



WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

# Volume 59 Hepatitis Viruses

## Summary of Data Reported and Evaluation

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# HEPATITIS B VIRUS (Group 1)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 59 (1994) (p. 45)

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Hepatitis B virus (HBV) is a small DNA virus made up of an outer envelope, bearing hepatitis B surface antigen (HBsAg), and an internal nucleocapsid. The nucleocapsid contains the hepatitis B core antigen (HBcAg), DNA polymerase/reverse transcriptase and the viral DNA genome. The viral genome is a circular, partially double-stranded DNA molecule about 3.2 kilobases long. It has four open reading frames, which encode for the different viral antigens, including hepatitis B e antigen (HBeAg) and hepatitis B x antigen (HBxAg), and replicates asymmetrically by reverse transcription of an RNA intermediate. Naturally occurring HBV mutants have been identified, but their pathobiological significance has not been defined. HBV belongs to a group of hepatotropic DNA viruses (hepadnaviruses) which include the hepatitis viruses of the woodchuck (*Marmota monax*), Beechey ground squirrel (*Spermophilus beecheyi*) and domestic duck (*Anas domestica*). These viruses are highly species specific; they infect primarily hepatocytes.

Current serological methods of detection are highly sensitive and specific and are based on the detection of viral antigens, antibodies to viral antigens and viral DNA. The presence of HBsAg or HBV DNA indicates current HBV infection. The presence of HBeAg indicates a high level of viral replication. Seroconversion to anti-HBe is usually associated with reductions in replication and in disease activity. The presence of immunoglobulin M class anti-HBc indicates acute HBV infection; the immunoglobulin G class anti-HBc appears after acute HBV infection and persists during chronic HBV infection.

Transmission of infection in areas of high prevalence is predominantly between children; mother-to-child (perinatal) transmission plays a particularly important role in Asia. The modes of transmission in childhood are unclear. In areas of intermediate and low endemicity, the pattern of perinatal, childhood and adult infection is mixed. In adults, sexual transmission is a major mode of transmission, although intravenous use of drugs plays an important role in some populations. In many cases in areas of low endemicity, the mode of transmission is unknown.

The course and clinical manifestations of HBV infection are highly variable and depend on age at infection, gender, the immune competence of the host and, possibly, viral factors. Infection perinatally and in early childhood is the major risk factor for chronicity, which frequently leads to progressive liver disease and cirrhosis.

The prevalence of chronic HBV infection varies markedly around the world. High rates of infection, defined as prevalences greater or equal to 8%, occur in China, Southeast Asia, the Pacific Basin, sub-Saharan Africa and the Amazon Basin. In western Europe, North America, Australia and New Zealand, the prevalences of chronic infection are low (< 2%), and infection occurs predominantly in adults. Intermediate prevalences of infection, between 2 and 7%, occur elsewhere in the world.

The incidence of infection is reduced by vaccination with plasma-derived or recombinant vaccines, which are highly immunogenic and confer long-lasting protection against acute hepatitis and chronic infection. The efficacy of vaccines against chronic infection is in excess of 85% in regions where child and adult infection predominate and greater than 70% in regions where perinatal infection plays an important role. The efficacy of vaccination in preventing perinatal infection is improved by the addition of hepatitis B immunoglobulin administration soon after birth.

## 5.2 Human carcinogenicity data

In 15 cohort studies, carrier status for HBV was determined by the presence of HBsAg in serum. In all studies, the risk for hepatocellular carcinoma increased in association with HBsAg seropositivity, with estimates of relative risk ranging from 5.3 to 148.

Many case-control studies have been reported on the association between hepatocellular carcinoma and chronic infection with HBV, as determined by HBsAg seropositivity. Most of the studies were conducted in Asia and in Africa, but some have been reported from Europe and North America. The studies were of variable quality, but the majority showed a strong association, with relative risks between 5 and 30.

