ZKBS
Zentrale Kommission
für die **Biologische Sicherheit**

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Recommendation of the ZKBS on the risk assessment of *Influenza D virus* as donor and recipient organism according to § 5 (1) GenTSV

General information

During the investigation of nasal swabs from pigs with mild flu-like symptoms in the U.S., a new orthomyxovirus was identified in 2011, which has since been classified as *Influenza D virus* (FLUDV). Just like influenza C viruses (FLUCV), the minus-strand RNA genome consists of seven segments [1], with the virus particles predominantly containing eight separate protein-coated RNA molecules. Whether one of the genome segments is double-packed or whether the eighth RNA molecule is of cellular origin has not yet been investigated [2]. In addition, FLUDV shows the highest sequence similarity to FLUCV with an amino acid sequence identity of 50%. However, antibodies against the new virus do not show cross-reactivity with FLUCV, which led to an initial classification as a representative of a new lineage of the species *Influenza C virus* [1]. Subsequent reassortment experiments with FLUCV confirmed incompatibility of the genome segments, which is why a new species was ultimately established for the virus [3].

Antibodies against FLUDV have now also been detected in cattle, goats, sheep, horses and dromedaries. Depending on the region, the seroprevalence in cattle was up to 80%. Of other farm animals, including pigs, only up to 10% were seropositive. So far, no antibodies have been detected in chickens or turkeys [4–6]. Based on these results, it is assumed that cattle are the natural reservoir for FLUDV. A study of archived serum samples also revealed that the virus has been circulating in U.S. cattle since at least autumn 2003. Due to evidence of antibodies in animals from Europe, North America, Africa and Asia, FLUDV is assumed to be distributed worldwide [6].

In cattle, infection with FLUDV is associated with enzootic bronchopneumonia (also known as bovine influenza or bovine respiratory disease). However, as this potentially fatal respiratory disease appears to be triggered or exacerbated by various factors, and other viruses, bacteria, parasites and fungi have also been associated with the disease, the causal involvement of FLUDV cannot be proven with certainty [5, 7]. Experimentally infected calves show only mild respiratory symptoms after infection of the upper and lower respiratory tract [8]. It is therefore assumed that FLUDV infection merely promotes secondary infection, primarily by bacterial pathogens, and thereby contributes to severe disease progression [5]. Symptomatic disease in other susceptible animal species, with the exception of pigs, has not been described. Experimental infection of guinea pigs, ferrets or mice is also asymptomatic. In these model animals, transmission appears to occur exclusively through direct contact [5, 9]. In calves, there are also indications of airborne transmission [10].

Like the exclusively human-pathogenic FLUCV, FLUDV uses surface proteins with 9-O-acetylated sialic acids as cellular receptors. Therefore, primary human bronchial epithelial cells can be infected in cell culture [11]. Antibodies against FLUDV have also been detected in humans

in various studies. There were some significant regional, temporal and occupational differences. Seroprevalence rates of 1–10% are typically found in the general population, but can rise significantly (to up to 45%) in certain years. High seroprevalence in humans appears to follow a wave of infection in cattle. A seroprevalence of over 90% has been reported among workers who come into daily contact with cattle [6, 12]. However, there are no reports of symptomatic infections in humans.

Recommendation

According to § 5 (1) GenTSV in conjunction with the criteria in Annex I GenTSV, *Influenza D virus* is assigned to **risk group 2** as donor and recipient organism for genetic engineering operations.

Rationale

Influenza D virus has a broad host range and can infect various farm animals and humans. It is of low pathogenicity in cattle and pigs, causing mild respiratory symptoms. No cases of disease in humans have been reported.

References

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