ZKBS
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Biologische Sicherheit

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Statement of the ZKBS on the risk assessment of alpharetroviruses as donor and recipient organisms according to § 5 (1) GenTSV

General information

This statement serves to update the ZKBS statement on the risk assessment of C-type retroviruses in chickens (Ref. 6790-10-27, March 1994).

Alpharetroviruses form a genus within the *Retroviridae* family with the nine species *Alpharetrovirus avicarmilhil2*, *Alpharetrovirus avifujsar*, *Alpharetrovirus avileu*, *Alpharetrovirus avimyebla*, *Alpharetrovirus avimyecyt29*, *Alpharetrovirus avirousar*, *Alpharetrovirus avisar10*, *Alpharetrovirus aviUR2sar* and *Alpharetrovirus aviY73sar*. In addition, other alpharetroviruses that have not yet been classified as species are also included in the genus (e.g. the lymphoproliferative disease virus, LPDV). An overview of the viruses assigned to the *Alpharetrovirus* genus can be found in the appendix (Table 1).

Alpharetroviruses are viruses with a linear, single-stranded RNA genome in positive orientation ((+)ssRNA) and a group-specific antigen (Gag) typical of the genus. The viral genome is present in two copies in the virus particle and contains the three genetic elements *gag*, *pol* and *env*, which encode the capsid, matrix protein and nucleocapsid (*gag*), reverse transcriptase, protease and integrase (*pol*) and envelope proteins (*env*) [1]. The earlier classification as a type C retrovirus is based on their morphology as visualized by electron microscopy, which is characterised by a concentric capsid and an inner and outer membrane [2]. When the viral genome is reverse transcribed into double-stranded DNA and then inserted into the host genome as a provirus, it is flanked by long terminal repeats (LTRs) [3]. If a complete proviral genome is present, new particles can be produced. If the proviral genome is defective, genes essential for replication are missing, but the virus can still encode individual retroviral proteins such as group-specific antigens [2, 4]. The viruses of the species *A. avirousar* and LPDV are replication-competent, while *A. avicarmilhil2*, *A. avifujsar*, *A. avimyebla*, *A. avimyecyt29*, *A. avisar10*, *A. aviUR2sar* and *A. aviY73sar* have replication defects due to deletions in the *gag*, *pol* and/or *env* genes. Replication-competent helper viruses of the species *A. avileu* can complement these defects.

Alpharetroviruses are widespread worldwide in landfowl (*Galliformes*) and some other birds, such as waterfowl (*Anseriformes*), pigeons (*Columbiformes*) and passerines (*Passeriformes*), and can cause leukaemia, sarcomas and other tumours in these birds within weeks to months.

Non-neoplastic diseases caused by alpharetroviruses include hepatitis, myocarditis, anaemia, consumption, arthritis and glomerulonephritis [5].

Transmission occurs predominantly vertically, either congenitally via the reproductive tract into the egg (egg white) with infection of the embryo during incubation, or through a provirus integrated into the germline cells [6, 4]. Horizontal transmission can occur through direct contact between animals via faeces, saliva and other secretions, as well as infected cells, with high incidences in a chicken flock [9, 12]. Transmission via insects, water or aerosols has not been described, but transmission via infected cannulas during injections of chicks has been reported [6, 7].

Replication-defective alpharetroviruses with oncogenes

Alpharetrovirus avicarmilhil2

Alpharetrovirus avicarmilhil2 is also known as Avian carcinoma Mill Hill virus 2 (AMV2) or Mill Hill-2 virus (MH2). It was isolated from a chicken ovarian tumour in 1927. AMV2 is a replication-defective retrovirus that can only form and release infectious particles with the help of a replication-competent virus of the species *A. avileu* [8]. AMV2 has a narrow host range in chickens. Its neoplastic transforming potential is high due to the *v-mil* and *v-myc* genes contained in its genome, meaning that liver and kidney carcinomas, as well as sarcomas and lymphomas, can be triggered in chickens within days to weeks after infection or transduction [9, 10].

