The liver, and to a lesser extent the kidney and intestine, are the major organs implicated in the metabolism of acetaminophen. After a therapeutic dose, APAP is mostly converted to pharmacologically inactive glucuronide (APAP-gluc, 52–57% of urinary metabolites) and sulfate (APAP sulfate, 30–44%) conjugates, with a minor fraction being oxidized to a reactive metabolite NAPQI (5–10%).Less than 5% of APAP is excreted unchanged.NAPQI is highly reactive and is primarily responsible for acetaminophen-induced hepatotoxicity. Detoxification of NAPQI occurs through its binding to the sulfhydryl group of glutathione (GSH) to form APAP-GSH, which is ultimately excreted in the urine as cysteine and mercapturic acid conjugates (APAP-cys). Acetaminophen disposition involves a complex inter-organ transport of metabolites between the liver, kidney and intestine, through bile and the blood stream, to be ultimately eliminated in urine. From the liver, most of glucuronide and sulfate metabolites get transported into the kidneys through the blood stream, while some APAP-gluc appears in the bile with subsequent transport through the intestines into the blood. The kidney is the main site of the disposition of APAP sulfate, either through direct excretion or through further biotransformation followed by renal excretion. Although most of NAPQI is formed in the liver, the kidney also metabolizes APAP to the toxic metabolite and releases cysteine

conjugate of APAP into the bile and blood for further elimination in urine.