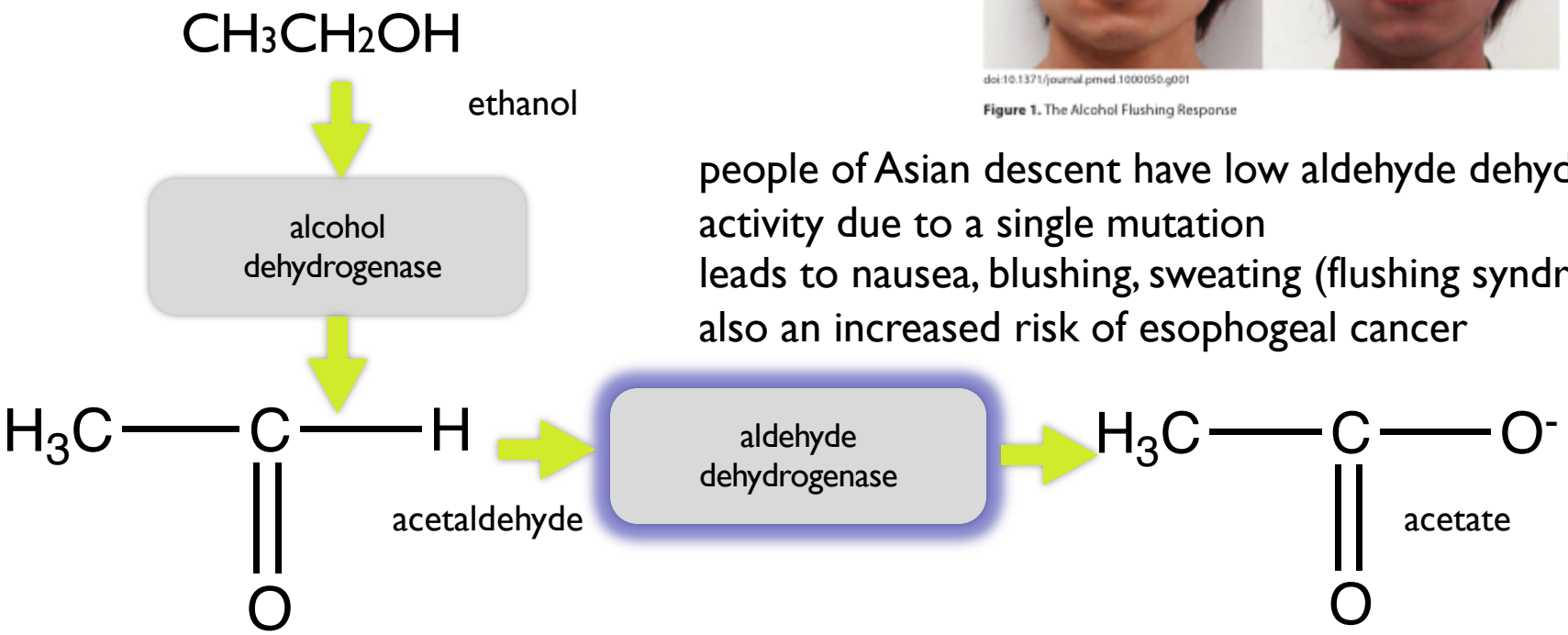


Major metabolic enzymes

Brooks et al., 2009 PLoS med6(3):258

doi:10.1371/journal.pmed.1000050.g001

Figure 1. The Alcohol Flushing Response

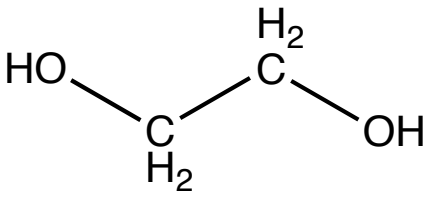


people of Asian descent have low aldehyde dehydrogenase activity due to a single mutation
leads to nausea, blushing, sweating (flushing syndrome) – also an increased risk of esophogeal cancer

Metabolic enzymes can form toxic products

- these enzymes can be hijacked by substances other than ethanol to produce toxic substances
- Some of the substances may not be particularly harmful themselves, but their metabolites cause physiological damage

