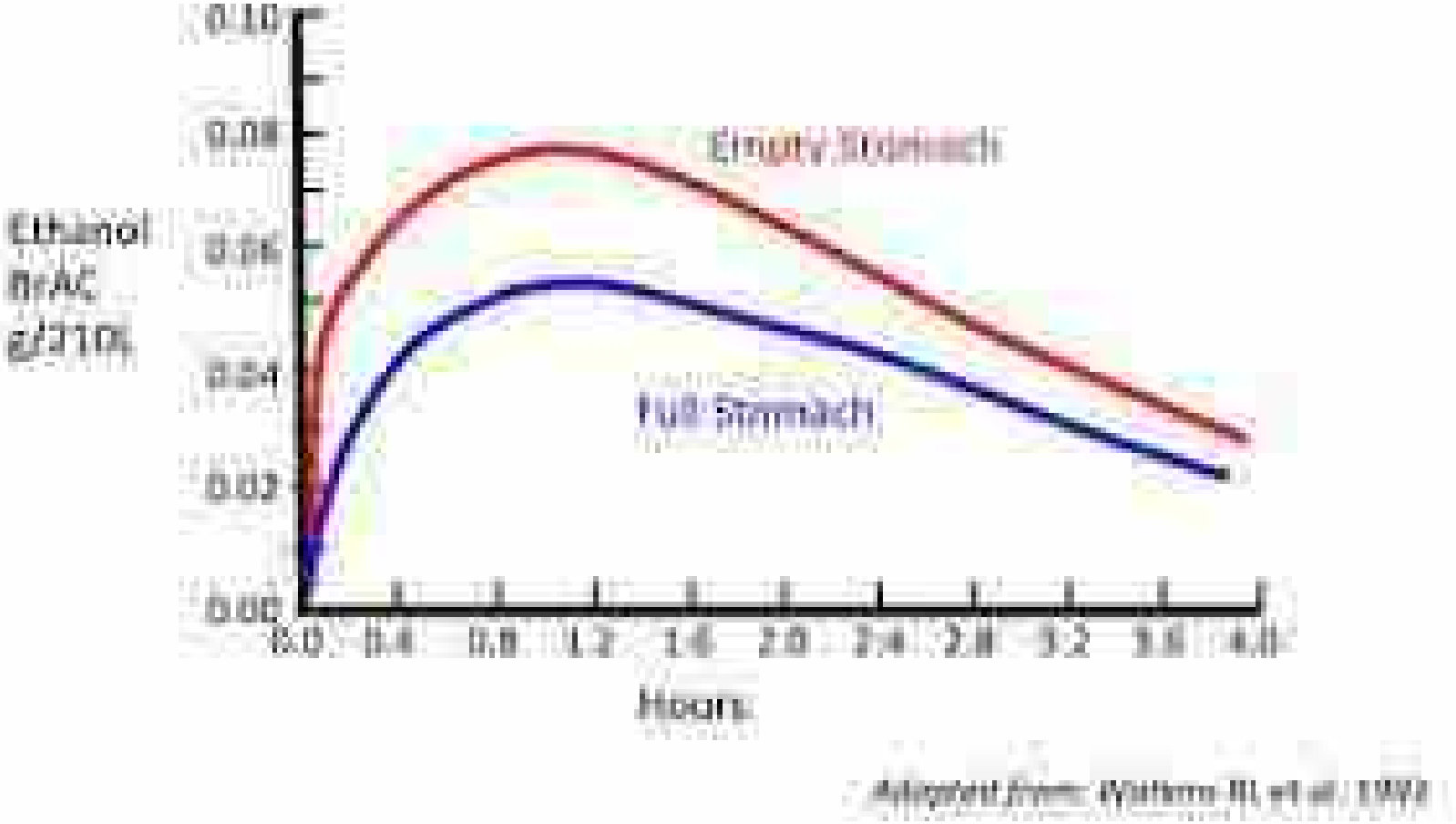
Breath alcohol concentration in full and empty stomach



Influence of portal blood flow

- Alcohol crosses the biological membrane by passive diffusion thus good blood flow will maintain the **concentration gradient** and promote absorption.
- Any stimulation of the sympathetic nervous system (e.g. emotional state or exercise) will reduce portal blood flow and gastric motility thus decreasing alcohol absorption.

Type of drink

- The type of drink consumed also plays a role.
- Drinks with alcohol content between 20-30% are absorbed quickest.
- Whereas drinks with a higher alcohol content are absorbed more slowly, because an alcohol content over 30% **irritates the gastric mucosa** increasing mucus secretion and decreasing gastric emptying.

Effect of mixer

- Thus drinks with an alcohol content above 30% can cause a faster rise in BAC if served diluted with a mixer, than if they are served without dilution.
- This is especially true if the mixer is a carbonated drink (like champagne) as this can also increase the **rate of absorption.**

Ethanol fatal dose

- The fatal dose of ethanol is 300-400 mL of pure ethanol (600-800 mL of 50% spirits), for the average adult if consumed in less than one hour.

Estimating blood alcohol concentration

- Blood alcohol content (BAC) can be calculated with simple information such as a person's weight, gender, and the amount of alcohol consumed in a given period.
- The most common formula for calculating BAC in this way is known as the **Widmark formula**.

