Excretion

Toxicants are eliminated from the body by several routes:

1. Kidney is the most important route (urine)
2. Feces (biliary excretion)
3. Gases (lung)

Many xenobiotics are biotransformed to more water-soluble products before they can be excreted.
Urinary Excretion
Toxic compounds are excreted in the same way that end products of normal metabolism are excreted:
1. Glomerular filtration
2. Tubular secretion
3. Tubular reabsorption
Kidneys receive about 25% of first pass cardiac output, and ~20% is filtered through the glomeruli (25 g/day of urea is filtered and excreted).

The glomerular capillaries have very large pores (70 nm) and allow compounds up to a molecular weight of 60 kDa (<albumin) to be filtered.

Passive transport
Tubular Secretion and Reabsorption

Tubular Secretion

- **active transport** for acids, bases, neutrals into renal tubules
  - OCT: organic cation transporter
  - OAT: organic anion transporter
  - MDR/MRP: multidrug resistant transporters

Tubular Reabsorption

- **Passive:** depends on ionization of xenobiotic; lipophilic substances will be reabsorbed from the tubules more than hydrophilic substances.
  - under high urinary pH, excretion of acids is increased
  - under low urinary pH, excretion of bases is increased
- **Active:** OCT’s, peptide transporters (PEP), MRPs
Renal Excretion and Reabsorption through Transporters

Excretion:
- Blood
  - Oat1,3
  - Oct1,2
  - Octn1,2
  - Oapt4c1
  - Glomerular Filtrate
    - Mrp2
    - Mrp4
    - Bcrp
    - Mdr1a, Mdr1b

Reabsorption:
- Glomerular Filtrate
  - Oat 5
  - Urat1
  - Oapt1a1
  - Oapt1a6
  - Oapt3a1
  - Pept 1,2
  - Blood
  - Mrp1
  - Mrp3
  - Mrp5,6
Urine

• Major excretory fluid
• Normal range pH of urine is slightly acidic: 6.0-6.5

\[
\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \quad \text{↔} \quad \text{H}^{+} + \text{HCO}_3^{-}
\]

Respiratory Alkalosis and Acidosis

\[\downarrow \text{CO}_2 \rightarrow \downarrow \text{H}^+ \rightarrow \uparrow \text{pH} \quad \text{alkalosis}\]

\[\uparrow \text{CO}_2 \rightarrow \uparrow \text{H}^+ \rightarrow \downarrow \text{pH} \quad \text{acidosis}\]
Respiratory acidosis —

a. Basis for insult: decreased ventilation $\rightarrow$ $\uparrow$P$\text{CO}_2$

Caused by damage to resp. center; drug CNS depression; obstruction of respiratory passages; breathing excess CO$_2$, neurological damage, pneumonia.

b. Effects & diagnosis: $\uparrow$P$\text{CO}_2$; $\downarrow$pH

c. Immediate compensation: difficult because of primary resp. problem.


e. Long term correction: repair respiratory deficit

f. Excretion:
   • Acids/glucuronides, carboxylic acid metabolite classes are excreted less efficiently
   • Bases excreted more efficiently.
Respiratory alkalosis — less common

a. Basis for insult: hyperventilation $\rightarrow \downarrow \text{P}CO_2$

Caused by excessive pulmonary ventilation; excitement; voluntary hyperventilation; high altitude

b. Effects & diagnosis: $\downarrow \text{P}CO_2; \uparrow \text{pH}$

c. Immediate compensation: same problem as respiratory acidosis.

d. Slower compensation: renal excretion of $\text{HCO}_3^-$

e. Long term correction: repair respiratory deficit

f. Excretion:
   - bases excreted less efficiently
   - acids excreted more efficiently
Metabolic acidosis —

a. Basis for insult: $\uparrow H^+$ or $\downarrow HCO_3^-

Caused by loss of alkali (e.g. diarrhea); failure of kidney to secrete $H^+$ (excretion of $HCO_3^-$); formation of excess metabolic acid (e.g., acetoacetate in diabetes); carbonic anhydrase inhibitors; CaCl$_2$ and NH$_4$Cl; high plasma K$^+$.

b. Effects and diagnosis: $\downarrow pH$ and $\downarrow HCO_3^-$

c. Immediate compensation: low pH drives respiratory response, effect is to reduce P$CO_2$ and tends to restore $HCO_3^-$/$CO_2$ ratio toward 20/1.

d. Long term correction: renal excretion of $H^+$; restoration of $HCO_3^-$
Metabolic alkalosis —

a. Basis for insult: ↓H\(^+\) or ↑HCO\(_3^-\)

Caused by ingestion of alkaline drugs; excessive vomiting; increase Na\(^+\) delivery to distal tubule (increases H\(^+\) secretion & loss); low plasma K\(^+\); excessive aldosterone.

b. Effects and diagnosis: ↑pH and ↑HCO\(_3^-\)

c. Immediate compensation: high pH slows respiratory drive. Effect is to accumulate CO\(_2\), i.e., elevate P\(\text{CO}_2\), and restore HCO\(_3^-\)/CO\(_2\) toward 20/1

d. Long term correction: renal excretion of excess HCO\(_3^-\)
Examples

- Amphetamines—causes euphoria, aggression, grandiosity, paranoia, anxiety through increasing the activity of dopamine and norepinephrine
- Phenylcyclidine (PCP)—formerly used as anesthetic agent—causes hallucinogenic effects
- Cocaine—stimulant that causes euphoria, increased motor activity, anxiety, paranoia
- PCP, amphetamine, cocaine excretion can be accelerated by acidosis through forced acid diuresis with ascorbic acid (vitamin C) or ammonium chloride
- Salicylate—anti-inflammatory agent and active metabolite of aspirin—acceleration of salicylate loss can be achieved through alkalosis by furosemide or sodium bicarbonate
**Biliary excretion** is the most important source of fecal excretion of xenobiotics and is important for the excretion of their metabolites.
Transporters on hepatic parenchymal cells

Many active transporters aid in excretion of acids, bases, neutrals and peptides. Substances with molecular weight of 350-740 are preferentially excreted in bile versus urine, as well as thiol (glutathione) conjugates of mercury, lead, copper.

Ntcp: Na dependent taurocholate peptide; Oatp: organic anion transporting peptide; Lst: liver specific transporter; Oct: organic cation transporter; Bsep: bile salt excretory protein; Mdr: multi-drug resistant protein; Mrp: multi-resistant drug protein.
Enterohepatic circulation causes increased retention of xenobiotics conjugated by glucuronic acid because they are deconjugated in the intestine and reabsorbed.
Example: Diethylstilbestrol (DES)

- Classified as endocrine disruptor—a synthetic nonsteroidal estrogen
- Exposure to DES occurs through dietary ingestion from supplemented cattle feed.
- From 1940s-1970s, was used in pregnant women to reduce complications, but caused vaginal cancer in daughters of women who used DES during pregnancy
- Undergoes enterohepatic circulation and is retained in the body by sequential conjugation and deconjugation.
Exhalation

• Substances that exist predominantly in the gas phase at body temperature are eliminated mainly by the lungs.

• The amount of liquid eliminated via the lungs is proportional to its vapor pressure (i.e. breathalizer test to determine ethanol concentration).

• Substances are eliminated via simple diffusion (no transport systems).

• Elimination of gases is roughly inversely proportional to the rate of their absorption (i.e. gases with low solubility in blood, such as ethylene are rapidly excreted).