Antifreeze metabolism

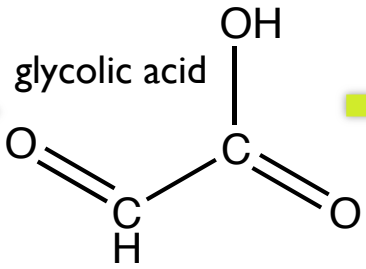


ethylene glycol

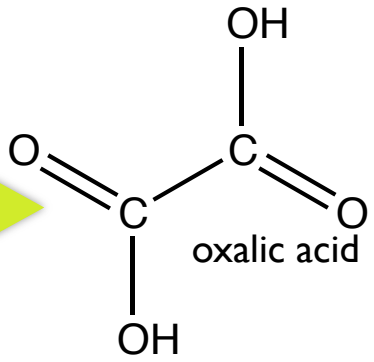
alcohol dehydrogenase

glycoaldehyde

aldehyde dehydrogenase



glycolic acid

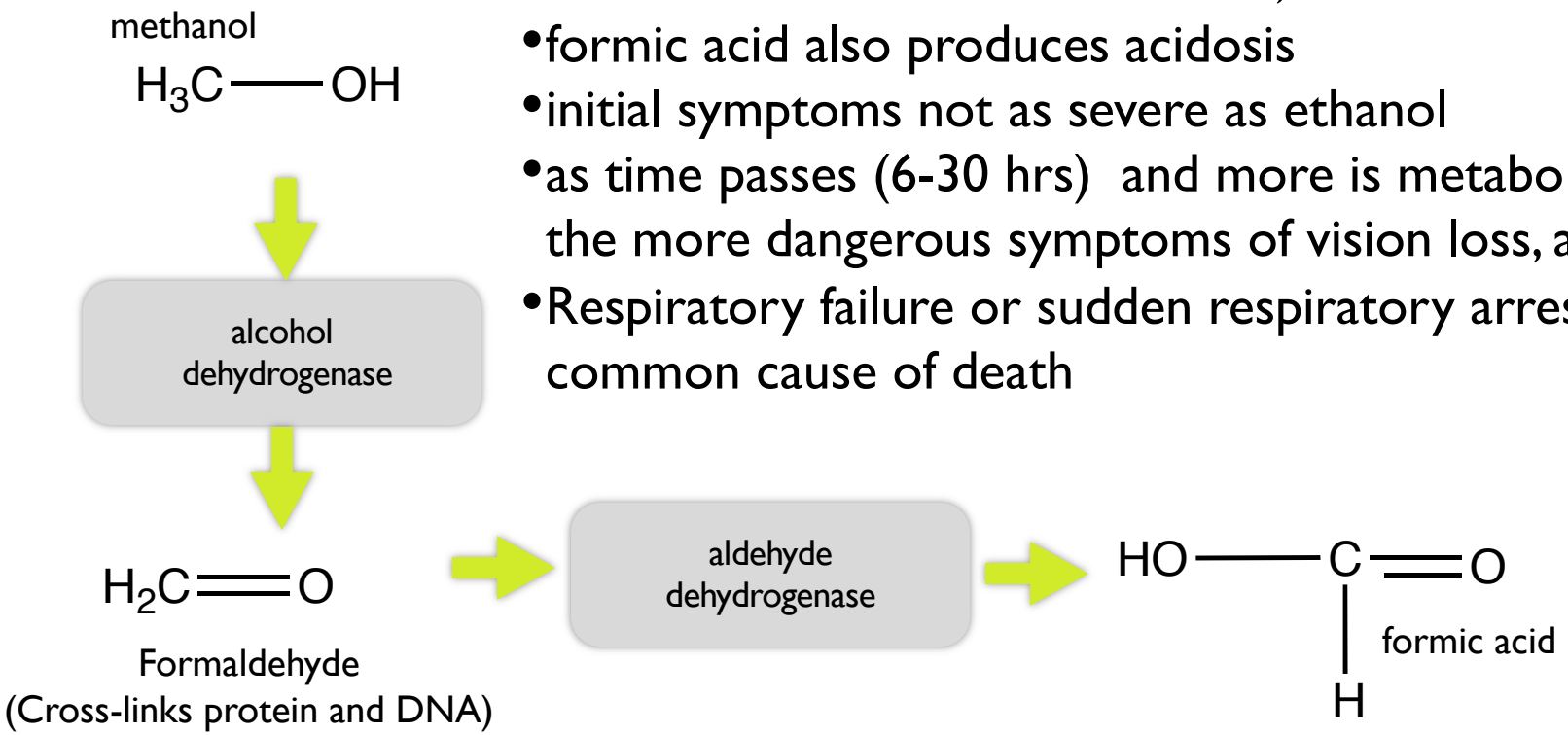


oxalic acid

- ethylene glycol is very sweet tasting
- initial stage: CNS depression - appear as though drunk, CNS depression, coma