Estimating blood alcohol concentration

$$\text{EBAC} = \frac{\text{Et (mL)} \times \text{concentration (\%)} \times 800}{\text{Vd (L/Kg)} \times \text{Weight (Kg)} \times 10}$$

First pass metabolism

- The bioavailability of alcohol is reduced by first pass metabolism (FPM).
- a) Oxidation of alcohol by gastric alcohol dehydrogenase (ADH) in the gastric mucosa accounts for a small proportion of FPM,
- b) The majority occurs via oxidation by ADH in the liver hepatocytes.

Distribution

- The proportion of alcohol that is absorbed, and escapes FPM enters the systemic circulation and is rapidly distributed throughout the body tissues via the blood plasma until an equilibrium between the BAC and tissue concentration is reached.
- The time until equilibrium is dependant upon the permeability (**water content**) and **rate of blood flow** but is generally achieved within 1-2 hours.

The concentration of alcohol in blood and tissue depends on the amount of total body water, since alcohol is soluble in water.

$$Vd = 0.6\ L/Kg$$

Total body water and volume of distribution

- Differences in TBW will influence alcohol pharmacokinetics because it determines the volume of distribution available for alcohol distribution within the body.
- Alcohol is preferentially distributed in tissues with **higher water contents** and a **good blood supply.**

Gender differences

- Gender differences in responses to ethanol are well recognized.

- Women are more sensitive to alcohol, and exhibit higher mortality at lower levels of consumption than men.

Gender differences

- Women exhibit somewhat higher blood levels than men following ingestion of equivalent doses of ethanol.

- This phenomenon appears to be due in part to more extensive ADH-catalyzed metabolism of ethanol by the male gastric mucosa. This would decrease the bioavailability of alcohol resulting in lower BAC.

- A second factor contributing to the higher blood ethanol levels and greater CNS effects in women is their smaller volume of distribution (higher body fat) for relatively polar solvents such as alcohols.

Ethanol metabolism

- A small proportion (2-5%) of the alcohol absorbed is excreted unchanged in the urine, sweat or breath but the majority (~ 90 %) is removed via oxidation by ADH.
- This can occur in various organs such as the *stomach* and *small intestine* but is primarily carried out by *hepatic ADH*.

Ethanol oxidation

- Oxidation by **ADH** converts alcohol to acetaldehyde, a reactive and toxic molecule that is rapidly oxidised by **aldehyde dehydrogenase** to harmless acetate.
- Under normal conditions acetate is then oxidised in the liver and peripheral tissues to carbon dioxide and water.

Zero-order kinetics

- The process that takes place at a constant rate independent of drug concentration involved in the process.

Zero-order ethanol metabolism

- The rate of ethanol metabolism is linear.
- Chemists refer to this as a Zero Order Reaction.
- Because the primary decay product of alcohol metabolism-*acetaldehyde-is poisonous*.
- The body must eliminate the acetaldehyde produced by the breakdown of alcohol before any more alcohol can be processed in order to avoid acetaldehyde poisoning.
- This slows down the rate of alcohol metabolism to a Zero Order Reaction rather than a First Order Reaction.

Rate of metabolism related to NAD

- The rate limiting step in the ADH pathway is the limited availability of **Nicotinamide adenine dinucleotide (NAD).**
- Alcohol metabolism is restricted to approximately **15 g per hour**.

