ZKBS
The Central Committee on Biological Safety

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**Position statement of the ZKBS**

**on the risk assessment of the lymphocytic choriomeningitis virus**

**as donor or recipient organism according to § 5 paragraph 1 of the GenTSV**

## General

The lymphocytic choriomeningitis virus (LCMV; species *Lymphocytic choriomeningitis mammarenavirus*) belongs to the *Arenaviridae* family of viruses. It has a bipartite RNA genome that contains four open reading frames in positive and negative polarity.

LCMV is prevalent worldwide. It has a broad host range and cell tropism [1]. It replicates in all organs as well as in lymphatic tissue and in the central nervous system (CNS) [2 – 5]. The virus was first isolated in 1933 from the liquor of a patient suffering from encephalitis. However, the encephalitis was not caused by LCMV, but by the *Saint Louis encephalitis virus* (family of *Flaviviridae*) [6].

Mice are the natural hosts of LCMV. In addition, hamsters and guinea pigs can also be carriers of the virus, and monkeys are also known to have been infected. The symptoms caused by an LCMV infection vary widely. Prenatal or neonatal infection in mice is generally asymptomatic and persistent. In contrast, infections in older mice are acute and can cause fatal lymphocytic choriomeningitis [1, 7, 8]. However, degree of pathogenicity and disease pattern in rodents depend on the specific test animal strain as well as on the LCMV strain under investigation [9]. The reason is, that LCMV-infections do not run cytopathic and therefore the pathogenity is a consequence of the hosts immune response to a specific LCMV strain [10]. In monkeys, too, LCMV infections cause a broad range of diseases. A case of LCMV infection of monkeys in two zoos, presumably transmitted by a wild mouse, resulted in fatal hepatitis [11, 12]. In an experimental infection of rhesus macaques, intravenous administration of the LCMV strain WE led to haemorrhagic fever, whereas no symptoms were observed after intragastric inoculation of the same dose [13]. Irrespective of the inoculation route, the infection of rhesus macaques with the LCMV strain WE caused liver diseases. In contrast, infection with the Armstrong strain remained symptomless [14].

LCMV-infected rodents shed infectious virus particles amongst others via saliva, urine and faeces. The virus can be transmitted to humans by uptake of droplets and aerosols via mucous membranes and the respiratory tract as well as through bite injury or stitch damage [1, 15, 16]. Typical sources of infection are wild mice and domestic hamsters as well as laboratory mice and hamsters [16, 17]. The seroprevalence of antibodies against LCMV in humans worldwide is between 1 and 5%. However, in regions of Slovakia and Croatia seroprevalences of approximately 35% were detected [18]. In humans, the clinical course ranges from an asymptomatic infection (35%), mild to moderate flu-like symptoms (50%) up to the CNS involvement with aseptic meningitis or meningoencephalitis (15%). In immuno-competent persons the infection usually resolves without or with only symptomatic treatment and does not lead to permanent damage. However, full recovery can take several months [1, 17 – 19]. To date no specific antiviral therapy or vaccine is available. Two severe disease cases occurred after laboratory infection and organ transplantation respectively. These patients were treated with the nucleoside analogon Ribavirin that is approved for treatment of *Hepatitis C virus* infections. Health condition in both patients improved. However, a causal correlation with the drug administration is not proven [20, 21].

LCMV infection following organ transplantation caused great concern in 2003 and 2011. The infection occurred in five clusters in 17 patients of which 14 eventually died. The cause of death was multiple organ failure with a dominant hepatitis in most cases [18 – 20]. Other horizontal transmissions from human to human have not been described to date [1].

In pregnant women, transplacental infection can lead to abortion or can seriously harm the foetus, triggering disorders such as hydrocephalus, chorioretinitis, macro- and microcephalus or blindness. Around 35% of affected infants eventually die within the first two years after birth from complications caused by the LCMV infection. Two-thirds of those who survive retain severe permanent neurological impairments [1, 18, 22].

In the European Council Directive on the protection of workers from risks related to exposure to biological agents at work (2000/54/EC) of 18 September 2000 neurotropic strains of LCMV initially were allocated to **risk group 3** and non-neurotropic strains of LCMV were allocated to **risk group 2**. However, because of the broad cell tropism of LCMV that comprises neuronal cells, this distinction of LCMV strains did not prove feasible. Neurological disorders depending on the status of the host immune system and are independent of the specific LCMV strain. In the amended directive on the protection of workers (revised by directive (EU) 2019/1833 of the commission from 24 October 24 2019) all strains of LCMV are assigned to **risk group 2**.

## Recommendation

In accordance with § 5 paragraph 1 of the German Genetic engineering safety regulations (GenTSV) in conjunction with the criteria listed in Appendix I of the GenTSV, all strains of *Lymphocytic choriomeningitis mammarenavirus* are classified as donor and recipient organisms for genetic engineering operations in **risk group 2**.

## Reasons

LCMV has a broad host range and cell tropism. It is pathogenic for humans, primates and rodents. The hazard potential for immune competent persons is low. However, an increased hazard potential for pregnant and immunocompromised persons cannot be excluded.

## Note

For handling of LCMV attention should be paid to the Maternity protection act.

## References

1. **Schwarz TF** (2005). Lymphozytäres Choriomeningitis-Virus. *Hofmann - Handbuch der Infektionskrankheiten* – 13. Erg. Lfg. 11/05

2. **Fazakerley JK, Southern P, Bloom F, Buchmeier MJ** (1991). High resolution in situ hybridization to determine the cellular distribution of lymphocytic choriomeningitis virus RNA in the tissues of persistently infected mice: relevance to arenavirus disease and mechanisms of viral persistence. *J Gen Virol.* **72**:11-25.

