Role of CYP2E1 in the hepatotoxicity of acetaminophen.

CYP2E1, a cytochrome P-450 that is well conserved across mammalian species, metabolizes ethanol and many low molecular weight toxins and cancer suspect agents. The cyp2e1 gene was isolated, and a mouse line that lacks expression of CYP2E1 was generated by homologous recombination in embryonic stem cells. Animals deficient in expression of the enzyme were fertile, developed normally, and exhibited no obvious phenotypic abnormalities, thus indicating that CYP2E1 has no critical role in mammalian development and physiology in the absence of external stimuli. When cyp2el knockout mice were challenged with the common analgesic acetaminophen, they were found to be considerably less sensitive to its hepatotoxic effects than wild-type animals, indicating that this P-450 is the principal enzyme responsible for the metabolic conversion of the drug to its active hepatotoxic metabolite.