ALCOHOL METABOLISM

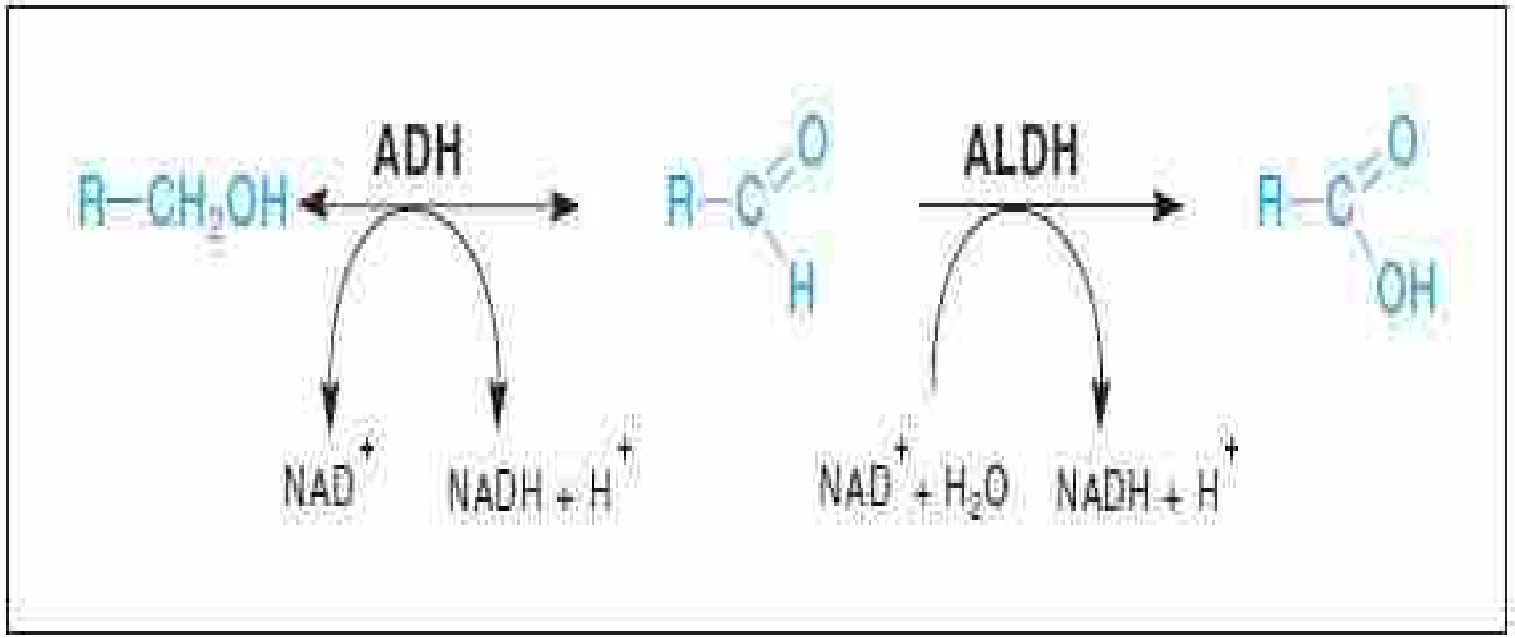


Figure 6-23. Oxidation of alcohols to aldehydes and carboxylic acids by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH).

Different metabolic pathways for ethanol

liver is the major organ to metabolize and eliminate alcohol.

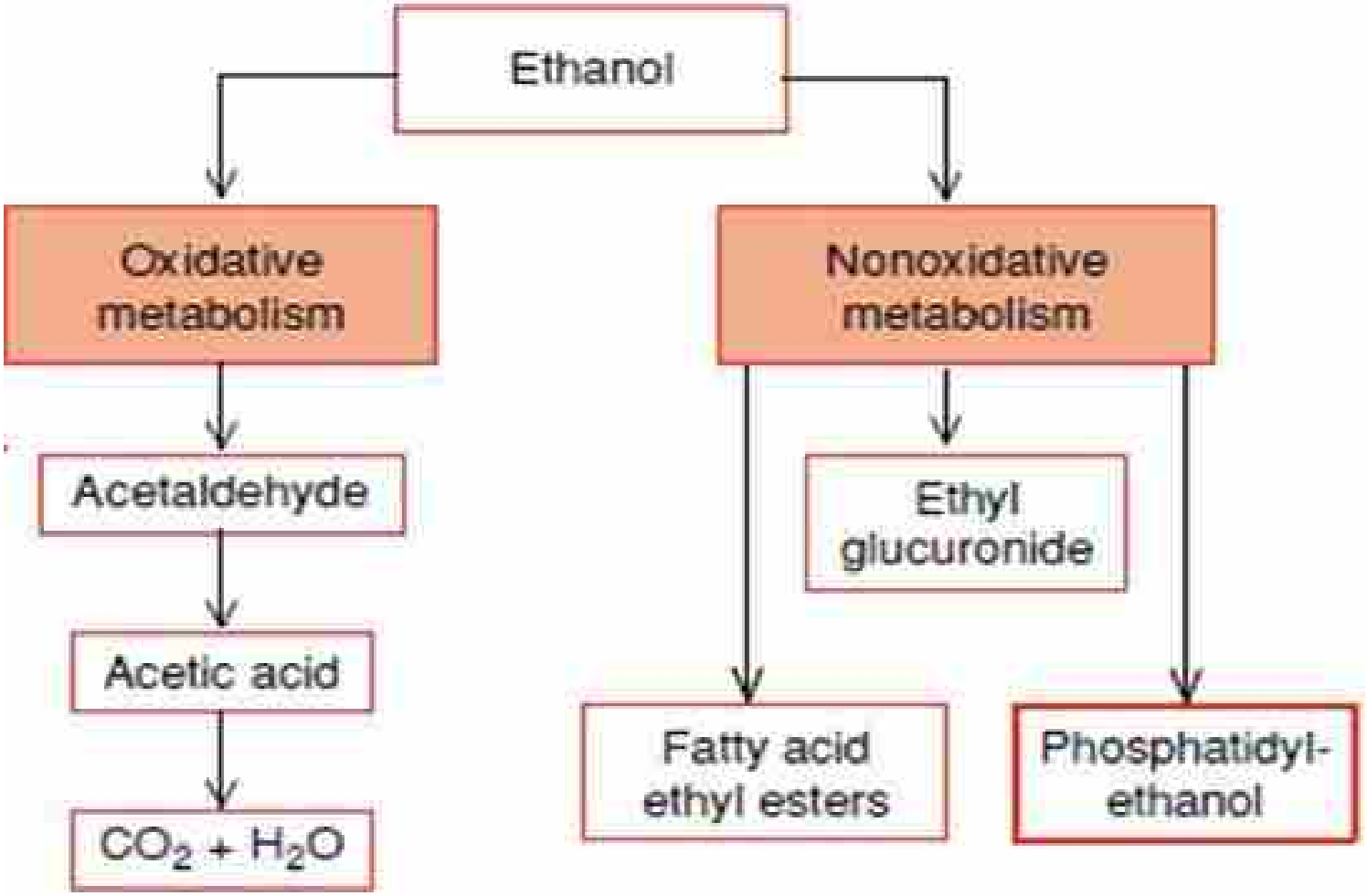
1- Hydrogen peroxidase

2- MEOS (inducible)

3- Alcohol dehydrogenase

Enzyme induction

- Pre exposure to a single high dose or multiple doses of ethanol can induce CYP2E1, thereby enhancing the metabolic activation and potentiating the toxicity of a considerable number of other solvents and drugs.

