

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Hepatitis C virus (HCV) is an RNA virus that is distantly related to flaviviruses and pestiviruses. The viral genome is a linear positive-strand RNA molecule about 9.4 kilobases long. It has a single, large open reading frame which encodes a polypeptide precursor of about 3000 amino acids. Viral isolates from different geographical regions display significant genetic diversity; in addition, different HCV genotypes can coexist in infected individuals. HCV infection has been detected only in humans, but the virus can be transmitted experimentally to chimpanzees.

HCV infection can be detected in serum by measuring antibody against HCV or directly measuring HCV RNA in blood. Seropositivity to HCV antibody correlates well with HCV infectivity; second-generation tests involving multiple antigenic epitopes show higher sensitivity and specificity than earlier methods. Measurement of HCV RNA is the most sensitive of the currently available tests and allows specific diagnosis in the early acute phase of infection. Replication of HCV in cell culture has been reported. Virus particles and identification of protective or neutralizing antibodies have not yet been demonstrated.

HCV causes most cases of non-A, non-B, post-transfusion hepatitis and a variable proportion of non-transfusion-associated, community-acquired non-A, non-B hepatitis. In most populations of the world, 0.5–2% of individuals have serological evidence of past or current infection. In most countries, prevalence increase with age in adult life and is approximately equal in men and women. A high prevalence of seropositivity is found in people with blood clotting disorders, in those on renal dialysis and in intravenous drug users. Transmission is mostly parenteral, although the route of infection in a significant proportion of cases of community-acquired infection is unknown. Both sexual and perinatal transmission occur.

The clinical course of acute HCV infection is mostly asymptomatic, but acute infection leads to chronic liver disease in about 50% of symptomatic patients and to liver cirrhosis in about 20% of those with chronic liver disease. Advanced liver disease and its complications may be the first clinical evidence of chronic HCV infection. Immunoprophylaxis for HCV infection is not available.

5.2 Human carcinogenicity data

Infection with HCV, as indicated by the presence of antibodies to HCV in serum, appeared to be associated with an increased risk for hepatocellular carcinoma in two cohorts of patients with chronic liver disease and in one cohort of the general population.

Over 20 case-control studies have evaluated the association between hepatocellular carcinoma and seropositivity for HCV antibodies, measured by either first- or second-generation tests. Odds ratio estimates ranging from 1.3 to 134 were observed in 17 studies in which first-generation tests were used and were significant in 15 of the studies. In six studies in which second-generation tests were used, the estimated odds ratios ranged from 1.1 to 52 and were significant in three of the studies.

In all 11 studies in which it could be evaluated, the risk for hepatocellular carcinoma was greater in subjects who were seropositive for antibodies to HCV and seronegative for hepatitis B surface antigen than in subjects seronegative for both. In the few studies in which the analysis took into account possible confounding of the effects of HCV by other risk factors for hepatocellular carcinoma, such as smoking and alcohol consumption, the association was not materially altered.

5.3 Animal carcinogenicity data

A single chimpanzee inoculated with serum from a human patient with non-A, non-B hepatitis developed chronic hepatitis; hepatocellular carcinoma occurred seven years after the first inoculation. Markers of hepatitis B viral infection were not found; the results of tests for HCV were not reported.

5.4 Other relevant data

HCV can replicate in hepatocellular carcinoma cells, but there is no evidence that DNA sequences are integrated into the host genome. Virtually all cases of HCV-related hepatocellular carcinoma occur in the presence of cirrhosis or significant chronic hepatitis.

5.5 Evaluation¹

There is *sufficient evidence* in humans for the carcinogenicity of chronic infection with hepatitis C virus.

There is *inadequate evidence* in experimental animals for the carcinogenicity of hepatitis C virus.

Overall evaluation

Chronic infection with hepatitis C virus *is carcinogenic to humans (Group 1)*.

¹For definition of the italicized terms, see Preamble, pp. 30–34.