

TOXICOLOGY OF ETHANOL

- **General Properties**

Ethanol is a liquid, volatile, colorless, flammable, miscible with water and most organic solvents.

Boiling point: 78°C. Dialyzable. Absorbed in the gastrointestinal tract. Oxidizable and esterifiable.

It is produced by fermentation of glucose, distillation, or from ethylene, and is used as a solvent, biofuel, disinfectant, and in beverages (which differ by raw material origin and alcohol content).

Alcohol degree = volume of pure alcohol / volume of liquid

Exposure may be occupational or domestic.

Toxicokinetics

Absorption

- Pulmonary +++
- Percutaneous: low (higher in young children)
- Digestive:
 - Stomach: slow, low (20%)
 - Intestine: 80% (passive diffusion)
- Plasma peak < 1 hour

Factors influencing absorption

- Alcohol concentration
- Gastric emptying state
- Sex
- Presence of drugs

Distribution

- Very rapid to highly vascularized organs (brain, lungs, liver)
- Volume of distribution:
 - 0.6 L/kg (women)
 - 0.7 L/kg (men)
- Tissue concentration \approx blood concentration \rightarrow importance of blood measurement
- No plasma protein binding \rightarrow measured in whole blood
- Crosses placenta \rightarrow fetal concentration = maternal concentration

Widmark formula

Blood alcohol = amount ingested (g) / weight (kg) \times diffusion coefficient

Metabolism

- Hepatic: 85%
- Extra-hepatic: 5–10% (stomach, intestine, kidneys)

Minor pathway: glucuronidation → ethyl glucuronide

1. Oxidation of ethanol to acetaldehyde

Occurs in hepatocytes

a) Main pathway: Alcohol dehydrogenase (ADH)

- Cytosolic
- Non-specific
- Saturable (>1 g/L)
- Inhibited by pyrazole and 4-methylpyrazole
- Coupled to ATP synthesis
- Genetic polymorphism (ADH2)

b) Secondary pathways

Activated in chronic alcoholism or high ethanol levels

b1) MEOS (microsomal ethanol oxidizing system):

- Cytochrome P450
- Produces free radicals → hepatotoxicity
- Not coupled to ATP → heat production

b2) Catalase:

- Peroxisomes
- Active if H₂O₂ available and high alcohol levels

b3) Radical oxidation:

- Via hydroxyl radicals

2. Oxidation of acetaldehyde to acetate

- ALDH1: cytosolic, inhibited by disulfiram
- ALDH2: mitochondrial (polymorphism)

Acetaldehyde is more toxic than ethanol and highly reactive

3. Acetate metabolism

- 25% hepatic, 75% extra-hepatic
→ $\text{CO}_2 + \text{H}_2\text{O}$

Elimination

- Unchanged (5–10%):
 - Urine: 2–3%
 - Sweat: 1%
 - Saliva, tears, milk
 - Expired air: 2–3%
- Metabolized (~90%)

Mechanism of Toxic Action

- **Central Nervous System**
- Acute: ↑ membrane fluidity
- Chronic: ↑ rigidity

Receptors

- Acute: ↑ GABA effect, ↓ glutamate → sedation
- Chronic: ↓ GABA sensitivity, ↑ glutamate → excitation

Factors influencing metabolism

- Genetic polymorphism (ADH, ALDH)
- CYP2E1 induction
- Fructose increases metabolism

Cellular damage

- White matter reduction
- Brain atrophy (reversible after withdrawal)
- Neuronal loss (hippocampus) → Korsakoff syndrome

Liver Damage

1. Metabolic disturbances

- Carbohydrates: ↓ ATP, ↓ gluconeogenesis
- Lipids: triglyceride accumulation → steatosis
- Proteins: ↓ synthesis
- Vitamins: ↓ absorption (A, B6, B9, B12, C, D, E)

2. Kupffer cell activation

→ cytokines (TNF- α) → hepatotoxicity

Drug Interactions

- Kinetic: absorption, metabolism
- Dynamic: CNS depressants, antihypertensives, hypoglycemics, anticoagulants

Acute Intoxication

1. Excitation phase (0.5–1 g/L)

- Euphoria, excitation

2. Intoxication phase (1.5–3 g/L)

- Ataxia, confusion, tremors
- Hallucinations, vomiting

3. Depressive phase (>3 g/L)

- Coma, hypothermia, dehydration
- Respiratory depression
- Metabolic acidosis
- Shock

4. Hangover

- Headache, fatigue, bad breath

Treatment of Acute Intoxication

- Rewarming
- Ventilation
- Glucose infusion (if hypoglycemia)
- Correct acidosis
- Hemodialysis if >5 mg/mL

⚠ Contraindicated in pregnancy → fetal alcohol syndrome

Analytical Toxicology

- **Blood Sampling**
 - No alcohol disinfectant
 - 2 tubes (analysis + control)
- **Methods**
 - Chemical (Cordebard, Widmark)
 - Enzymatic (ADH, ALDH)
 - Physical: gas chromatography (reference)
- **Breath Analysis**
 - Alcotest (qualitative)
 - Alcometer (quantitative, IR)
- **Other Samples**
 - Urine, hair

Alcoholuria / Alcholemia ratio

- Low: absorption phase
- High: elimination phase
- **Ethyl Glucuronide (EtG)**
 - Urine: 80 hours
 - Hair: 1 month

- **Markers of Alcoholism**

Direct markers

- Ethanol
- Ethyl glucuronide
- Ethyl sulfate
- Fatty acid ethyl esters
- Phosphatidylethanol

Indirect markers

- MCV
- GGT
- AST, ALT