Alpharetrovirus avifujsar

Alpharetrovirus avifujsar is also known as Fujinami sarcoma virus (FuSV). It was first isolated in 1914 from a soft tissue sarcoma in a chicken. *A. avifujsar* is replication-defective and requires a replication-competent helper virus of the species *A. avileu* to form infectious particles. The virus contains the oncogene *v-fps*, which is derived from the viral *gag* gene linked to a domain of the cellular *proto-fps* gene and encodes a tyrosine protein kinase [11]. Under natural conditions, only chickens are infected; no other hosts have been described. After experimental infection of chickens and ducklings, sarcomas form within 10 days [12].

Alpharetrovirus avimyebla

Alpharetrovirus avimyebla is also known as avian myeloblastosis virus (AMV). It was first isolated in 1908 from tissue samples from chickens with visceral lymphomatosis and erythroblastic and myeloblastic leukaemia. *A. avimyebla* is replication-defective and requires a helper virus of the species *A. avileu*, e.g. MAV-1 and MAV-2, to form infectious particles [13]. The viral genome contains the oncogene *v-myb* [14]. In tissue cultures, AMV transforms haematopoietic cells and fibroblasts from chickens. Depending on the route of application in experimental infections, the morbidity rate in chicken embryos is 7 to 35%. The host range is limited to chickens [13].

Alpharetrovirus avimyecyt29

Alpharetrovirus avimyecyt29, also known as avian myelocytomatosis virus 29 (AMCV29), was first isolated in Bulgaria in 1961 [15]. The OK10 virus, isolated from a chicken liver tumour, is also classified as belonging to this species [16, 17]. It is replication-defective and requires a replication-competent helper virus, e.g. Rous-associated virus type 1 (RAV-1) or ALV-F, to form infectious particles [18]. The *v-myc* oncogene present in the viral genome can transform haematopoietic cells and fibroblasts of chickens [19, 20]. The host range includes gallinaceous birds, in which it causes myelocytomas and tumours in the liver, pancreas and kidneys. While chickens, guinea fowl and the Japanese quail mainly develop myelocytomas, turkeys, pheasants and rock partridges predominantly develop haematoblastosis [15].

Alpharetrovirus avisar10

Alpharetrovirus avisar10, formerly known as Avian Sarcoma Virus CT10 (ASV-CT10) or Claude's Chicken Tumor-10 Virus (CTV-10), is replication-defective and requires a helper virus of the species *A. avileu* to form infectious particles. It contains the oncogene *v-crk*, which is structurally similar to phospholipase C [21, 22]. The virus particles can be passaged in embryonic chicken fibroblasts. Experimental infection of chicks with *A. avisar10* leads to tumour formation at the injection site within two weeks [21].

Alpharetrovirus aviUR2sar

Alpharetrovirus aviUR2sar, formerly UR2 sarcoma virus (UR2SV), is replication-defective and requires a helper virus of the species *A. avileu* to form infectious particles. It was isolated from chicken fibrosarcomas in 1969 [23]. It contains the oncogene *v-ros* with tyrosine kinase activity [24, 25]. The host range includes chickens, but cells from turkeys and quails have also been transformed experimentally. Experimental infection of chickens leads to the formation of sarcomas after about two weeks [23].

Alpharetrovirus aviY73sar

Alpharetrovirus aviY73sar, formerly Y73 sarcoma virus (Y73SV), is replication-defective and requires a helper virus of the species *A. avileu* to form infectious particles. It was isolated in 1973 from a tumour in a White Leghorn chicken in Japan. It contains the oncogene *v-yes*, a viral variant of the cellular *c-yes* gene. The virus transforms embryonic chicken fibroblasts. The host range comprises chickens. After intramuscular or subcutaneous administration in 7-day-old chicks, fibrosarcomas and myxofibrosarcomas form at the injection site [26].

Replication-competent alpharetroviruses without oncogenes

Alpharetrovirus avileu

The *Alpharetrovirus avileu* species (formerly avian leukaemia viruses, ALV) comprises replication-competent alpharetroviruses that are divided into 11 subgroups based on their host range, the amino acid sequence of the envelope protein and the receptor utilisation patterns in susceptible and resistant bird cells [6]. Subgroups A, B, C, D and K occur in gallinaceous birds,

subgroup E in gallinaceous and anserine birds. While no ALV-C could be detected in samples from wild ducks, experimental infection of duck cells leads to effective replication and persistence. ALV-C-infected duck embryos develop consumption and haematological diseases after hatching [27]. Subgroups F and G occur in the Golden Pheasant [45], H in the partridge and I in the Gambel's quail, all of which belong to the *Galliformes* [6]. Subgroup J has the broadest host range of the alpharetroviruses and infects gallinaceous birds, anseriform birds and passerine birds. Subgroups E, F, G, H and I are exclusively endogenous in the germ line [6].