3. **Gold LH, Brot MD, Polis I, Schroeder R, Tishon A, de la Torre JC, Oldstone MB, Koob GF** (1994). Behavioral effects of persistent lymphocytic choriomeningitis virus infection in mice. *Behav Neural Biol.* 62:100-9.

4. **McGavern DB, Homann D, Oldstone MB** (2002). T cells in the central nervous system: the delicate balance between viral clearance and disease. *J Infect Dis.* 1 Suppl 2:S145-51.

5. **Homann D, McGavern DB, Oldstone MB** (2004). Visualizing the viral burden: phenotypic and functional alterations of T cells and APCs during persistent infection. *J Immunol.* 172:6239-50.

6. **Armstrong C, Lillie RD** (1934). Experimental lymphocytic choriomeningitis of monkeys and mice produced by a virus encountered in studies of the 1933 St. Louis encephalitis epidemic. *Public health rep* (Wash) **49**:1019-27.

7. **Lehmann-Grube F, Martínez-Peralta L, Bruns M, Löhler J** (1983). Persistent infection of mice with the lymphocytic choriomeningitis virus. In "*Comprehensive Virology*" (H. Fraenkel-Conrat and R.R. Wagner, eds.), Vol 18, pp 43-103. Plenum Press, New York und London.

8. **Kunz S, Rojek MJ, Roberts AJ, McGavern DB, Oldstone MBA, de la Torre JC** (2006). Altered central nervous system gene expression caused by congenitally acquired persistent infection with lymphocytic choriomeningitis virus. *J Virol.* **80**:9082-92.

9. Dutko FJ**, Oldstone, MB** (1983). Genomic and biological variation among commonly used lymphocytic choriomeningitis virus strains. *J Gen Virol.* **64**:1689-98.

10. **Kang SS, McGavern DB** (2008). Lymphocytic choriomeningitis infection of the central nervous system. *Front Biosci.* **13**:4529-43.

11. **Montali RJ, Scanga CA, Pernikoff D, Wessner DR, Ward R, Holmes KV** (1993). A common-source outbreak of callitrichid hepatitis in captive tamarins and marmosets. *J Infect Dis.* **167**:946-50.

12. **Asper M, Hofmann P, Osmann C, Funk J, Metzger C, Bruns M, Kaup FJ, Schmitz H, Günther S** (2001). First outbreak of callitrichid hepatitis in Germany: genetic characterization of the causative lymphocytic choriomeningitis virus strains. *Virology*. 284:203-13.

13. **Lukashevich IS, Djavani M, Rodas JD, Zapata JC, Usborne A, Emerson C, Mitchen J, Jahrling PB, Salvato MS** (2002). Hemorrhagic fever occurs after intravenous, but not after intragastric, inoculation of rhesus macaques with lymphocytic choriomeningitis virus. *J Med Virol.* **67**:171-86.

14. Lukashevich IS, Rodas JD, Tikhonov II, Zapata JC, Yang Y, Djavani M, Salvato MS (2004). LCMV-mediated hepatitis in rhesus macaques: WE but not ARM strain activates hepatocytes and induces liver regeneration. *Arch Virol.* **149**:2319-36.

15. Hotchin J**, Sikora E, Kinch W, Hinman A, Woodall J** (1974). Lymphocytic choriomeningitis in a hamster colony causes infection of hospital personnel. *Science*. **185**:1173-4.

16. **Bowen GS, Calisher CH, Winkler WG, Kraus AL, Fowler EH, Garman RH, Fraser DW, Hinman AR** (1975). Laboratory studies of a lymphocytic choriomeningitis virus outbreak in man and laboratory animals. *Am J Epidemiol.* **102**:233-40.

17. **Rousseau MC, Saron MF, Brouqui P, Bourgeade A** (1997). Lymphocytic choriomeningitis virus in southern France: four case reports and a review of the literature. *Eur J Epidemiol.* **13**:817-23.

18. **Laposova K, Pastorekova S, Tomaskova J** (2013). Lymphocytic choriomeningitis virus: invisible but not innocent. *Acta Virol.* **57**(2):160-70.

19. Roebroek RM **Postma BH, Dijkstra UJ** (1994). Aseptic meningitis caused by the lymphocytic choriomeningitis virus. *Clin Neurol Neurosurg. 96:178-80.*

20. Fischer SA**, Graham MB, Kuehnert MJ, Kotton CN, Srinivasan A, Marty FM, Comer JA, Guarner J, Paddock CD, DeMeo DL, Shieh WJ, Erickson BR, Bandy U, DeMaria A, Davis JP, Delmonico FL, Pavlin B, Likos A, Vincent MJ, Sealy TK, Goldsmith CS, Jernigan DB, Rollin PE, Packard MM, Patel M, Rowland C, Helfand RF, Nichol ST, Fishman JA, Ksiazek T, Zaki SR, LCMV in Transplant Recipients Investigation Team** (2006). Transmission of lymphocytic choriomeningitis virus by organ transplantation. *N Engl J Med.* **354**:2235-49.

21. **Aebischer O, Meylan P, Kunz S, Lazor-Blanchet C** (2016). Lymphocytic choriomeningitis virus infection induced by percutaneous exposure. *Occup Med (Lond).* **66**(2):171-3.

22. **Mets MB, Barton LL, Khan AS, Ksiazek TG** (2000). Lymphocytic choriomeningitis virus: an underdiagnosed cause of congenital chorioretinitis. *Am J Ophthalmol*. **130**:209-15.