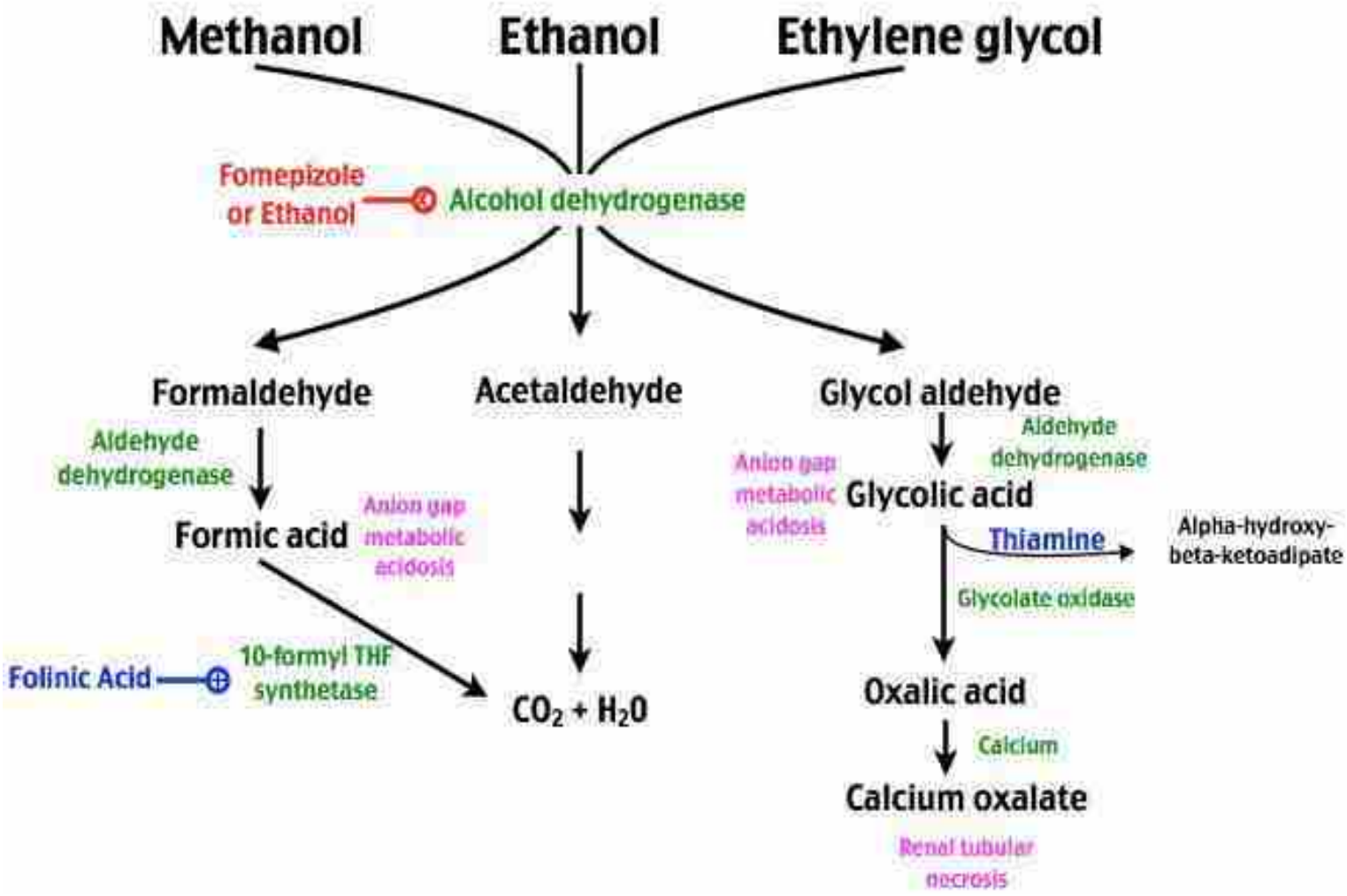


Comparison of the metabolites of ethanol produced by oxidative and nonoxidative metabolic pathways.

Use of metabolic pathway in treatment

- Ethanol interacts with other solvents that are also metabolized by ADH and CYP2E1.
- Ethanol can be an effective **antidote** for poisoning by methanol, ethylene glycol, and diethylene glycol.
- As ethyl alcohol has a relatively high affinity for ADH, it competitively inhibits the metabolic activation of other alcohols and glycols.

Toxic Alcohol Metabolism



Ethnic factors in ethanol metabolism

- An individual's genetics can also influence the pharmacokinetics of alcohol.
- At least four different isoenzymes of ADH exist and each has a different affinity for alcohol, which will affect the overall rate of alcohol metabolism.
- Several isoenzymes of aldehyde dehydrogenase also exist, which can lead to some ethnic groups producing adverse reactions to alcohol.

Excretion

Zero order elimination process

- Alcohol elimination was originally believed to be a zero-order process, meaning that alcohol was removed from the body **at a constant rate**, **independent of the concentration of alcohol**.
- ADH is saturated at low concentrations of alcohol, hence, the overall elimination process proceeds at maximal velocity and is independent of the alcohol concentration.

Pharmacokinetic

- Excretion

  some unchanged in breath and urine

  In nonalcoholic adults: 15-24 mg%/h

  In social drinkers: 15 mg%/h

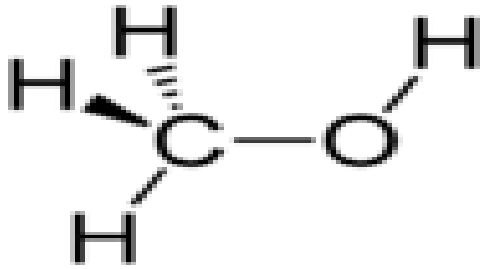
  In alcoholic adults: 15-49 mg%/h

  In children: 20-30 mg%/h

Methanol

Introduction

- Methanol (CH_3OH) is the simplest alcohol, and is a light, colorless, volatile, slightly sweet-tasting with a mild alcoholic odour when pure.
- It is **miscible with water** and organic solvents such as acetone.