- second stage: cardiopulmonary dysfunction – acidosis (mostly from glycolic acid) - low blood pH can be fatal
  - hyperventilation, heart arrhythmia, pulmonary edema
- third stage: renal dysfunction - kidney failure - urine production ceases - may be a few days after initial contact
- 30 ml can cause death

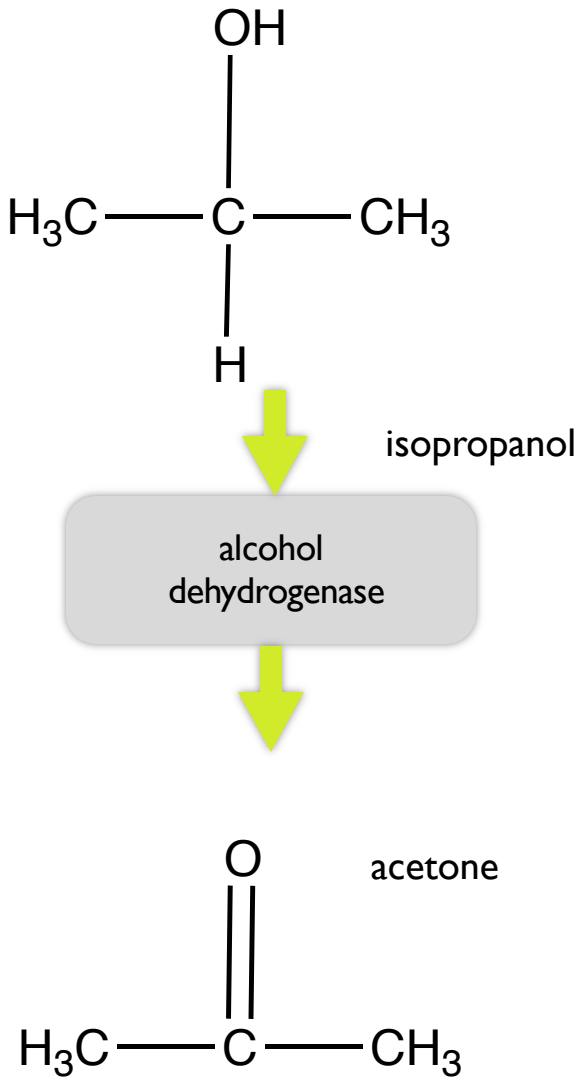
oxalic acid can bind with calcium to form crystal that precipitate out throughout the body including kidneys, lungs

