Review Summary of the National Institute of Environmental Health Sciences (NIEHS/NTP)
RoC Review Committee (RG1)

Nomination: Hepatitis B Virus (HBV)
Review Committee: RG1
Date: 2003 May 7

Major issues discussed

Application of criteria

Exposure: HBV clearly meets the criteria for exposure: over one million US residents are chronically infected. The prevalence rate is about 5% and declining slightly. The annual incidence rate has declined to 3.3 per 100,000 in 1998. In the US, most cases result from heterosexual transmission (41%), intravenous drug use (15%), and homosexual transmission (9%).

Human studies: Studies of human cancer clearly indicate a causal relationship between HBV infection and risk of hepatocellular cancer. In 1994, an IARC working group concluded that chronic HBV infection is *carcinogenic to humans.* Subsequent cohort and case-control studies conducted in diverse populations have provided additional support for that conclusion. Studies have used sensitive and specific markers of infection and have accounted for other risk factors including alcohol use, aflatoxin exposure, and HCV infection. A meta-analysis of 32 epidemiology studies from different worldwide regions reported a summary odds ratio for hepatocellular carcinoma of 13.7 (95% CI 12.2 to 13.4) for HBV infected people vs. uninfected people. A recent study of hepatocelluar carcinoma cases in the US showed increased risk of hepatocellular carcinoma in individuals positive for HBsAg (OR 12.6). Risk was higher in individuals positive for both HBsAg and anti-HBc (OR 23.8). Other studies have shown a synergistic effect on hepatocelluar carcinoma of co-infection with both HBV and HCV.

Experimental animal studies: Only great apes and tree shrews can be infected with human HBV. Risk of hepatocellular carcinoma is not increased in chimpanzees infected with human HBV. Studies of HBV in the tree shrews are inadequate to access potential carcinogenesis in this animal model. Transgenic mice that express the entire HBV genome do not have an increased risk of hepatocellular carcinoma, but mice expressing the HBx or HBs genes do. Chronic infection with species-specific hepatitis virus increases risk of hepatocellular carcinoma in woodchucks and ground squirrels.

Genotoxicity and mechanism: In chronic HBV infection, cycles of cell death and regeneration may progress to liver fibrosis and cirrhosis. Cirrhosis related to chronic HBV infection is more likely to progress to hepatocellular carcinoma than cirrhosis from other causes. The regenerative nodules that arise from cell death are considered to be precursors to hepatocellular carcinoma. During chronic HBV infection, viral DNA may be integrated into the host genome and may alter expression of growth regulatory genes. Viral integration can also lead to genetic instability, with loss of tumor suppressor genes. Expression of some HBV proteins may contribute to oncogenesis.

Other concerns: None noted.

Recommendation: RG1 recommended (4/0) that HBV be listed as *known to be a human carcinogen,* based on overwhelming evidence of a causal association between chronic HBV infection and increased risk of hepatocellular carcinoma in humans and supporting mechanistic evidence.