Australian Government
Department of Health
Office of the Gene Technology Regulator

The biology of bovine herpesvirus 1

(BoHV-1)

August 2005

CONTENTS

LIST OF ABBREVIATIONS

AFFA	Agriculture, Fisheries and Forestry – Australia
BoHV-1	bovine herpesvirus 1
BRD	bovine respiratory disease
CSIRO	Commonwealth Scientific and Industrial Research Orgnisation
IBR	infectious bovine rhinotracheitis
ICTV	International Committee on Taxonomy of Viruses
IPB	infectious pustular balanoposthitis
IPV	infectious pustular vulvovaginitis
OIE	Office International des Epizooties
SCAHAW	Scientific Committee on Animal Health and Animal Welfare (European Commission)

INTRODUCTION

PURPOSE

The aim of this document is to review of the biology of *Bovine herpesvirus 1* (BoHV-1), with particular regard to the characteristics, attributes and properties of the virus that relate to the health and safety of humans, to host organisms and to the environment.

This review is divided into four main sections. *Host range* and *Disease* provide an overview of the interaction of BoHV-1 with the environment. *Virology* and *Immunology* then provide details of the biology of the virus and of how the virus interacts with the host immune response.

NOMENCLATURE

Bovine herpesvirus 1 (abbreviated to BoHV-1, BHV1 or BHV-1) is the official species name of the virus. *Infectious bovine rhinotracheitis virus* (IBR virus) is an alternative name (ICTV 2002). Both names (BoHV-1 and IBR) are currently in common use: BoHV-1 is used in studies of the virus; and IBR is used in studies of the disease.

Former names used to describe BoHV-1 include 'infectious bovine rhinotracheitis (IBR)-like' and 'infectious pustular vulvovaginitis (IPV)-like'. These descriptions of clinical signs are now known to relate either to subtypes BoHV1-1.1 and -1.2a, or to subtype BoHV-1.2b, respectively.

BoHV-1 subtypes

Subtyping of BoHV-1 strains is based on analysis of differences in the viral DNA detected by restriction endonuclease digestion or by polymerase chain reaction. DNA analysis corresponds to disease patterns and antigenic properties of the virus subtypes (Engels et al. 1981; Mayfield et al. 1983; Metzler et al. 1985; Metzler et al. 1986; Engels et al. 1986; Smith et al. 1993; Rijsewijk et al. 1999). The section *Disease* discusses the differences in disease caused by different BoHV-1 subtypes.

Australian strains are only of the BoHV-1.2b subtype; V155 is a reference strain (Snowdon 1964; Studdert 1989; Smith et al. 1993; Young et al. 1994; Smith et al. 1995). Overseas, the more virulent BoHV1.1 strains predominate.

HOST RANGE

BoHV-1 is an alphaherpesvirus. These viruses have restricted host ranges, and do not commonly or stably cross species barriers (Brake & Studdert 1985).

Viral host range is determined by both host and viral factors. Successful viral infection depends upon, at least, attachment and penetration of the virus into a host cell, followed by replication and viral export. Virus-host interactions are complex: the factors that are involved in these interactions are discussed in detail in the *Virology* and *Immunology* sections of this document.

NATURAL INFECTION

In Australia, BoHV-1 infects cattle and water buffalo, causing respiratory and genital disease (Animal Health Australia 2004b). Attempts to isolate BoHV-1 from Australian sheep under either field or experimental conditions have been unsuccessful (Young 1993).

Overseas, BoHV-1 has been shown to infect and cause disease in goats and sheep (Whetstone & Evermann 1988). Antibodies to BoHV-1 have been detected in captive Asian elephants (*Elephas maximus*) (Metzler et al. 1990, Bhat et al. 1997) However no disease resulting from BoHV-1 infection of elephants has been listed. BoHV-1 has been isolated from pronghorn antelope, wildebeest, mink and ferrets in the absence of disease (Porter et al. 1975), and from the soft-shelled tick *Ornithodoros coriaceus* (Taylor et al. 1982). It remains unclear if ticks are able to transmit the virus. Face flies (*Musca autumnalis*) carry BoHV-1 after feeding on live virus cultures, but the flies do not transmit the virus to cattle (Johnson et al. 1991).

