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Risk of infection from chronic wasting disease prions and atypical chronic wasting disease prions via consuming cervid meat

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Executive Summary

Chronic wasting disease (CWD) is a transmissible spongiform encephalopathy (TSE) caused by the CWD prion and affects a number of species in the mammalian Cervidae family. While no cases of CWD have been reported in the UK cervid population to date, CWD has been reported in cervids for many years in many USA states and Canada and more recently in Norway. Two prion strains have been identified in Norway (CWD prions which have infected reindeer *Rangifer tarandus* and atypical CWD prions which have infected the moose *Alces alces*. The strain that affects moose seems unusual and could be a novel strain of CWD while the reindeer strain appears very similar if not identical to that previously recognised in N. America. Therefore, the hazards identified in this assessment were CWD prions and atypical CWD prions in meat and derived products from Cervidae.

Six deer species inhabit the UK countryside and all can enter the food chain. Given exposure to an infectious dose of CWD prions, most deer species (although fallow deer appear not to be susceptible) in the UK could become infected with CWD. At present it is not possible to indicate whether any UK deer species could become infected with atypical CWD prions, if this strain were to be introduced into the UK.

CWD is readily transmitted among cervids and genetic factors play a role in modulating disease progression. There is no evidence as yet to suggest that non-cervids can be naturally infected including other food producing animals such as sheep and cattle.

A notable amount of UK produced cervid meat enters the food chain each year and steady but variable amounts of imported cervid meat including a proportion from Nordic countries. While cervids in advanced stages of infection are unlikely to enter the food chain, the possibility of infected asymptomatic cervids entering the food chain cannot be ruled out completely. CWD prions can be distributed almost ubiquitously throughout diseased cervid hosts but there is a lack of information relating to prion distribution throughout disease progression. Atypical CWD prions are more likely to be localised in and around CNS tissue.

The resistance of prions to heat means that processes such as cooking meat thoroughly will not have any impact in reducing exposure to CWD prions in contaminated cervid meat, pies, sausages etc. Curing and fermenting will also likely be ineffective. As prions are resistant to most disinfectants and can tightly bind to steel and plastic surfaces, decontamination of areas within abattoirs, butchers' shops, kitchen surfaces and utensils used for food preparation will be difficult if exposure to CWD-infected meat has occurred and this could potentially serve to facilitate cross-contamination either directly or via person to person contact.

As yet there have been no reports of CWD transmission to humans despite ongoing surveillance in exposed areas for many years and there is evidence that a strong species barrier exists in humans. While there is good evidence to indicate the presence of a strong species barrier for humans, a small number of studies indicate that a negligible risk of transmission cannot be assigned at this stage. Additionally, there is uncertainty relating to the incubation period (if any) for humans.

The risk of developing CWD from eating (and handling) cervid meat and products infected with CWD prions is likely to be **very low** with a high level of uncertainty. Given the lack of information relating to atypical CWD prions at this stage, it has not been possible to assign the level of risk associated with this hazard, though it is likely that general aspects of prion behaviour such as heat resistance might be exhibited.

Risk of infection from chronic wasting disease prions and atypical chronic wasting disease prions via consuming cervid meat

Statement of purpose

- **What is the risk of CWD and atypical CWD infection in the UK human population via meat and derived products from Cervidae and other food producing animals.**

Hazard Identification

1. Chronic wasting disease (CWD) is a highly infectious transmissible spongiform encephalopathy (TSE) caused by the CWD prion. Like other TSEs, CWD is a neurodegenerative disease caused by a prion that affects a number of species in the mammalian family Cervidae. Further details relating to prions including CWD prions will be provided in the hazard characterisation sections below.

2. Chronic wasting disease was first identified as a clinical disease of captive mule deer in Colorado in 1967 and later classified as a TSE in 1978 (Williams & Miller, 2003). The origin of the disease is unknown and may have been a spontaneous TSE that arose in deer (DEFRA, 2017).

3. While no cases in Cervidae have been reported in the UK to date, CWD has been reported in Cervidae in many USA states and Canada and occasional outbreaks in South Korea following imports of infected animals. In USA and Canada, natural CWD infections have been reported in mule deer (*Odocoileus hemionus hemionus*), black-tailed deer (*Odocoilius hemionus columbianus*), white-tailed deer (*Odocoileus virginianus*), captive red deer (*Cervus elaphus elaphus*), Rocky Mountain elk (*Cervus elphus nelson*), Shira's moose (*Alces alces shirasi*) and mule deer and while-tail deer hybrids (CFSPH, 2016).