ALV-A and **-B** were the most common alpharetroviruses responsible for high economic losses in chicken farming worldwide. In Western countries, they do no longer occur on commercial chicken farms due to strict containment measures, testing, culling and long-term monitoring, and are considered eradicated here, as are **ALV-C** and **-D** [3]. However, infections continue to occur in hobby breeding or in wild poultry [6]. In China, ALV, especially ALV-J and ALV-K, but also imported ALV-A cases, continue to pose a major economic problem [28]. Before the spread of ALV-K, **ALV-J** was the most common ALV in China. It was first isolated in the United Kingdom in the 1980s. ALV-J was initially known as the cause of myelocytomatosis in broiler chickens, while from 2006 onwards, many cases of haemangioma were described [29, 30]. ALV-J causes mild symptoms in chickens, such as growth disorders and a weakened immune response to vaccinations [31, 32]. **ALV-K** was first identified in 2012 [1]. It has often been isolated from clinically healthy chickens, but is also associated with the formation of gliomas in poultry in Japan [31, 33, 34].

In chickens, ALV cause lymphatic leukaemia, erythroblastosis and gliomas [6, 35, 36] with low efficiency and long latency (months to years), which can be attributed to insertion mutagenesis. The viral genome integrates nearby or within a proto-oncogene and activates it. In addition, ALV also cause liver lesions, osteopetrosis, anaemia, fertility disorders, growth disorders, loss of appetite, diarrhoea and severe immune deficiency [6, 37]. If they circulate in a flock of chickens, the loss rates are approximately 1 to 2% [6].

Chickens infected with endogenous, replication-competent **ALV-E** not only pass it on vertically to their offspring, but can also shed virus particles. ALV-E persists in the host but is not pathogenic. Infections may lead to a reduction in egg production or body weight [38]. In rare cases, a possible link between ALV-E infection and disease has been described. For example, experimental infection of 30 chickens with strain JS1208 (a naturally occurring chimeric virus consisting of ALV-K (backbone) and ALV-E (*gp85* gene)) led to tumour-like lesions in two animals, one of which died as a result [1]. Furthermore, the ALV-E strain RAV-60 caused myelocytomatosis in a quail, but did not cause tumours in chickens [39]. In addition to chickens, ALV-E has also been detected in wild ducks that died from known (e.g. caught in nets or pesticide poisoning) or unknown causes [40]. The endogenous ALV-F strain RAV-61 was isolated from pheasants in the USA in 1973 [41]. It caused lymphatic leukaemia in 12 to 20% of infected animals and neoplasia in 25 % of chickens tested. While some chicken breeds were not susceptible to infection with the ALV-F RAV-Ringnecked pheasant virus (RAV-RPV) [39], others developed angiosarcomas, fibrosarcomas, neuroblastomas or blood cysts after infection [41, 37]. The endogenous **ALV-G** (RAV-Golden pheasant virus, RAV-GPV) did not lead to the formation of tumours after experimental infection of chicken embryos [39]. RAV-62 was isolated from partridge embryos and assigned to subgroup H [42]. Of two ALV-I isolates

described in 1985, one isolate is spontaneously formed and released by Gambel's quail cells and replicates very slowly. The second isolate results from a naturally occurring recombination event between Gambel's quail sequence and RSV and replicates well in embryonic chicken fibroblasts [43].

