# Acetaminophen (Paracetamol)

CAS: 103-90-2
MF: $C_8H_9NO_2$
FW: 151.2
Soluble in water.

**Major use**
Acetaminophen is analgesic and anti-pyretic drug, with some anti-inflammatory activity.

**Human toxicity**
Initial adverse effects of poisoning may be non-specific (nausea or vomiting) or absent. Clinical signs include e.g. hepatic necrosis, metabolic acidosis; renal tubular necrosis; myocardial damage; neurological signs; coma; hematological abnormalities including thrombocytopenia; pancreatitis; coma and even death [1].

Therapeutic dose in adults is 1- 4 g/day. The minimum lethal dose in adults is 5-15 g; the acute lethal dose ranges from 13 to 25 g [2]. Ingestion of as little as 150 mg/kg or 7.5 grams has caused liver injury. Hepatotoxicity usually develops 24-36 hours after ingestion, whereas renal insufficiency may develop 2 to 4 days after toxic ingestion. Generally, hepatotoxicity is complicated by acute renal failure [1].

Therapeutic blood (its serum or plasma) concentrations range from 5 to 20 mg/l. Toxic blood concentrations are in the range of 25-150 mg/l [2, 3]. The minimum lethal blood concentration is 160 mg/l [3]. Mean lethal blood concentration is 300 mg/l [2].

**Kinetic data**
*Absorption*: acetaminophen is rapidly and almost completely absorbed from the gastrointestinal tract.

Acetaminophen exhibits dose-dependent kinetics (first-order rate constant).

*Volume of distribution*: approximately 0.75-1 l/kg [3].

*Peak plasma concentration* of acetaminophen is usually reached within 30 min - 4 hours post ingestion.

*The plasma half-life* of acetaminophen is about 2-3 h at the therapeutic dose, but following an overdose, the peak plasma level is not usually reached for 4 hours, and sometimes it may exceed 12 h, indicating very likely a hepatic coma [3].

*Plasma protein binding* for acetaminophen is between 20 and 50%.

*Passage of blood-brain barrier* is restricted.

*The elimination* of metabolized drug is via kidney [3, 4].

**Metabolism and excretion**
About 90% of acetaminophen is biotransformed by cytochrome P-450 in the liver. Main metabolites are sulphate (about 52%) and glucuronide (about 42%) conjugates.

About 4% of the drug is biotransformed to N-acetyl-p-benzoquinoneimine (NAPQI), which is a highly reactive cytotoxic intermediate. NAPQI is detoxified by conjugation with glutathione and excreted in the urine as cysteine and mercapturic acid [3, 4].

*Excretion*: 90-100% of an ingested dose is excreted in urine during about 24 h [4]. At therapeutic dosage, acetaminophen is excreted as glucuronide (45-55%), sulfate (20-30%), and cysteine (15-55%). Approximately 2 % of acetaminophen is excreted unchanged [5].

**Toxicological mechanism**
At the overdose of acetaminophen, glutathione is depleted by binding to NAPQI. When glutathione is depleted 70% or more, NAPQI can no longer be detoxified by that pathway, and the excess of NAPQI binds covalently to cellular protein macromolecules in the liver, causing cell death and hepatic necrosis [6].

**Target organs**: histopathological lesions in liver and kidney; CNS.

**References**


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4. Dart, R.C. ed. (2004) *Medical Toxicology*, 3rd ed., , Lippincott, Williams & Wilkins.
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