EXPERIMENTAL INFECTION

BoHV-1 does not infect mice, rats, guinea pigs or chick embryos (Gibbs & Rweyemamu 1977), although immunocompromised mice that lack interferon receptors can be infected if the virus is injected into the peritoneal cavity (Abril et al. 2004).
Rabbits can be experimentally infected with BoHV-1 if the virus is injected into the conjunctival sac of the rabbits' eyes (Rock & Reed 1982; Rock et al. 1987; Rock et al. 1992) or through holes drilled into the sinuses (Brown & Field 1990a; Brown & Field 1990b).

Infection of humans

There are no reports of human infection with BoHV-1. There is no evidence that human cells can support BoHV-1 replication. Studies *in vitro* in cell culture show that BoHV-1 can bind weakly to human HveC (nectin-1) or to the human poliovirus receptor (Geraghty et al. 1998; Connolly et al. 2001), although no viral replication is detectable.

DISEASE

SIGNS OF DISEASE

BoHV-1 causes disease in cattle, with the severity of disease relating to the subtype and strain of the virus. The clinical signs of acute disease are caused by the destruction of BoHV-1-infected cells (Engels & Ackermann 1996): binding of the virus triggers programmed host cell death (apoptosis) (Lovato et al. 2003). BoHV-1 infection can cause respiratory, ocular, reproductive, central nervous system, enteric, neonatal and dermal disease in cattle (Gibbs & Rweyemamu 1977; Biuk-Rudan et al. 1999; Kahrs 2001), and can cause mastitis under experimental, but not field, conditions (Wellenberg 2002).

Infections with BoHV-1 alone do not cause death in healthy mature cattle (Kahrs 2001). Deaths from BoHV-1 occur when viral infection is established throughout the blood and the body (viremia). BoHV-1 infection does not cause viremia in healthy mature cattle (Engels & Ackermann 1996). However, BoHV-1 infections can cause foetal infection, viremia, death and abortion following genital infection of pregnant cows (Gibbs & Rweyemamu 1977; Kahrs 2001), and can cause fatal viremia in newborn calves in the absence of maternal antibodies in milk (Mechor et al. 1987).

Acute BoHV-1 infection, whether or not there are clinical signs of disease, leads to latent infection (see *Latency*). Latently infected cattle show no disease unless the latent infection is reactivated.

BoHV-1 subtype differences

BoHV-1 causes respiratory disease (IBR) or venereal disease (IPV in cows or infectious pustular balanoposthitis in bulls) (Gibbs & Rweyemamu 1977). BoHV-1.1b strains are associated with venereal disease, and BoHV-1.1 and -1.2b strains are associated with respiratory disease (Wentink et al. 1993).

BoHV-1 subtypes have differing virulence (capacity to produce disease) (Msolla et al. 1983). BoHV-1.1 strains have been most widely studied, both because they are prevalent in North America and Europe, and because they cause the most severe disease associated with BoHV-1 infection. Subtype 1.2b strains, the only strains of BoHV-1 present in Australia, show the least severe clinical signs and the least viral shedding (Edwards et al. 1991). BoHV-1.2b strains give clinical signs of only mild rhinitis or mild vaginitis (Snowdon 1964; Studdert 1989; Smith et al. 1993; Young et al. 1994; Smith et al. 1995).

V155

Strain V155 is an Australian BoHV-1.2b strain first isolated in 1964 (Snowdon 1964; Brake & Studdert 1985; Smith et al. 1993). V155 is a mildly pathogenic strain that replicates poorly in the upper respiratory tract and causes mild transitory signs of disease following experimental infection (Bagust 1972; Young et al. 1994). V155 is registered with the Australian Pesticides and Veterinary Medicines Authority under the name 'Rhinogard', and is used as a vaccine for feedlot cattle.