Potential confounding by aflatoxin, infection with hepatitis C virus, cigarette smoking and alcohol drinking appears to have been excluded in studies in which those factors were evaluated.

Serological patterns of HBV markers other than HBsAg, such as anti-HBc and anti-HBs, have been examined in many studies, but variability in methods of determination and reporting of results precluded evaluation of their association with hepatocellular carcinoma.

In general, cohort studies have not reported increased risks for cancers other than hepatocellular carcinoma. No consistent evidence of increased risk was found in case-control studies of other cancers (including cholangiocarcinoma of the liver).

## 5.3 Animal carcinogenicity data

### Hepatitis B virus

Studies over the past two decades have shown that chimpanzees can be infected with HBV and can become carriers, exhibiting mild hepatitis. Progressive liver disease, including hepatocellular carcinoma, is not known to develop in HBV-infected chimpanzees, although reporting of long-term studies of infected animals is sparse and inadequate. A single report suggested that Asian macaques are susceptible to HBV infection and to progressive liver lesions; a possible hepatocellular carcinoma developed in an HBV-infected macaque.

In three studies in transgenic mice on the expression of integrated HBV genes (pre-S, S and/or X genes) in hepatocytes, increased numbers of liver tumours were associated with a high level of expression of the large surface antigen and X proteins. The relevance of the finding that hepatocellular carcinomas are produced in these transgenic mice for evaluating the carcinogenicity of HBV is unclear.

### Other hepadnaviruses

Woodchucks are susceptible to infection with the related hepadnaviruses, woodchuck and ground squirrel hepatitis viruses (WHV and GSHV), both of which lead to chronic hepatitis but not to cirrhosis. In one study of naturally infected, captive adults, one study of experimentally infected adults and newborns and one study of experimentally infected newborns, infection with WHV was associated with development of hepatocellular carcinoma in up to 85% of woodchucks with chronic infection. Uninfected animals did not develop hepatocellular carcinoma. Newborn woodchucks experimentally infected with GSHV also developed hepatocellular carcinoma. Beechey ground squirrels are susceptible to infection with GSHV, with the development of mild chronic hepatitis but not cirrhosis. In one study of Beechey ground squirrels captured in the wild, 11/24 (45%) animals naturally infected with GSHV developed hepatocellular carcinoma, while 2/26 (8%) uninfected animals developed the tumour. One study showed that captive Richardson ground squirrels may be infected with a similar but poorly characterized hepadnavirus, but the association of viral infection and hepatocellular carcinoma in this species has not been firmly demonstrated. Domestic ducks are susceptible to infection with a hepadnavirus, duck hepatitis B virus (DHBV). Hepatocellular carcinoma has been observed in free-ranging ducks infected with DHBV, but in three studies of experimentally infected animals and one study of congenitally infected ducks, no increase in the incidence of hepatocellular carcinoma was observed.

## 5.4 Other relevant data

The mechanisms whereby HBV may induce hepatocellular carcinoma are uncertain. HBV does not contain a known oncogene. HBV DNA is integrated into host DNA in the great majority of hepatocellular carcinomas in HBV carriers, and chromosomal translocations associated with integrated HBV sequences have been reported. In only three cases of hepatocellular carcinoma have HBV DNA sequences been shown to be integrated into any known host gene. This molecular event is, however, common in woodchucks: in about 50% of hepatocellular carcinomas arising in animals infected chronically with WHV, viral DNA sequences were integrated in or adjacent to *c-myc* or *N-myc* genes. In humans, sequences of the S and X genes of HBV are almost always present in integrated HBV DNA, and X gene protein has been shown to *trans*-activate both HBV and cellular genes. There is no well documented evidence for overexpression of known oncogenes as a result of HBV DNA integration in human hepatocellular carcinoma. Deletions on multiple chromosomes and mutations of the *p53* tumour suppressor gene occur in hepatocellular carcinoma, but no pattern of these changes has been found to be specific to hepatocellular carcinomas arising in chronically HBV-infected humans.