methanol metabolism



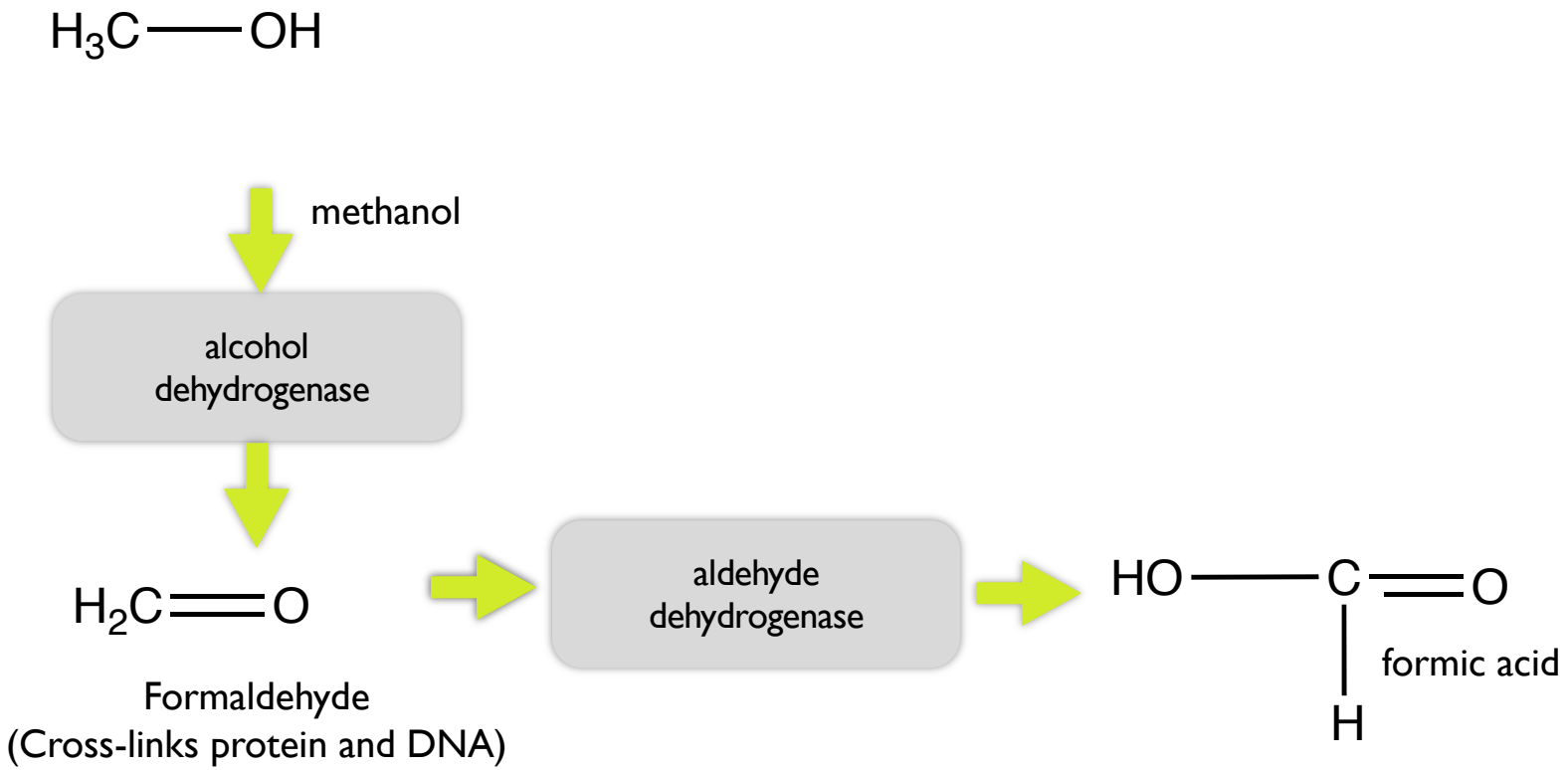
- Formic acid primarily responsible for optic nerve damage via disruption of mitochondrial function
- as little as 10 ml causes blindness, can be lethal at 30 ml
- formic acid also produces acidosis
- initial symptoms not as severe as ethanol
- as time passes (6-30 hrs) and more is metabolized, get the more dangerous symptoms of vision loss, acidosis
- Respiratory failure or sudden respiratory arrest the most common cause of death