Methanol other names

Methanol
Carbinol
Hydroxymethane
Methyl alcohol
Methyl hydrate
Methyl hydroxide
Methylic alcohol
Methylol

Sources of methanol

- Certain products including:
  - **Illicit alcohols**
  - Antifreeze
  - Windshield washer fluid
  - Carburetor fluid
  - Dry gas
  - Glass cleaners
  - Inks
  - Embalming chemicals

may contain high concentrations of methanol

Embalming with methanol

- **Embalming chemicals** are a variety of preservatives, disinfectant agents and additives used in modern embalming to temporarily prevent decomposition and restore a natural appearance for viewing a body after death.
- A mixture of these chemicals is known as **embalming fluid** and is used to preserve cadavers.
- Typically embalming fluid contains a mixture of formaldehyde, **methanol**, and other solvents.
- The methanol content may range from 9 to 56 percent.


SUPREMOL
EMBALMING
FLUID
BLEACHOL
GLASS THIS SIDE UP WITH CARE
HYDROL
EMBALMING
FLUID

Toxic and lethal dose of methanol

Toxic dose > 10ml

Fatal dose>15 ml (one tablespoon) of %40 methanol

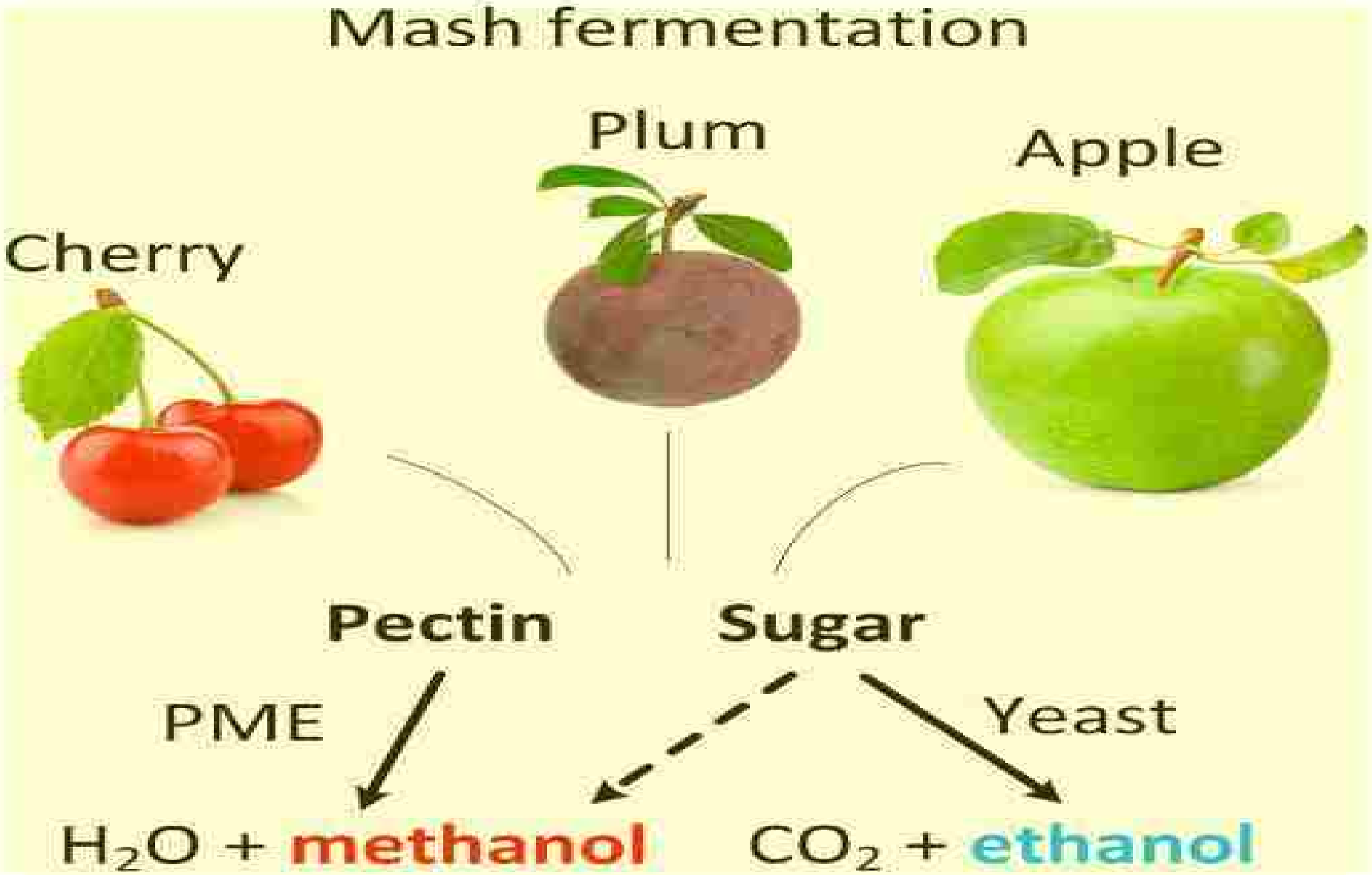
From a pediatric perspective, the ingestion of only 1.5 mL of 100% methanol in a toddler (0.15 mL/kg) is sufficient to produce a toxic blood level of 20 mg/dL.