The great majority of hepatocellular carcinomas that arise in association with chronic HBV infection occur in conjunction with cirrhosis or chronic hepatitis. Chronic HBV infection is generally established in early childhood, and several decades of chronic hepatitis usually precede development of the cancer. Studies of HBV integration have demonstrated that many regenerative nodules in cirrhotic liver have independent clonal origins; clonal regeneration reflects the extensive cell turnover that renders host DNA more susceptible to mutagenesis.

## 5.5 Evaluation

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

There is *inadequate evidence* in experimental animals for the carcinogenicity of hepatitis B virus. Some hepadnaviruses closely related to hepatitis B virus produce hepatocellular carcinoma in susceptible species.

## Overall evaluation

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

For definition of the italicized terms, see [Preamble Evaluation](#).

# HEPATITIS C VIRUS (Group 1)

For definition of Groups, see [Preamble Evaluation](#).

**VOL.:** 59 (1994) (p. 165)

## 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 Evaluation

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)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

# HEPATITIS D VIRUS (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

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## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Hepatitis D virus (HDV) exists as a satellite agent of hepatitis B virus (HBV). The viral genome is a circular RNA molecule about 1700 bases long, and HDV antigen is the only known protein that it encodes. The antigen is required for viral replication in hepatocytes. Because hepatitis B surface antigen forms the envelope of HDV, HBV infection is a prerequisite for formation of HDV particles. HDV infection has been detected only in humans, although the agent can be transmitted to HBV-infected chimpanzees and to woodchucks infected with woodchuck hepatitis virus.

HDV infection can be identified in serum by detecting antibody to HDV (anti-HD) and/or HDV RNA; HDV antigen can also be detected immunohistochemically in hepatocytes. In co-infection, HDV RNA and immunoglobulin M class anti-HD appear, followed by the transient appearance of immunoglobulin G class anti-HD. Superinfection usually results in chronic infection, viraemia and persistence of anti-HD.

In countries where endemicity for HBV is low, the prevalence of HDV infection is low, except among intravenous drug users and recipients of blood products. In areas of intermediate and high endemicity for HBV, the prevalence of HDV infection is highly variable. In general, it is rare in Asia, but up to one-half of individuals with chronic HBV infection in parts of southern Europe, the Middle East, Africa, the Pacific Basin and the Amazon region may be infected with HDV. Marked variations in the prevalence of HDV infection are found within countries and sometimes between ethnic groups.

The predominant route of transmission in countries of high endemicity is unknown, that in countries of low endemicity appears to be parenteral. Sexual transmission also occurs.

HDV co- or superinfection generally results in a more severe clinical course than HBV infection alone. HDV superinfection is associated more frequently with progressive liver disease and cirrhosis than HBV infection alone.

Immunoprophylaxis with HBV vaccine is presumed to protect the individual against co-infection but cannot protect HBV carriers against superinfection with HDV. Immune globulin does not protect against HDV superinfection, and no specific HDV vaccine is available.

### 5.2 Human carcinogenicity data

Several case series showed no evidence of HDV infection among cases of hepatocellular carcinoma, while others reported high levels of infection.

In two case-control studies of hepatocellular carcinoma and HDV infection among subjects seropositive for hepatitis B surface antigen, there were no anti-HD-seropositive individuals among cases or controls. Three further case-control studies suggested a positive association but had limited statistical power.

### 5.3 Animal carcinogenicity data

No adequate data were available to the Working Group.

#### **5.4 Other relevant data**

Case series suggest that chronic hepatitis and cirrhosis develop more rapidly in patients infected with both HBV and HDV than in those infected with HBV alone.

#### **5.5 Evaluation**

There is *inadequate evidence* in humans for the carcinogenicity of infection with hepatitis D virus.

There is *inadequate evidence* in experimental animals for the carcinogenicity of infection with hepatitis D virus.

#### **Overall evaluation**

Infection with hepatitis D virus is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

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