Isopropanol (rubbing alcohol) metabolism



- acetone - solvent in nail polish remover (fruity smell on breath)
- isopropanol and acetone are CNS depressants
- relatively safe at low levels
- at high levels, vomiting, coma

to prevent poisoning



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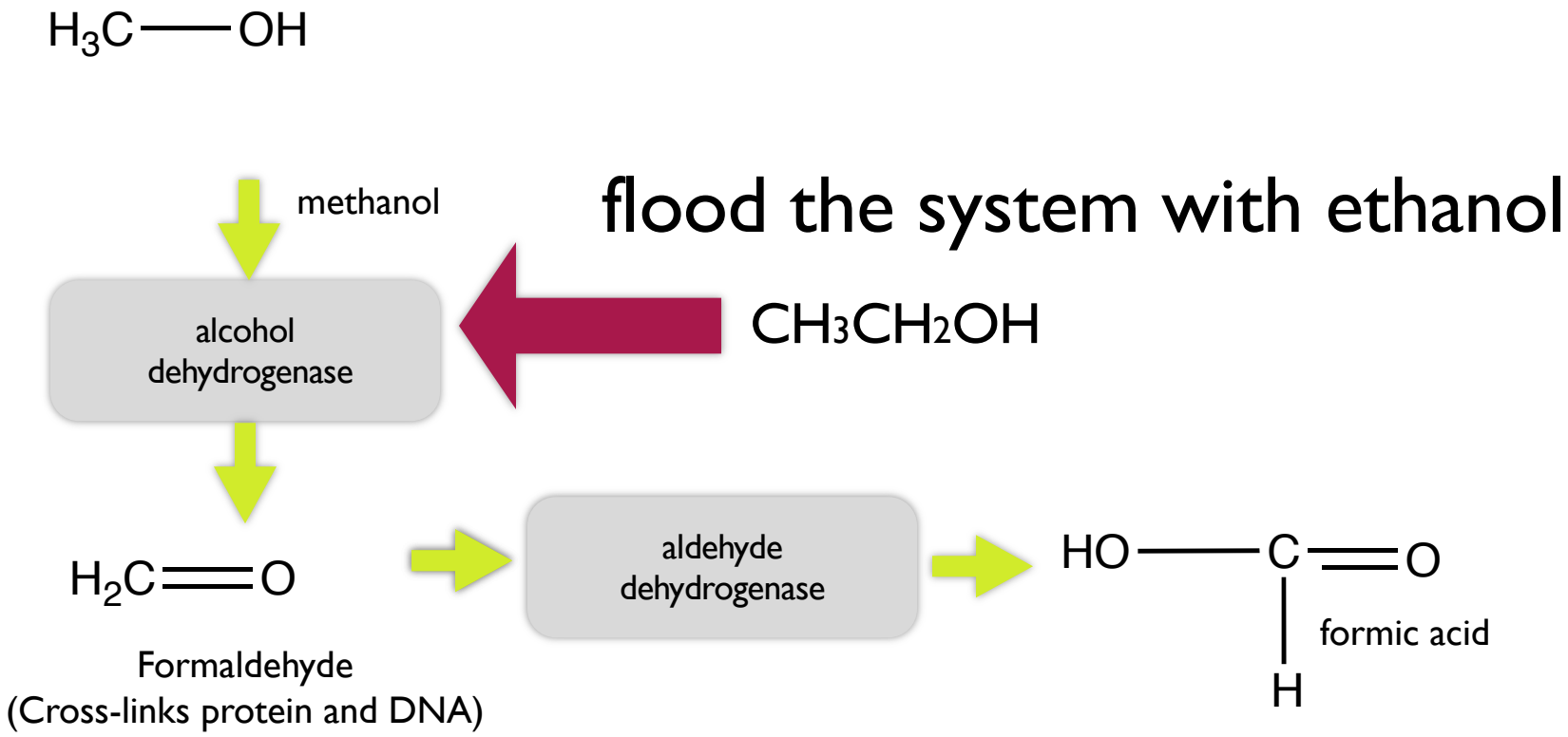

