Human hepatocytes support the hypertrophic but not the hyperplastic response to the murine nongenotoxic hepatocarcinogen sodium phenobarbital in *in vivo* study using chimeric mouse with humanized liver

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In rodent tumor bioassays high doses of sodium phenobarbital (NaPB), a constitutive androstane receptor (CAR) activator, have been shown to produce hepatocellular tumors. Previous mode of action (MOA) studies have demonstrated that NaPB induces hepatic microsomal cytochrome P450 (CYP) 2B enzymes and hepatocyte replicative DNA synthesis in rodents, suggesting that the MOA for rodent liver tumor formation is a mitogenic activity via CAR activation. In this study the effects of NaPB on liver weight and histopathology, CYP2B activity, replicative DNA synthesis, and mRNA expression of CYP2B/3A and selected genes related to cell proliferation, were examined after 1-week treatment with NaPB at 500, 1000, 1500, and 2500 ppm in male CD-1 mice, Wistar Hannover (WH) rats, and humanized mice (chimeric mice with human hepatocytes). The treatment of humanized mice with 1000-1500 ppm NaPB resulted in plasma levels around 3~5 fold higher than those observed in human subjects given therapeutic dose of NaPB. NaPB produced dose-dependent increases in liver weight, CYP2B activity, and CYP2B/3A mRNA in CD-1 mice and WH rats and also produced effects on these parameters in humanized mice. While NaPB produced a dose-dependent increase in hepatocyte replicative DNA synthesis in CD-1 mice and WH rats, no increase in replicative DNA synthesis was observed in humanized mice. In addition, NaPB produced no increases in Ki-67, PCNA, GADD45β, and MDM2 mRNA expression in humanized mice, whereas significant increases were observed in CD-1 mice and/or WH rats. Thus, while NaPB could activate CAR/PXR, as demonstrated by increased CYP2B/3A mRNA levels, NaPB did not increase cell proliferation in human hepatocytes of the chimeric mice. As human hepatocytes are refractory to the mitogenic effects of NaPB, the data demonstrate that the MOA for NaPB-induced rodent liver tumor formation is not relevant for humans.