Bovine respiratory disease complex

BoHV-1 is one of the agents that cause bovine respiratory disease (BRD). BRD, or 'shipping fever', is a serious pneumonic condition that affects up to 50% of cattle in Australia, causing the death of up to 5% of all cattle (Meat & Livestock Australia 2001), costing the Australian feedlot industry around $60m each year (CSIRO 2005).

BRD results from a combination of stress and infectious agents, in particular the viruses BoHV-1, *Bovine viral diarrhoea virus*, *Parainfluenza-3 virus* or *Bovine respiratory syncytial virus* and the bacteria *Mannheimia haemolytica* or *Pasteurella multocida* (Yates 1982). BoHV-1 can initiate BRD by causing immunosuppression (Winkler et al. 1999; Lovato et al. 2003), allowing secondary infections that lead to severe pneumonia and death (Hanon et al. 1998; Lovato et al. 2003).

AUSTRALIAN DISEASE STATUS

IBR/IPV is present in Australia (Animal Health Australia 2004a). Whilst BoHV-1 infection is common, only BoHV-1.2b strains have been isolated from Australian cattle (Snowdon 1964; Studdert 1989; Smith et al. 1993; Young et al. 1994; Smith et al. 1995).

Studies on the prevalence of BoHV-1 in Australian cattle show differing results, from about 30% (Smith et al. 1995), to a range of 15% to 96% reported between studies (AFFA 2000). One study of feedlot cattle shows that 13% of cattle have antibodies to BoHV-1 on entry to feedlots, rising to 39% of cattle after 6 weeks in the feedlots (Dunn et al. 1994).

Australia has no program to control or eradicate BoHV-1. The need for such a program has been assessed by Agriculture, Fisheries and Forestry – Australia, thus: '*[an] eradication program is not likely to be feasible in Australia, nor is there any need for such a program in view of the mild subtypes of [BoHV-1] in Australia and the presence of [BoHV-1] in those countries that are most important to the Australian livestock export trade*' (AFFA 2000).

INTERNATIONAL DISEASE STATUS

The World Organisation for Animal Health (Office International des Epizooties; OIE) lists IBR/IPV as a List B notifiable disease (OIE 2004). OIE List B diseases are transmissible diseases that are of socio-economic and/or public health importance, and that are significant in international trade.

BoHV-1 is common in cattle around the world (OIE 2000). Eradication programs involving vaccination, herd isolation, border control and slaughter are in place in several European countries (Kahrs 2001). Denmark, Finland, Sweden, Austria and the province of Bolzano in Italy have successfully eradicated BoHV-1, and are recognised as free from IBR under European Union legislation (SCAHW 2000).

VACCINES

BoHV-1 vaccines include inactivated, attenuated, subunit or gene-deleted (marker) vaccines. Vaccines are used to reduce the severity of disease, but cannot always prevent infection due to the endemic nature of BoHV-1 infection (Fenner et al. 1993). There are two vaccines registered for use in Australia: Rhinogard (live BoHV-1.2b strain V155); and IBEPUR, a subunit vaccine (APVMA 2004). Over 2 million Australian feedlot cattle have been vaccinated with Rhinogard (AFFA 2000).

Various conventional vaccines and marker vaccines (used to differentiate between vaccinated and unvaccinated animals) are available overseas, often in combination with vaccines against other pathogens as multivalent vaccines to control BRD (Fulton et al. 2003). Both modified live and inactivated vaccines have drawbacks such as contraindication for young or pregnant cattle, uncertain efficacy, interference with serological diagnosis, and live vaccine transmission to unvaccinated cattle (Kahrs 2001; Lovato et al. 2003).

DNA vaccines are being developed: research in mice shows that they may overcome the maternal antibody-mediated suppression of the immune response to conventional BoHV-1 vaccines (Lewis et al. 1999; Deshpande et al. 2002).

