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

Nomination: Hepatitis C Virus (HCV)
Review Committee: RG1
Date: 2002 November 13

Major issues discussed

Application of criteria

Exposure: HCV clearly meets the criteria for listing in the RoC. Approximately 3 to 4 million individuals are infected in the United States.

Human studies: Multiple cohort and case-control studies in various populations worldwide and in the United States have clearly shown that HCV infection is associated with hepatocellular carcinoma. IARC (1993) listed HCV as *carcinogenic to humans,* and numerous cohort and case-control studies published since then have supported this finding. A meta-analysis of 32 studies calculated an odds ratio of 11. Recent studies assessed HCV infection with sensitive and specific biomarkers of infection, and show unequivocally that the association is independent of infection with hepatitis B virus (HBV) and other risk factors for hepatocellular carcinoma. HCV and HBV have a synergistic effect on risk of hepatocellular carcinoma, and heavy alcohol intake also enhances risk associated with HCV infection. The committee felt the evidence for an association of HCV and hepatocellular cancer was compelling.

Experimental animal studies: The chimpanzee and tree shrew are the only animals susceptible to HCV infection. Evidence of an association of HCV infection with hepatocellular carcinoma from either animal model is inadequate. Some but not all lines of mice transgenic for the HCV core gene have developed hepatocellular carcinomas. The committee felt that the animal evidence was limited but consistent with the epidemiologic data.

Genotoxicity and mechanistic concerns: The mechanism of HCV-related hepatocarcinogenesis is unclear. The HCV core protein regulates cellular promoters and proto-oncogenes and induces tumors in some lines of transgenic mice. HCV-related liver cancer usually occurs in the presence of cirrhosis, suggesting that inflammation, fibrosis and hepatocyte regeneration play a role in cancer development. The committee felt that the mechanistic evidence was limited but consistent with the epidemiologic data.

Other concerns: None noted.

Recommendation: The committee voted unanimously (7/0) to list *hepatitis C virus* as *known to be a human carcinogen,* based on significant exposure in the US population and overwhelming positive cancer epidemiology data in humans.