ZKBS
Zentrale Kommission
für die Biologische Sicherheit

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Recommendation by the ZKBS on the risk assessment of hepatitis B virus as a donor or recipient organism according to § 5 para. 1 GenTSV

General Information

The hepatitis B virus (HBV) (species *Hepatitis B virus*) belongs to the family *Hepadnaviridae*. Humans are its natural hosts. The virus multiplies primarily in liver tissue [1]. However, HBV DNA has also been detected in cells of other tissues [2, 3]. The virus is globally distributed. According to a report released by the World Health Organization up to 2 billion people are seropositive, 257 million of whom are chronically infected [1, 4].

An HBV infection can take a subclinical course. However, it can also cause acute, self-limiting or – in rare cases – fulminant hepatitis [1, 5, 6]. The fatality rate for acute infections is 0.5 – 1 % [6]. The likelihood of an infected person developing chronic hepatitis depends on their age at the time of infection [1, 5, 6]. 15 - 25% of chronically infected individuals die of liver cirrhosis or hepatocellular carcinoma [1]. In the year 2015 this have been approximately 890 000 individuals [4].

The hepatitis B virus is transmitted horizontally (parenterally or through sexual contact) and vertically (perinatally). It is not transmitted via the aerogenic route or through food or water [1, 5, 6].

HBV particles are physically stable. Outside of the host organism they retain their infectivity for up to seven days [5].

An approved vaccine containing the HBV surface protein (HBsAg) is available. The vaccine, which is produced via genetic engineering in *Saccharomyces cerevisiae*, normally provides effective protection against HBV infection over many years. Only adults over the age of 40 sometimes fail to develop an adequate antibody titre against the HBsAg following immunisation [1]. Additionally, the vaccine and/or an immune globulin may be used as post-exposure prophylaxis.

The treatment of acute HBV infection is supportive [6]. A number of different antiviral drugs are available for the treatment of chronic infections [5, 6].

According to Annex III to the “European Council Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work” (last update on October 24th 2019) HBV is assigned to **risk group 3****. Likewise, HBV is assigned to **risk group 3**** in the TRBA 462 “classification of viruses into risk groups” (last updated on November 10th 2020) according to the Biological Agents Ordinance (BioStoffV). However, in Annex I of the Genetic Engineering Safety Regulations (GenTSV), published on October 24th 1990, HBV was

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assigned to **risk group 2**. Newer versions of these regulations (last updated on August 12th 2019) do not contain a list of the risk groups of organisms.

Recommendation

According to § 5 para. 1 GenTSV in conjunction with the criteria in Annex 1 GenTSV the *Hepatitis B virus* is assigned to **risk group 2** as a donor and recipient organism for genetic engineering operations.

Reasoning

An effective prophylactic vaccine is available against HBV. Additionally, this vaccine and an immune globulin may be used as post-exposure prophylaxis.

With proper handling by trained personnel, the risk of infection in a genetic engineering facility is assessed as low due to the possible routes of transmission of the virus. HBV is not transmitted via the aerogenic route, by food or water. One possible source of infection is through injury while handling contaminated instruments. This should be avoided by implementing additional precautionary measures. For these reasons, level 2 safety measures provide adequate protection against infection and safeguard the goods and interests listed in § 1 of the German Genetic Engineering Act (GenTG).

Note

There are certain amino acid substitutions described for HBV that are associated with an immune escape. These mutations occur predominantly within the major hydrophilic region (MHR, amino acids 99 – 169), especially the so-called a-determinant (amino acids 124 – 147) of the small HBsAg. The exact substitutions can be found in the scientific literature, e. g. [7].

If immune escape variants of HBV are present, the vaccine or the immune globulin-based post-exposure prophylaxis may not provide sufficient protection against an HBV infection. Deviating from the general assessment of HBV, mutants and isolates that contain sequence variations associated with an immune escape are therefore assigned to **risk group 3****. Genetic engineering operations, in which the genomic DNA or pre-genomic RNA of patient isolates is going to be introduced into susceptible cell cultures, can only be performed under safety measures of level 2, if the presence of such mutations can be ruled out by sequencing.

Additional Recommendation

The ZKBS recommends the vaccination against HBV and the periodic monitoring of the immune status to all persons conducting genetic engineering operations with HBV. According to the Ordinance on Preventive Occupational Health Care (ArbMedVV) mandatory health care must be arranged before the start of genetic engineering operations with HBV.

Literature

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