BoHV-1 as a vaccine vector

BoHV-1 is a potential candidate for a recombinant vaccine vector due to its large size, which allows the insertion of large vaccine genes, and its restricted host range (Bello et al. 1992; Young & Smith 1995; Mahony et al. 2002; Mahony et al. 2003). BoHV-1 vectors have been used to express proteins from *Pseudorabies virus* (a pig pathogen), *Bovine respiratory syncytial virus*, *Foot and mouth disease virus* and *Bovine viral diarrhoea virus* (Otsuka & Xuan 1996; Ikeda et al. 2000; Takashima et al. 2002); (Schrijver et al. 1997; Kuhnle et al. 1998; Taylor et al. 1998) (Kit et al. 1991a; Kit et al. 1991b) (Kweon et al. 1999). The *Bovine viral diarrhoea virus* study, in which the *Bovine viral diarrhoea virus* E2

protein from a *Bovine viral diarrhoea virus* type 1 viral strain was expressed in an attenuated BoHV-1vector with a deletion of the *thymidine kinase* gene, showed reduced disease compared with unvaccinated calves following BoHV-1 challenge, and delayed cytopathic effect compared with wild type BoHV-1 in cell culture (Kweon et al. 1999).

VIROLOGY

VIRAL CLASSIFICATION

Family	*Herpesviridae*
Subfamily	*Alphaherpesvirinae*
Genus	*Varicellovirus*
Species	*Bovine herpesvirus 1* (ICTV 2002)

HERPESVIRUS STRUCTURE

Herpesviruses are large, enveloped, double-stranded DNA viruses (Harrison 2001). Typical herpesvirus virions consist of: a core containing linear double-stranded DNA; an icosadeltahedral capsid of about 100 nm diameter containing 162 capsomeres; a tegument surrounding the capsid, and an envelope containing viral glycoprotein spikes on its surface (Roizman & Pellett 2001).

VIRUS GENES AND PROTEINS

BoHV-1 has a 136 kilobasepair double-stranded DNA genome. The complete sequence of the BoHV-1 genome has been determined using a composite of the Cooper, p8-2, 34 and Jura strains of BoHV-1 (Schwyzer et al. 1997). The BoHV-1 genes are named after their *Herpes simplex virus 1* counterparts (Manservigi & Cassai 1991).

All herpesviruses encode a large number of proteins involved in nucleic acid metabolism, DNA synthesis and protein processing (Roizman & Pellett 2001). At least 33 of the BoHV-1 encoded proteins are structural proteins (Misra et al. 1981). Of these, 13 are probably associated with the envelope (Liang et al. 1996) and ten of these have the potential to encode glycoproteins (Schwyzer & Ackermann 1996). There are 8 known glycoproteins: gB, gC, gD, gE, gH, gI, gK and gL; the major envelope glycoproteins are gB, gC and gD. The gC, gD, gE, gG, gI, UL49h and *thymidine kinase* genes are involved in viral virulence (Kit et al. 1985; Kit et al. 1986; Smith 1991; Smith et al. 1994; van Engelenburg et al. 1994; Young & Smith 1995; Van Oirschot et al. 1996; Liang et al. 1997; Kaashoek et al. 1998). There is no evidence either *in vitro* or *in vivo* that BoHV-1 produces toxins.

BoHV-1 LIFE CYCLE

In order for a virus to have a complete life cycle and produce infective virus, the virus must be transmitted to a host, be able to infect host cells and then produce infective virus.

Virus transmission

Viruses exist only in relationships with hosts and cannot replicate outside their hosts. BoHV-1 is inactivated by normal environmental conditions outside the host (Gibbs & Rweyemamu 1977; Elazhary & Derbyshire 1979; Kahrs 2001), and by common disinfectants and solvents (Gibbs & Rweyemamu 1977).

Transmission of BoHV-1 occurs by contact with mucosal droplets from infected cattle (Kahrs 2001); infectious virus is nasally shed for 10–14 days during acute respiratory infection (Gibbs & Rweyemamu 1977), and virus is also shed following reactivation from latency. Contaminated materials, including semen, can transmit the virus (Mars et al. 2000). Australian isolates of BoHV-1, which are all of the subtype 1.2b, cannot be transmitted to the foetus of infected pregnant cows (Young et al. 1994).

