Review Summary
NTP Executive Committee Working Group for the Report on Carcinogens (RG2)

Nomination: Hepatitis B Virus (HBV)

Date: July 22, 2003

Major issues discussed

Application of criteria

Exposure: Approximately 1 to 1.25 million individuals are chronically infected with HBV in the United States. The major risk factor for HBV infection is sexual transmission.

Human studies: IARC classified HBV as a *known human carcinogen* in1994 based on sufficient evidence in humans. Numerous cohort and case-control studies conducted in different geographical populations have demonstrated a causal relationship between chronic HBV infection and hepatocellular carcinoma. These studies show that the association between chronic HBV infection and hepatocellular carcinoma remains after adjustment for hepatitis C virus (HCV) and other possible confounders. A meta-analysis of 32 studies reported an ORs of 13.7 (95% CI=12.2 to 15.4). The meta-analysis also suggested a synergistic interaction between HBV and HCV co infection on the risk of hepatocellular carcinoma. Other studies have suggested a synergistic relationship between chronic HBV infection and exposure to aflatoxin or alcohol.

Experimental animal studies: Apes and tree strews are the only animals that can be infected with HBV; however, hepatocellular carcinoma has not been observed in HBV-infected chimpanzees and has not been assessed in tree shrews. Hepatocelluar carcinoma has developed in some lines of transgenic mice expressing high levels of the HBs gene or the HBx gene but not in mice expressing the entire HBV genome. Hepatocellular carcinomas have also developed in woodchucks and ground squirrels infected with species-specific hepatitis viruses.

Genotoxicity and mechanism: HBV can integrate into the host genome, which can result in the alteration of gene expression of grown regulatory genes, expression of novel proteins that possess transactional function, and lead to genomic instability. The HBx and HBs antigens may also participate in HBV carcinogenicity as evidence by the development of hepatocellular carcinoma in some transgenic lines expressing these proteins. HPV cellular carcinomas usually emerges after 30 years of chronic infection, which is characterized by chronic inflammation and cycles of cell death and regeneration suggesting a role of the host immune system in cancer development.

Recommendation

Motion:

Recommend that HBV be listed as *known to be a human carcinogen,* based on strong evidence from human studies that demonstrate a causal relationship between chronic HBV infection and hepatocellular carcinoma in humans.

Vote on the motion: 8 yes votes to 0 no votes.