The species poses no hazard to humans. Twenty years after the administration of yellow fever vaccine batches contaminated with subgroup A viruses in the 1960s, no link to the development of tumours was found in vaccinated individuals compared to a control group. The vaccine batches were produced in 7- to 9-day-old embryonated chicken eggs [37]. Furthermore, no ALV-specific antibodies were detected in vaccinated individuals [44–46]. ALV particles were also detected in vaccines against measles and mumps in the 1960s, but there is no evidence of any health effects in vaccinated individuals [47]. In a self-experiment in 1939, J. G. Carr injected himself subcutaneously with two doses of an alpharetrovirus of subgroup A at two-week intervals and was still symptom-free 21 years later [48]. There are no reports of tumours in mammals caused by leukosis or leukaemia viruses. Although experimental infections of certain human (embryonic and foetal) cell lines with viruses of subgroups A (Rous-associated virus type 1), C (Bratislava 77) and D (Rous sarcoma virus Schmidt-Ruppin) are possible, no natural infections have been described to date. Furthermore, there is only a slight tendency for integration into transcription-active genes in human cells [34]. An overview of the viruses assigned to the species *A. avileu* can be found in the appendix (Table 2).

Lymphoproliferative disease virus

LPDV is an exogenous lymphotropic replication-competent virus. It is an unclassified alpharetrovirus without a gene with neoplastic transforming potential [49]. The natural hosts are turkeys. Under experimental conditions, the virus also replicates in chicken cells, but not in duck or goose cells. After infection of 4-week-old turkeys, lymphoproliferative lesions appeared in the spleen, thymus and pancreas approximately 14 days after inoculation. The mortality rate in affected turkey flocks is approximately 25%. Outbreaks were reported in several countries in the 1980s and 1990s, but there have been no cases on commercial farms in recent years. Although wild turkeys are frequently infected, they show few clinical symptoms and deaths are rare [50].

Replication-competent alpharetroviruses with oncogenes

Alpharetrovirus avirousar

Alpharetrovirus avirousar, formerly known as Rous sarcoma virus (RSV), was isolated in 1911. It is replication-competent and does not require a helper virus. The virus carries the *v-src* gene, which codes for a tyrosine kinase and is a homologue of the cellular proto-oncogene *c-src*. It leads to the formation of cysts and sarcomas. The host range depends on the subgroup and includes pigeons, turkeys, pheasants, ducks, turkeys, quails and rock partridges [6]. Small amounts of RSV particles have been detected in naturally occurring sarcomas in hamsters and rats [51–53]. Administration of the virus to three newborn monkeys (*Macacus rhesus, Macacus nemestrinus* and *Papio hamadryas*) led to the formation of fibrosarcomas in less than a month. While *Macacus nemestrinus* died on day 79, the respective tumours in the other two monkeys

regressed after about 100 days [54]. Under experimental conditions, *A. avirousar* is capable of transforming mammalian cells in addition to chicken cells [55].

In TRBA 462 all alpharetrovirus species, with the exception of LPDV which is not listed, are classified in **risk group 1** with the comments "t2"[1] and "onc"[2] [56].

Recommendation

According to § 5 (1) GenTSV in conjunction with the criteria in Annex 1 GenTSV, alpharetroviruses are assigned to the following risk groups as donor and recipient organisms for genetic engineering operations:

1. Replication-defective alpharetroviruses of the species *A. avicarmilhil2*, *A. avifujsar*, *A. avimyebla*, *A. avimyecyt29*, *A. avisar10*, *A. aviUR2sar* and *A. aviY73sar* are assigned to **risk group 1**.
2. Replication-competent alpharetroviruses of the species *A. avileu* of the subgroups E, G, H and I are assigned to **risk group 1**.
3. Replication-competent alpharetroviruses of the species *A. avileu* of subgroups A, B, C, D, F, J and K, as well as the Lymphoproliferative disease virus, are assigned to **risk group 2**.
4. Replication-competent alpharetroviruses of the species *A. avirousar* are assigned to **risk group 2**.

Rationale

Risk group 1 includes alpharetroviruses that are replication-defective, as well as replication-competent endogenous alpharetroviruses that do not cause clinical symptoms in gallinaceous birds. Risk group 2 includes replication-competent alpharetroviruses that cause clinical symptoms in some orders of birds and, in isolated cases, in rodents and mammals.

- Regarding 1.:

  These are replication-defective alpharetroviruses that require a helper virus for replication. The host range is limited to gallinaceous birds; transmission to other animals has not been observed to date. They can cause leukaemia, tumours and sarcomas in the long term through insertion mutagenesis. A hazard to humans can be ruled out.

- Regarding 2.:

  These are endogenous replication-competent alpha retroviruses that do not present a hazard to gallinaceous birds. A hazard to humans can be ruled out.