Airborne transmission of BoHV-1.1 can occur under experimental conditions at distances of 3.85 m, although this is probably not a major route of transmission (Wentink et al. 1993) and is dependent upon environmental temperature and relative humidity (Elazhary & Derbyshire 1979; Mars et al. 1999). Vectors do not appear to spread the virus (see *Host Range*).

Cell specificity

BoHV-1 can only cause a productive infection in certain cell types, since only some cells produce the proteins required for virus entry and subsequent virus production. BoHV-1 infects epithelial cells of the upper respiratory tract, vaginal or prepuce mucous membranes, and the tonsils and conjunctivae (Tikoo et al. 1995a), as well as CD4+ T cells (Lovato et al. 2003), monocytes and macrophages (Nyaga & McKercher 1979; Forman et al. 1982).

Physical barriers, such as skin, mucous and the immune response restrict access of the virus to certain sites within the body. When these barriers are compromised, the virus is able to establish infection throughout the body (Mechor et al. 1987). Latent infections are established at immunoprivileged sites following acute infection (OIE 2000).

Virus entry into host cells

Herpesviruses enter cells by fusing with the cell plasma membrane in a complex process of attachment and penetration. Virus entry requires the presence of complementary binding partners on the virus and on the host cell. Studies show that the BoHV-1 glycoproteins gB, gC, gD, gE, gH, gK and gL are required for virus entry (Li et al. 1995; Schroder & Keil 1999; Dasika & Letchworth, III 1999; Hanon et al. 1999). BoHV-1.1 and BoHV-1.2 subtypes differ in gC epitopes, which may alter viral attachment and account for subtype differences of viral virulence (Rijsewijk et al. 1999).

Although the host cell proteins required for BoHV-1 entry are not fully understood, the virus initially binds to cell surface heparan sulphate (Hanon et al. 1998; Tyler & Nathanson 2001) via BoHV-1 gB and gC (Li et al. 1996). After this initial binding, BoHV-1 gB and gD then bind further cell surface receptors (that have yet to be identified) with high affinity (Li et al. 1995). Studies to identify these high affinity receptors have shown that BoHV-1 gD can weakly bind HveC or the human poliovirus receptor expressed in human or hamster cell lines (Geraghty et al. 1998; Connolly et al. 2001). This weak binding indicates that viral

entry in a natural host may be mediated by receptors other than bovine HveC or poliovirus receptor homologues (Geraghty et al. 1998; Connolly et al. 2001).

Virus replication and release

After entry into the host cell, BoHV-1 is transported along microtubules to the nucleus for replication using host cell proteins. The virus becomes enveloped as it buds through the nuclear envelope and is then transported within intracellular vesicles to the cytoplasmic membrane and released from the cell (Knipe et al. 2001; Hunter 2001). BoHV-1 replication starts within two hours of infection in cattle (Meurens et al. 2004b), with cell surface antigen expression within 3-4 hours after infection and viral release and spread starting at 8 hours after infection (Babiuk et al. 1996).

Latency

BoHV-1 is maintained within the host animal by latent infection. There is no evidence for persistent productive infection with BoHV-1. BoHV-1 latency occurs at immunoprivileged sites in the peripheral nervous system following productive viral infection (Rock et al. 1987; Rock et al. 1992; OIE 2000). Latency may also occur in tonsillar lymphoid cells and peripheral blood lymphocytes (Mweene et al. 1996). Latent virus only produces latency-related proteins, which protect latently infected cells from apoptosis (Schang et al. 1996). Infectious virus is not present during latent infection (Rock 1994; Engels & Ackermann 1996).

Cattle that are seronegative for BoHV-1 antibodies may be latently infected with BoHV-1 (Hage et al. 1998). Young calves can have latent infections and have antibody responses due to infection in the presence of maternal antibodies (SCAHW 2000). Inoculation with live vaccine strains of BoVH-1 can also lead to latent infection (Kit et al. 1985; SCAHW 2000).