4. In April 2016, a wild 3-4 year old female reindeer (*Rangifer tarandus*) displayed abnormal behaviour and died shortly before being diagnosed with CWD in the Nordfjella region of Norway. In May of the same year, two female moose (*Alces alces*) in the Selbu region of Norway also tested positive for TSE prion protein but the exact nature of the diagnosis remains uncertain as investigations have not been completed. The moose cases were located approximately 300 km north of the reindeer case. In August 2016, a wild reindeer bull was shot and subsequently diagnosed with CWD, followed by a fifth CWD diagnosis in a wild reindeer cow shot by hunters in September (the

fourth and fifth cases were also in the Nordfjella region (VKM, 2017). The Norwegian scientific committee for food safety concluded that, there is an ongoing outbreak of CWD in the wild reindeer population of the northern part of Nordfjella wild reindeer range. A further CWD case has now been reported in a reindeer in the Nordfjella region. The animal was a clinically healthy, young reindeer, caught and anaesthetised, sampled and released with a radio collar. Samples from gut lymphoid tissue tested positive (Helen Roberts, APHA, personal communication).

5. To put these findings into context, in Norway, since March 2016, 8770 samples from wild cervids have been tested for CWD (moose n = 4,629, red deer n = 2,550, wild reindeer n = 860, and roe deer n = 627, unknown species n = 104), of which 5 were CWD-positive or atypically CWD positive (2 moose, 0 red deer, 3 wild reindeer, 0 roe deer) as detailed in paragraph 4 above (VKM 2017). One additional case has also been recently reported as in paragraph 4.

6. By the end of May 2018, 41,685 animals had been tested (including 10,627 moose, 4,658 free ranging reindeer, 14,914 semi-domesticated reindeer and 6,711 red deer). In Nordfjella the Norwegian authorities have analysed 2,469 free ranging reindeer and with 19 positive, this suggests a cluster prevalence of around 1% (http://apps.vetinst.no/skrantesykestatistikk/NO/). Recently the Norwegian authorities have announced a mass cull of reindeer in the Nordfjella region has been completed in an effort to eliminate the disease. The land will be left fallow for a period of 5 years following the end of the cull (This para has been updated in June 2018).

7. Two other TSE-like cases were detected in Norway– an additional one in moose and one in a red dear (*Cervus elaphus*) although all appeared to have limited tissue distribution of the prion protein, restricted to the nervous tissue, and therefore presumed to be a spontaneous or atypical CWD-like disease.

8. In March 2018, a 15 year old wild moose, was found dead in Kuhmo region, Finland near the border with Russia. The moose tested positive for prion protein and results were confirmed by the EU reference laboratory. Finland has tested ~2,500 cervids since 2003 and this is the first case to be detected. The Finish Authorities have confirmed the tissue distribution was similar to the cases detected in moose and red deer in Norway (EVIRA, 2018).

9. Six deer species inhabit the UK countryside (red deer/*Cervus elaphus*), sika deer/*Cervus nippon*, roe deer/*Capreolus capreolus*, Reeves' muntjac deer/*Muntiacus reevesi*, fallow deer/*Dama dama* and Chinese water deer/*Hydropotes inermis*). Only red deer and roe deer are truly indigenous. Fallow deer were introduced to the UK by the Normans and the remaining three species arrived in the late nineteenth and early

twentieth centuries (British Deer Society, 2015). All the deer species listed contribute to the UK venison food supply chain (British Deer Society, personal communication).

10. Within the UK, there is a demand for deer meat (and derived products including sausages) which has been offered in mainstream retail outlets and restaurants for many years. There has been an annual growth in the demand of total deer carcases from *circa* 137,000 in 2011 to 160,000 in 2015 predominantly of wild deer. The number of holdings undertaking these activities averaged 73 different sites throughout the UK over this time period.

11. In the UK, farmed deer constitutes approx. 3% (4,675 per annum) of total deer carcases slaughtered on average annually, with a relatively stable annual throughput across some 20 sites (2011-15). In contrast the high throughput of wild deer carcases (approx.143,500 per annum.) has seen an increase of 18% across some 50 sites on average, between 2011-2015.

12. Based on the confirmed CWD diagnoses in wild Norwegian reindeer and various members of the Cervidae family in N. America and the atypical CWD presentation in Norwegian moose and red deer, **the hazards in the scope of this food safety assessment can be identified as CWD prions and atypical CWD prions in meat and derived products from Cervidae.** Other food producing animals (sheep, cattle) have been considered in this assessment and it has been concluded that these animals are unlikely to provide a significant input into potential CWD human infection from eating and handling contaminated meat.

Exposure assessment

Transmission in animals

13. Exposure to CWD prions via food could potentially occur through consuming meat, meat products such as sausages, offal, pies or tissues from infected deer or via handling of infected deer and parts during processing and preparation. More unusual pathways such as ingesting antler velvet, or powdered deer horn which are used in Asian cultures as a traditional medicine (Anderson *et al*., 2007) are not the focus of this assessment as are not legally permitted to be on the EU market. However, there is **uncertainty** about whether these products may be available through other routes. Airborne transmission of CWD may also be worthy of acknowledgement, during the preparation and processing of infected cervid meat for example in plants, though this will not be the focus of this assessment. Denkers *et al*., 2013 reported aerosol transmission of CWD in white tailed deer with a prion dose >20-fold lower than that used in previous oral inoculations.