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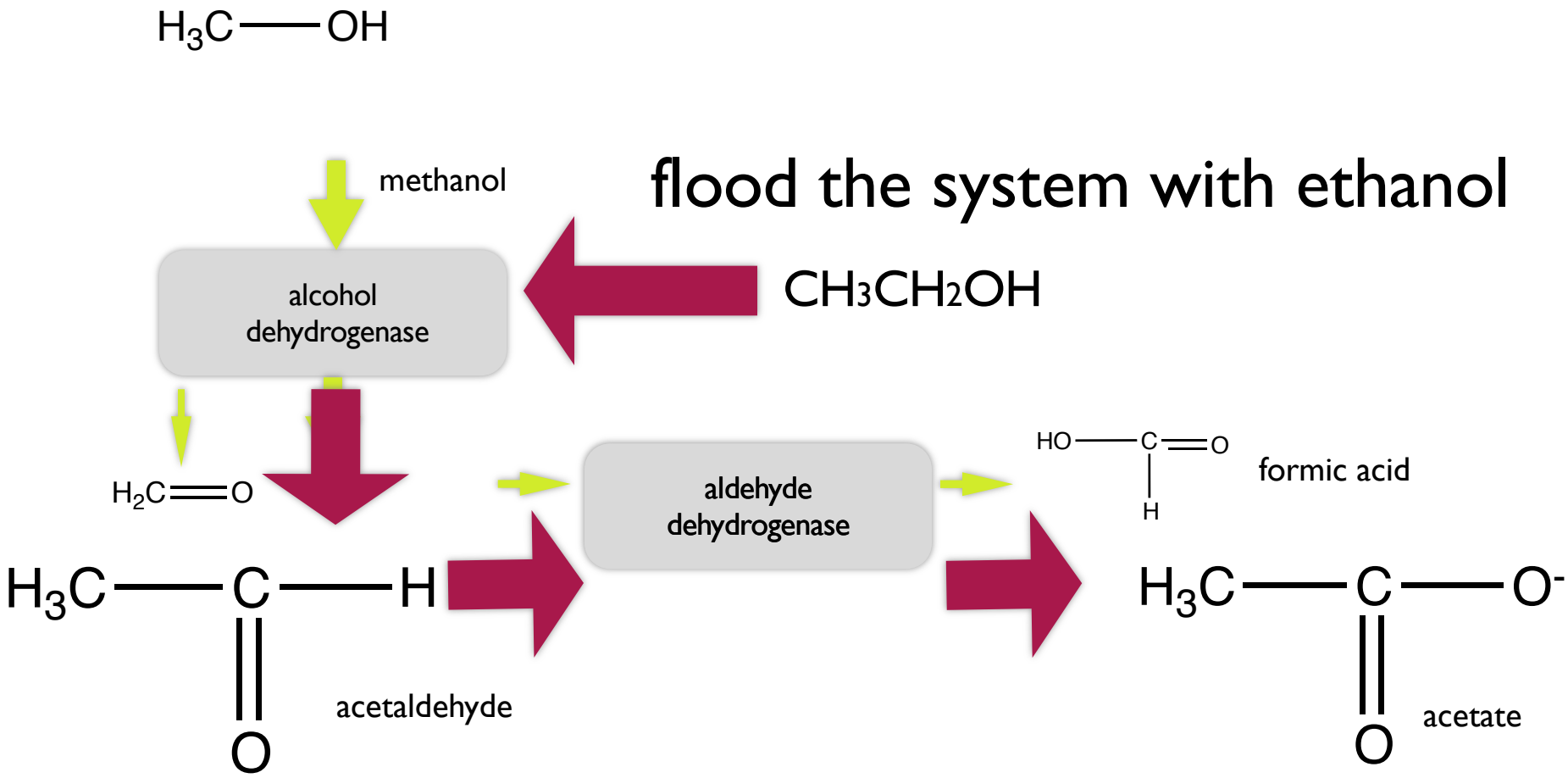
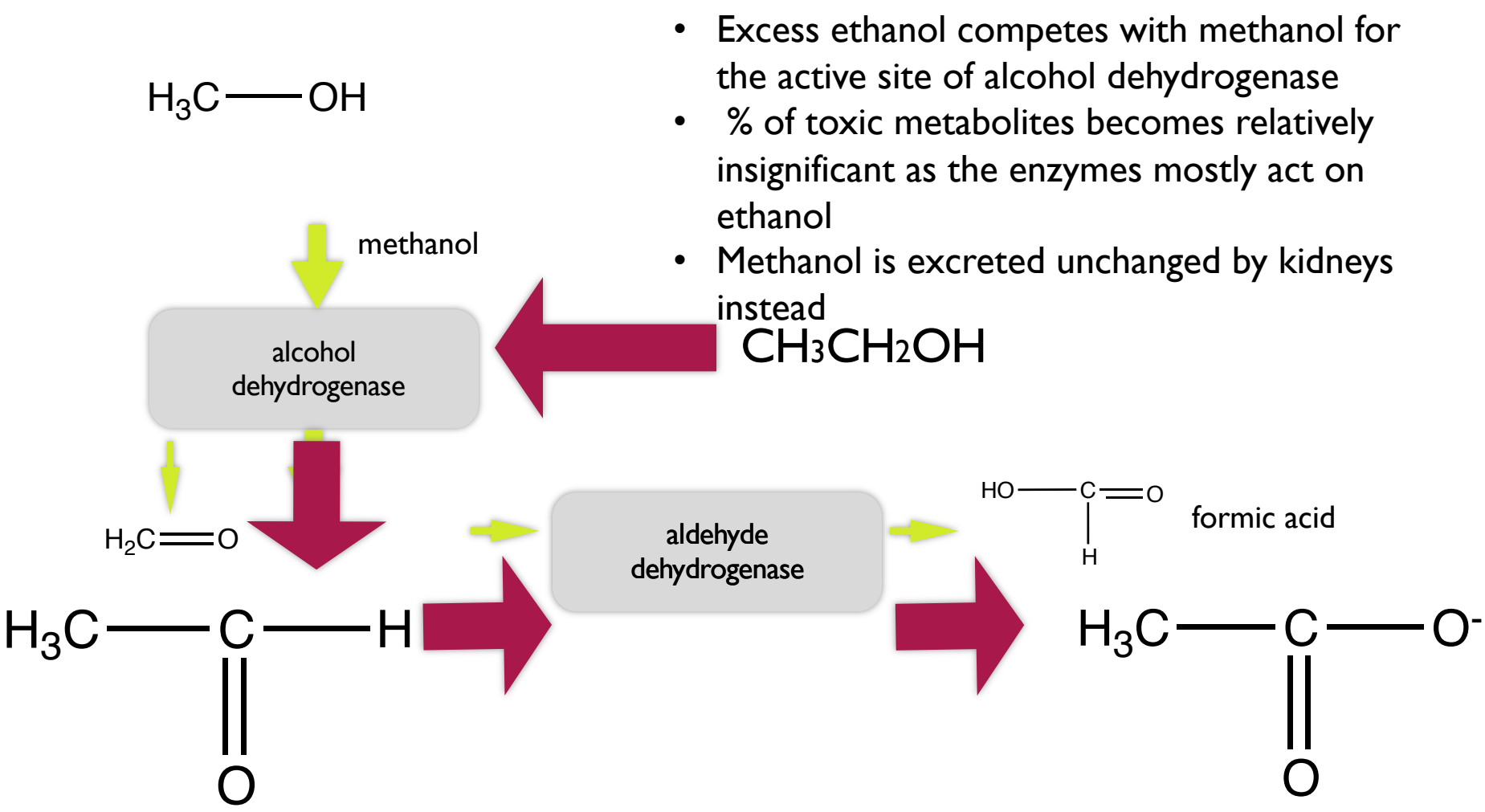


to prevent poisoning



- Excess ethanol competes with methanol for the active site of alcohol dehydrogenase
- % of toxic metabolites becomes relatively insignificant as the enzymes mostly act on ethanol
- Methanol is excreted unchanged by kidneys instead

Fomepizole

- inhibit alcohol dehydrogenase with fomepizole, a competitive inhibitor of the enzyme
- used in ethylene glycol and methanol poisoning
- Longer duration of action than ethanol but more expensive
- Minimal adverse effects compared to ethanol
- non-metabolized compounds excreted by kidneys