Reactivation of latent BoHV-1 infections occurs in response to stress, and productive infection of the epithelial cells recurrs. The stress of transport has been shown to cause viral reactivation, leading to virus shedding from days 1-4 after the day of transport (Thiry et al. 1987).

Cellular transformation

Some viruses are known to trigger cellular transformation, leading to tumour formation and the development of cancer. Each major DNA virus family, except the parvoviruses, includes viruses that are oncogenic (Nevins 2001). However, there is no evidence that alphaherpesviruses, including BoHV-1, are capable of transforming host cells.

Integration of viral genes into the host cell genome

Virus genes that are integrated into the host cell genome are expressed in the host cell and are passed on with any cell division of the host cell. There is no evidence of the integration of BoHV-1 genes into the host cell genome. In contrast, long term viral survival is dependent upon the establishment of latency, in which a circularised genome is maintained extrachromosomally (Roizman & Pellett 2001).

Virus recombination

Virus recombination occurs when genes of one virus are transferred to another virus, during virus replication in a cell that is co-infected with more than one virus. Intraspecific recombination has been observed between different strains of the same alphaherpesvirus species and is dependent on the level of sequence similarity (Meurens et al. 2004a; Thiry et al. 2005). As sequence similarity diverges towards a species level, the likelihood of recombination also decreases.

Recombination of BoHV-1 has only been described following experimental co-infection (SCAHW 2000; Schynts et al. 2003). Recombination can only occur if two strains of BoHV-1 are inoculated in proximity within two hours of each other (Meurens et al. 2004b). After two hours, viral replication of the first virus has started in the host cell, which prevents infection of the cell with another viral strain (viral interference) (Chase et al. 1990; Dasika & Letchworth 2000). The co-infection of two viral strains within two hours would be very unlikely under field conditions.

A BoHV-1 vaccine has been studied to assess the ability of different strains of BoHV-1 to undergo recombination. A genetically modified BoHV-1 vaccine containing a deletion in the *thymidine kinase* gene was shown to persist in cattle in the field for at least 3 months, during which time no recombination or reversion to wild type virus was found (Kit et al. 1985).

VIRUS DETECTION

The OIE has established recognised standards for BoHV-1 diagnostic tests, which include collection and processing of samples, virus isolation, viral antigen detection, nucleic acid detection, differentiation of BoHV-1 subtypes and serological tests including virus neutralisation and enzyme-linked immunosorbent assay (OIE 2000).

IMMUNOLOGY

The immunology of BoHV-1 infection relates to both the host immune response to viral infection, and to mechanisms that the virus uses to overcome the host immune response.

THE IMMUNE RESPONSE TO BOHV-1 INFECTION

The immune response of cattle to BoHV-1 infection is unique. While there are similarities to immune responses to other alphaherpesviruses, the bovine response to BoHV-1 is not identical to that of *Herpes simplex virus* in mice or in humans, and does not correlate precisely with experimental BoHV-1 infection in mice (Babiuk et al. 1996).

The immune response to BoHV-1 infection is triggered when the virus begins to replicate (Babiuk et al. 1996). Adaptive cell-mediated and antibody-mediated immune response occur by 7 days after infection (Engels & Ackermann 1996; OIE 2000). Antibody is thought to be critical in preventing infection and viral spread, while cell-mediated immunity is involved in recovery from infection (Babiuk et al. 1996).

The antibody response

Antibodies are produced against the gB, gC, gD and gE glycoproteins (Tikoo et al. 1995a), protecting against viremia and associated severe disease (Mechor et al. 1987) The antibody response includes neutralising antibodies, and contributes to antiviral antibody-dependent cellular cytotoxicity (Tikoo et al. 1995a), which is enhanced by complement (Rouse et al. 1977).