Methanol toxic blood levels

- WHO (1997) stated that:
- Blood methanol concentrations > 20 mg/dL are associated with central nervous system (CNS) effects
- Concentrations > 50 mg/dL with severe acute toxicity
- Concentrations > 150-200 mg/dL with fatality in untreated patients

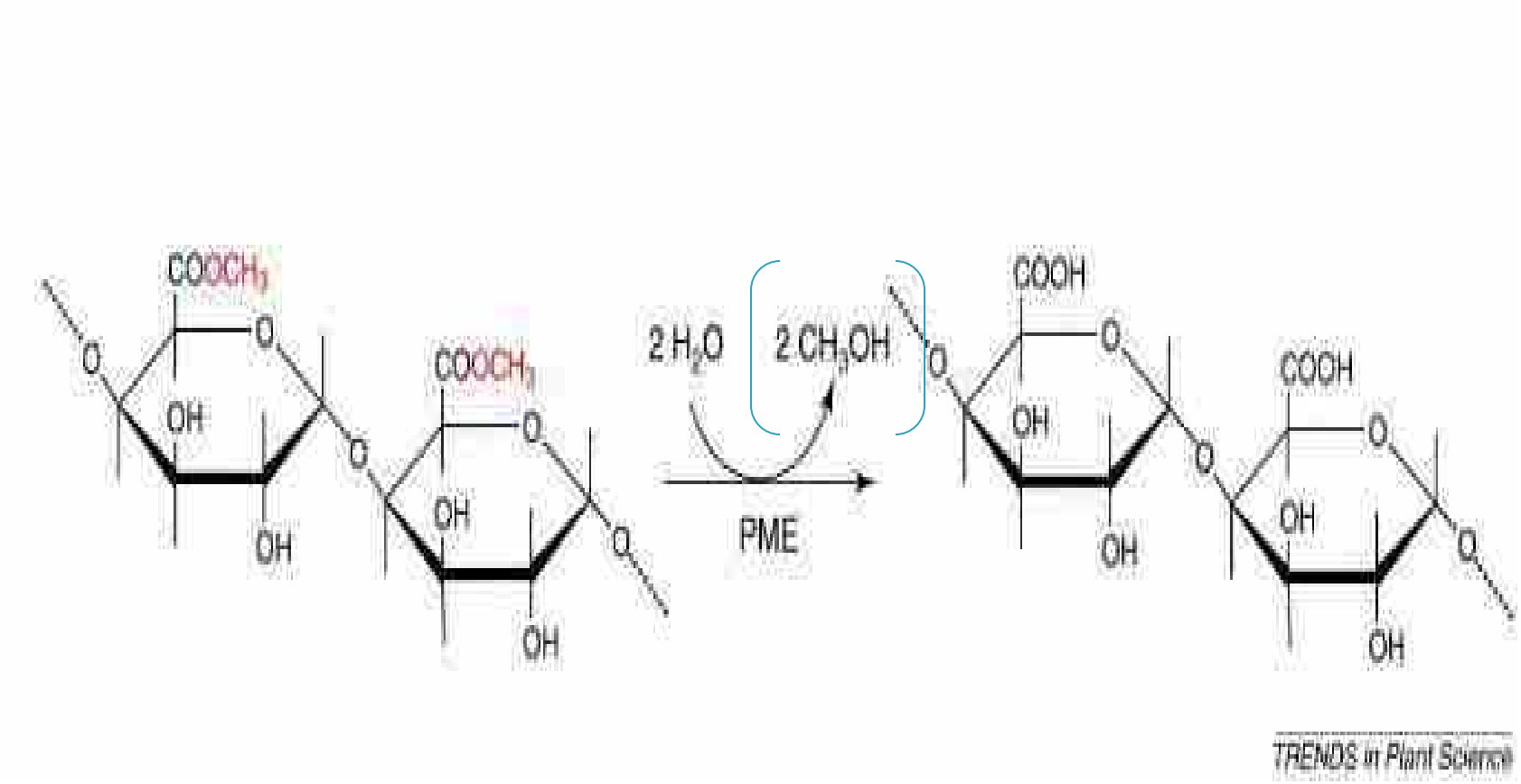
Methanol in alcoholic beverages

- Methanol is not a by-product of yeast fermentation but originates from pectins in the fruit when grapes and fruits are macerated.



During fruit sugar fermentation to ethanol by yeast, methanol is formed primarily through degradation of pectin by pectin-methylesterase (PME).

Pectin conversion to methanol



Methanol in alcoholic beverages

- Methanol also occurs at low concentrations in alcoholic drinks.
- **In these concentrations methanol is not harmful.**
- Problems arise when higher concentrations are formed during incorrectly managed distillation processes, but more particularly when methanol is deliberately added to fortify informally-produced spirits and illicit alcoholic drinks.

