Position statement of Central Biosafety Commission (ZKBS)
on the risk assessment of human hepatitis D virus (HDV) as a donor or recipient organism
in genetic engineering operations according to
§ 5 paragraph 1 of the Genetic Engineering Safety Regulations (GenTSV)

Human hepatitis D virus (HDV), also known as hepatitis delta virus, is not assigned to any specific virus family. It has a circular, single-stranded RNA genome of negative polarity with a length of 1700 nucleotides. This RNA is present in the virion as a nucleoprotein complex with the delta antigen, the sole protein encoded by HDV. Three distinct genotypes have been identified. HDV is a defective virus. Its infectivity depends on simultaneous hepatitis B virus (HBV) infection. The HBV surface protein, HBsAg, also forms the envelope for HDV. The virus is hosted by humans, but it can also be experimentally transmitted to woodchucks. Replication of the viral genome takes place in the nucleus of primary hepatocytes (1,2).

HDV is a global phenomenon, but the prevalence of infection varies in different geographical regions. It is quite rare in Germany, with higher infection rates in Mediterranean regions of southern Europe and in North Africa, the Middle East and South America (2, 3).

The course of the disease depends on which point in time the HDV infection coincides with HBV infection. Coinfection with HBV and HDV usually results in an acute, self-limiting infection. Chronic infection develops in less than 5% of coinfected patients. A superinfection occurs if chronic HBV carriers are infected with HDV. In 80% of cases, this results in severe, acute hepatitis and chronic progression of the HDV infection. Superinfection is often associated with a fulminant form of hepatitis. Chronic HDV infection leads to liver cirrhosis in 60% - 70% of patients. Hepatocellular carcinoma occurs in chronically infected patients with the same frequency as in patients who are chronically infected with HBV alone. The mortality rate is 2% - 20% (1,7).

Like HBV, the HDV virus is transmitted horizontally (parenterally or through sexual contact) and vertically (perinatal transmission). It is not transmitted by air, food or water (2, 3).

The range of therapeutic options to treat HDV is limited. Treatment with interferon alpha has shown low success rates. Better results were achieved by treatment with pegylated interferon (4). Antiviral therapies against HBV were ineffective against HDV. Nucleoside and nucleotide analogs that are effective against HBV are not effective against HDV. However, vaccination against HBV also protects against infection with HDV (2).

In accordance with Annex II of the European Council Directive 93/88/EEC issued on October 12, 1993, HDV was assigned to risk group 3**. In the Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines issued in April 2002), HDV was assigned to risk group 2 (Appendix B-II-D). As a donor and recipient organism for genetic engineering operations the HBV infection, upon which an HDV infection depends, is classified into risk group 2 in accordance with § 5 paragraph 1 in conjunction with Appendix 1 no. 1.
**Recommendation**

The human hepatitis D virus is classified as donor and recipient organism for genetic engineering operations of **risk group 2** in accordance with § 5 paragraph 1 in conjunction with Appendix 1 no. 1.

**Reasons**

An effective prophylactic vaccine is available for hepatitis B.

With expert handling by trained personnel, the risk of laboratory-acquired infection is assessed as low. The infectivity of HDV requires a concurrent infection with HBV. Protection against infection requires monitoring of all potential infection sources and transmission routes. HDV is not transmitted through air, food or water. One source of infection could be through injury while handling contaminated instruments, a scenario to be avoided by implementing additional precautionary measures. Furthermore, level 2 safety measures are considered adequate to protect against infection and to safeguard the goods and interests listed in § 1 of the Genetic Engineering Act (GenTG).

**Additional recommendation**

The Central Biosafety Commission (ZKBS) recommends that HBV-infected persons should be disqualified from participating in genetic engineering operations with HDV. Furthermore, persons carrying out genetic engineering operations with HDV should be vaccinated against HBV and have their immune status monitored.

**References**