- Regarding 3.:

[1] Because of the vertebrate pathogenicity it may be necessary under animal disease law to take safety measures which, in a comparable way to safety measures of protection level 2, minimise the escape of prokaryotes into the external environment or other working areas.
[2] Oncogen. Virus contains gene that can cause malignant tumours in the natural host (humans or animals).

These are replication-competent alpharetroviruses with a low hazard potential for gallinaceous birds. The host range of *A. avileu* is limited to gallinaceous birds; transmission to other animals has not been observed to date. The viruses can cause lymphatic leukaemia, erythroblastosis or growth retardation and immune deficiency in infected animals. A hazard to humans can be ruled out.

Lymphoproliferative disease virus is a virus that is pathogenic to turkeys. It has not yet been characterised in detail. A hazard to humans can be ruled out.

- Regarding 4.:

  These are replication-competent alpharetroviruses that contain genes with neoplastic transforming potential. In addition to chickens, turkeys, pheasants, ducks and quails, the host range may also include rodents and other mammals. It can cause leukaemia, tumours and sarcomas in infected animals. A low hazard to humans cannot be ruled out.

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Appendix

Table 1: Overview of the genus *Alpharetrovirus*

ICTV (2025)	Statement C-type retroviruses of chicken (1994)	replication competent / defective	oncogene	host range	risk group
Alpharetrovirus avicarmilhil2	Poultry leukosis sarcoma viruses with oncogenes (RG 1)	defective	*v-mil*, *v-myc*	*Galliformes*	1
Alpharetrovirus avifujsar		defective	*v-fps*	*Galliformes*, *Anseriformes*	1
Alpharetrovirus avimyebla		defective	*v-myb*	*Galliformes*	1
Alpharetrovirus avimyecyt29		defective	*v-myc*	*Galliformes*	1
Alpharetrovirus avisar10		defective	*v-src*		1
Alpharetrovirus aviUR2sar		defective	*v-crk*		1
Alpharetrovirus aviY73sar		defective	*v-ros*		1
Alpharetrovirus avileu subgroups E, G, H and I	acute leukemia/sarcoma viruses	competent	N/A	*Galliformes*, *Anseriformes*, *Passeriformes*	1
Alpharetrovirus avileu subgroups A, B, C, D, F, J and K	acute leukemia/sarcoma viruses	competent	N/A	*Galliformes*, *Anseriformes*, *Passeriformes*	2
Lymphoproliferative disease virus	Lymphoproliferative disease virus of the turkey	competent	N/A	*Meleagris gallopavo* (*Galliformes*)	2
Alpharetrovirus avirousar	Poultry leukosis sarcoma viruses with oncogenes (RG 1)	competent	*v-yes*	*Galliformes*, *Anseriformes*, *Columbiformes*	2

Table 2: Overview of viruses of the species *Alpharetrovirus avileu*

A. avileu subgroup	endogenous/ exogenous	recombination	receptor	host	e.g. strains	risk group
A	Ex	ALV-J	Tva	*Galliformes*, *Anseriformes*	RAV-1, RAV-3, RAV-4, RAV-5, MAV-1, MAV-A, RSA	**2**
B	Ex	ALV-J, ALV-E	Tvb	*Galliformes*, *Anseriformes*	MAV-B, RAV-2, RAV-6, MAV-2	**2**
C	Ex	ALV-J	Tvc	*Galliformes*	RAV-7, RAV-49	**2**
D	Ex		Tvb	*Galliformes*	RAV-50, CZAV	**2**
E	En	ALV-A, ALV-B, ALV-C, ALV-J, ALV-K	Tvb	*Galliformes, Anseriformes*	ev-1, ev-2, RAV-60	**1**
F	En			*Chrysolophus pictus*	RAV-61	**2**
G	En			*Chrysolophus pictus*	GPV	**1**
H	En			*Perdix perdix*	RAV-62	**1**
I	En			*Callipepla gambelii*		**1**
J	Ex	ALV-A, ALV-B, ALV-C	chNHE1	*Galliformes*, *Anseriformes*, *Passeriformes*		**2**
K	Ex	ALV-E	Tva	*Galliformes*		**2**