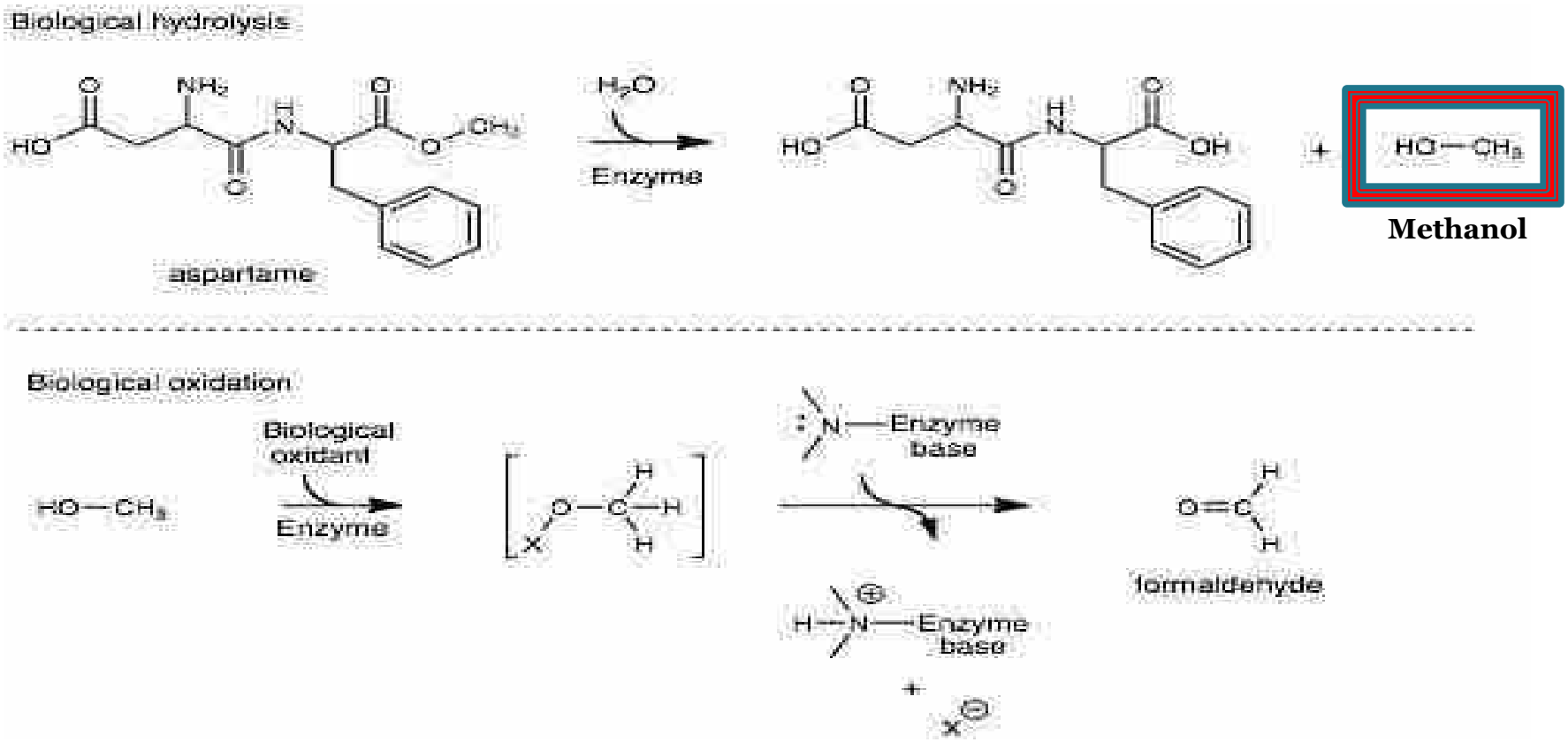
Regulatory limit on methanol in alcoholic beverages

- EU general limit for naturally occurring methanol of **10 g methanol/L ethanol** [which equates to 0.4% (v/v) methanol at 40% alcohol] provides a greater margin of safety.

Aspartame conversion to methanol

- The artificial sweetener aspartame is a methyl ester of a dipeptide consisting of aspartic acid and phenylalanine.
- It is rapidly broken down in the gastrointestinal tract by peptidases and esterases, and releases a maximum of 10% methanol by weight.

Aspartame conversion to methanol



Methanol pharmacology

Methanol toxicity mechanism

- Methanol is slowly metabolised to formaldehyde which is rapidly metabolised to formate, mainly responsible for methanol toxicity.
- Formate metabolism depends upon the folate pool. Therefore, formate accumulates during methanol intoxication and is mainly responsible for the metabolic acidosis in the early stage of intoxication.
- This tissue hypoxia caused by formate may explain the ocular as well as the general toxicity.

Methanol pharmacokinetics

Absorption

- Methanol is readily absorbed from the gastrointestinal and respiratory tracts, and also by the percutaneous route.
- Blood levels peaks 30 to 60 minutes after ingestion.
- Although ingestion dominates as the most frequent route of poisoning, *inhalation* of high concentrations of methanol vapor and *percutaneous* absorption of methanolic liquids are as effective as the oral route in producing acute toxic effects.

Distribution

- After absorption, methanol is widely distributed in total body water with a volume of distribution of 0.6 to 0.7 L/kg .
- There is no protein binding.
- Undissociated formic acid readily crosses the blood-brain barrier.
- Aggressive alkali treatment is therefore important to keep most formic acid dissociated.
- It is distributed poorly in fatty tissues.

Biological half-life

- The elimination of methanol is of zero order with a rate of 8.5 g/L/hour, i.e. about half of that of ethanol in high doses.

- If methanol metabolism is blocked by ethanol or fomepizole, methanol elimination is very slow (about 50 h) and occurs by pulmonary and renal excretion.

Metabolism

- The majority (%90) of methanol is converted to formaldehyde, principally in the liver, by alcohol dehydrogenase (ADH).
- Formaldehyde is then converted to formate by aldehyde dehydrogenase and other enzymes.
- Studies have shown that the rate of formate oxidation is regulated by the hepatic concentrations of tetrahydrofolate.