Antibodies persist at detectable levels for 3 years following BoHV-1 vaccination (Hage et al. 1998). The antibody response to the V155 strain of BoHV-1 persists at maximal levels from 7 to 21 days after infection (Bagust 1972). Maternal antibody to BoHV-1 persists for 123 days after weaning at two months of age (Fulton et al. 2004). Newborn calves are protected from BoHV-1 infection after being fed colostrum of vaccinated cows (Mechor et al. 1987), although maternal antibody is not completely protective since calves can have latent BoHV-1 infections early in life in the presence of maternal antibody (SCAHW 2000).

The cell-mediated immune response

The cell-mediated immune response to BoHV-1 infection includes macrophages, interleukin-2 and interferon -γ production, natural killer cells and natural killer-like activity, proliferation of viral gC- and gD-specific CD4+ T cells and stimulation of cytotoxic T lymphocyte activity (Hutchings et al. 1990; Tikoo et al. 1995b). Interferon-γ, interferon-α and interferon-β have been shown to both protect against infection and to prevent viral spread in experimental infection in mice (Abril et al. 2004). Responses to BoHV-1 infection are broad based and include both T helper 1 and T helper 2 responses (Babiuk et al. 1996), although, as with other intracellular pathogens, there is a skew towards a T helper 1-type response (Mena et al. 2002).

Allergenicity

There are no reports of BoHV-1 encoding known allergens or causing an allergic response.

VIRAL MANIPULATION OF THE IMMUNE RESPONSE

Immune evasion

BoHV-1 evades the host immune response by interfering with antigen processing and presentation and by infecting monocytes and macrophages (Nyaga & McKercher 1979; Forman et al. 1982). Alphaherpesviruses, including BoHV-1, also have immunomodulatory activity mediated by herpesvirus proteins that mimic key molecules of the host immune system (Raftery et al. 2000). For example, these viruses express proteins that bind complement C3 in a species-specific manner and thus alter the host immune response to allow viral infection (Huemer et al. 1993; Engels & Ackermann 1996).

Additionally, latency is a means of immune evasion. During latency viral proteins are not expressed, and infection occurs at immunoprivileged sites that do not express major histocompatability class I antigens (Tyler & Nathanson 2001).

Immunosuppression

BoHV-1 causes a broad immunosuppression in infected cattle, which often leads to secondary viral and bacterial infections (Winkler et al. 1999), contributing to BRD.

Immunosuppression is caused by impairment of macrophage, polymorphonuclear neutrophil and lymphocyte function (Tikoo et al. 1995a), and by decreased IL-2 receptor expression, decreased mitogenic stimulation of peripheral blood mononuclear cells and reduced numbers of circulating T lymphocytes (Winkler et al. 1999). Infection of monocytes and macrophages leads to impaired phagocytosis, impaired antibody-dependent cellular cytotoxicity function and poor T cell stimulation (Forman et al. 1982). The effect of immunosuppression is partly mediated by the BoHV-1 gG glycoprotein, a broad-spectrum chemokine-binding protein that blocks chemokine binding and activity (Bryant et al. 2003). BoHV-1 also infects CD4+ T cells, inducing a loss of CD4 expression followed by apoptosis of these cells (Winkler et al. 1999; Lovato et al. 2003).

CONCLUSIONS

The key points that arise from this review of BoHV-1 in relation to the health and safety of humans, host organisms and the environment are as follows.

- The host range of BoHV-1 does not include people. There is no evidence that BoHV-1 can infect people.
- BoHV-1 causes disease in cattle, water buffalo, sheep and goats.
- BoHV-1 is one of the causative agents of Bovine Respiratory Disease, a disease that affects the Australian cattle industry.
- BoHV-1.2b is the only strain of BoHV-1 that has been isolated in Australia. This strain causes mild disease in cattle and water buffalo but has not been detected in sheep or goats in Australia.
- Vaccination programs against the virus are unlikely to be completely effective due the endemic nature of BoHV-1.
- There is no evidence that BoHV-1 is capable of cellular transformation or host cell integration.
- There is no evidence that BoHV-1 encodes toxins or allergens.

To conclude, the literature discussed in this review indicates that the BoHV-1.2b strain present in Australia and used as a vaccine strain is a relatively innocuous virus with a limited host range.

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