Rate of methanol metabolism

- The rate of metabolism is independent of the plasma concentration, is slow, and is approximately one-seventh that of ethanol.

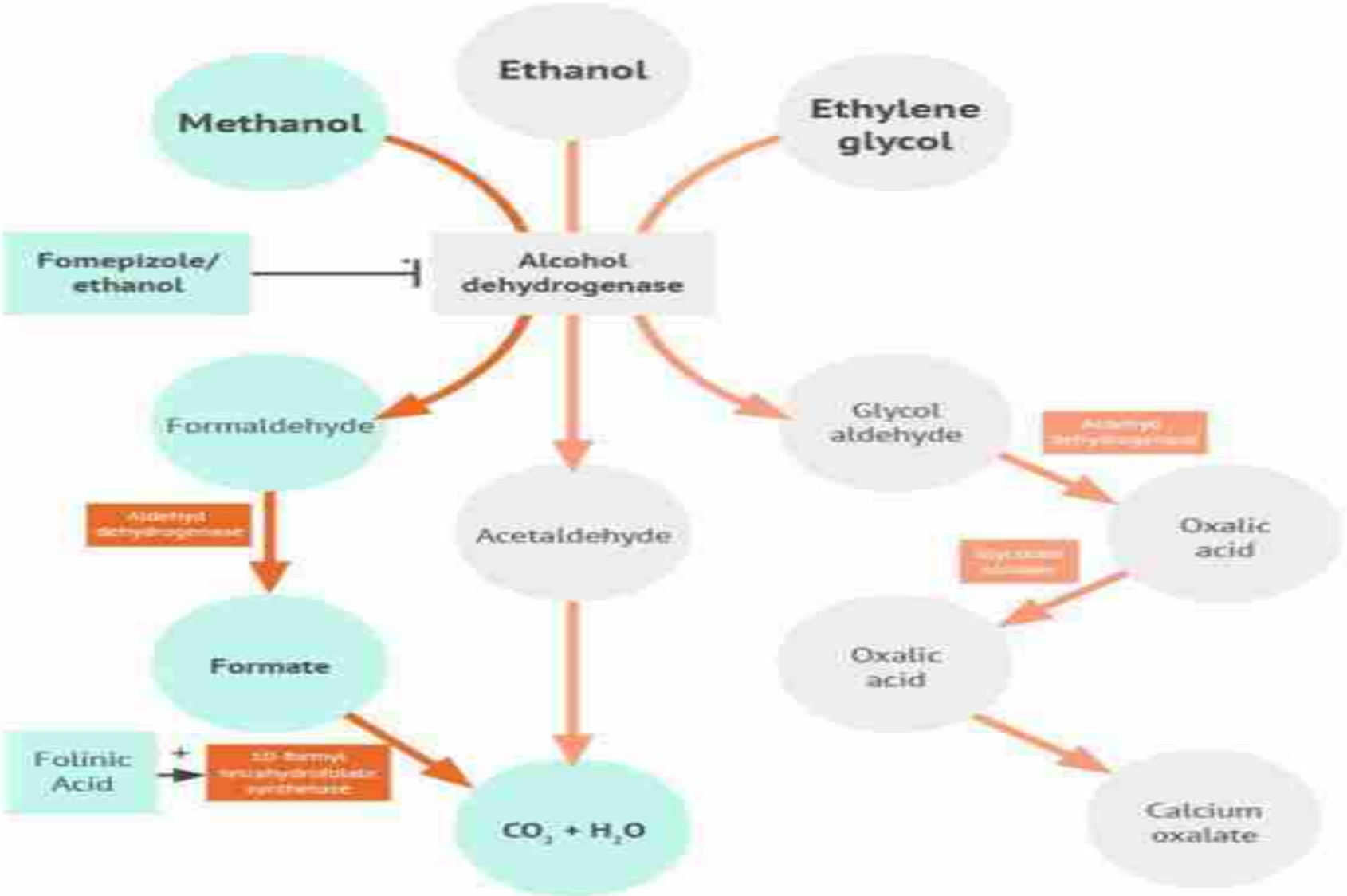
- Complete oxidation and excretion of methanol can require several days.

Rate of methanol metabolism

- Since ethanol has an affinity for ADH that is at least 20 times greater than that of methanol, it preferentially serves as the substrate for this enzyme.

- Administration of ethanol (or fomepizole) reduces the rate of oxidation of methanol and delays its clinical and biochemical effects.

The Metabolism of Methanol



Clearance of methanol from body

- At low concentrations, methanol elimination follows **first order kinetics.**

- The clearance of unmetabolised methanol via urine and exhaled air follows first order kinetics.

It is proportional to the concentration of methanol remaining in body water

Clearance of methanol from body

- When **concentrations of methanol are low**, its metabolism to CO_2 and subsequent clearance also follows first order kinetics, but this is a saturable process and, once saturated (which occurs at higher methanol concentrations), it follows zero order kinetics.

It proceeds at a constant rate that is independent of concentration in body water

Normal Blood methanol level

- According to the IPCS Poisons Information Monograph (PIM, 1991):
  - **Normal blood methanol concentrations are in the order of 1.5 mg/dL (range 0.2-3 mg/dL)**
- **Urinary methanol concentrations have been reported to be up to 0.3 mg/dL in individuals not occupationally exposed to methanol**

Analytical methods for forensic alcohol analysis