UK Cervid susceptibility

14. Six deer species inhabit the UK countryside. These are: (red deer/*Cervus elaphus*), sika deer/*Cervus nippon*, roe deer/*Capreolus capreolus*, Reeves' muntjac deer/*Muntiacus reevesi*, fallow deer/*Dama dama* and Chinese water deer/*Hydropotes inermis*).It is possible that a proportion of these will be in proximity to zoos and wildlife parks where other cervids may be kept.

15. In terms of deer species and CWD susceptibility, in general terms the following applies:

    - Red deer – Susceptible
    - Roe deer – Lack of susceptibility information **(uncertainty)**
    - Muntjac – Susceptible and susceptibility can be considered comparable to white tailed deer
    - Fallow- Do not appear susceptible
    - Sika – Susceptible
    - Chinese water deer – Unknown susceptibility at present **(uncertainty)**

Therefore, on the basis of current scientific understanding, it is likely that given exposure to an infectious dose of CWD prions, most deer species in the UK could potentially become infected with CWD **(uncertainty)** (DEFRA, 2017). At present it is not possible to indicate whether any UK deer species could be infected with atypical CWD prions if this strain were to be introduced in the UK by whatever means, however, the affected Norwegian moose species *Alces alces* is present in the UK only as part of animal collections in a zoo or managed setting.

Prevalence of CWD in cervids in N. America and the EU

16. Until recently, CWD was restricted to North America with the exception of imported infected animals into South Korea from Canada. In North America, in 2016, the prevalence of CWD in wild cervids is reported to be < 5% in deer and < 2.5% in elk (*Cervus elaphus* nelson) in many affected areas. However, it differs between regions, and can be higher (e.g., < 15% of deer in parts of Colorado and Wisconsin). In a few localised "hot spots," CWD has been detected in up to 10-12% of elk and up to 50% of wild deer. The vast majority of cases found during the surveillance of wild deer and elk in N. America are subclinical (CFSPH, 2016). Further discussions relating to asymptomatic CWD infection of cervids will be discussed in subsequent paragraphs.

17. Surveys of wild and farmed cervid populations in the EU between 2006 and 2010 did not identify any TSEs (EFSA, 2011). In Norway, CWD

prevalence in reindeer is estimated to be around 1% in the Northern zone of Nordfjella wild reindeer area, which includes approx. 2000 animals. There are no indications of CWD in reindeer in other areas but a large amount of testing was only carried out in two populations outside Nordfjella so further surveillance may be useful **(uncertainty)** (VKM report, 2017). **See paragraph 6 for update made in June 2018.** As yet, there have been no reports of CWD infection in the UK cervid population and it is unlikely that CWD is currently present in the UK, however, improved surveillance would be extremely useful in reducing the level of **uncertainty** relating to this.

Transmission of CWD to cervids

18. The rate of horizontal transmission of CWD between cervids has been reported to be as high as 30% and can approach 100% among captive animals in endemic areas, suggesting a density dependent effect (Safar *et al*., 2008). The efficiency of CWD transmission is unparalleled among TSE diseases (EFSA, 2011).

19. CWD prions can be transmitted horizontally between cervids by direct contact through behaviours such as licking for example, or environmental contamination or a combination of these routes. Experimental transmission of CWD prions between deer by the oral and intranasal routes, in aerosols and by blood transfusion has been reported (CFSPH, 2016).

20. In deer, CWD prions have been detected in saliva, blood, urine, faeces and antler velvet, and some sources (e.g., saliva, faeces, urine) can be contaminated with CWD prions before the animal develops clinical signs. It is not known whether CWD prions can be shed in milk**.** While the concentration of prions in urine and faeces is very low, the volume of these excretions could make a significant contribution to environmental contamination over the course of the infection and as a result, play an important role in maintenance of the disease in affected areas (CFSPH, 2016; DEFRA, 2017). It is reported that grazing is an important method for acquiring CWD prions from the environment as are communal salt licks which have now been banned in Norway (Helen Roberts, APHA, personal communication). Prions are capable of binding to soils and retaining infectivity for cervids, though persistence differs depending on soil type. Prion infectivity has been reported on pastures. CWD cases have been reported following exposure to infected carcasses left to decompose in pastures two years earlier (CFSPH, 2016).

21. The DEFRA animal health risk assessment has reviewed other potential sources of CWD transmission to UK cervids which could include; importation of live deer (including reindeer, other cervids), importation of deer urine lures, importation of other products derived from cervid species (e.g. trophy items including antlers, semen),

importation of animal feed, hunters and other tourists (skiers and walkers) and British servicemen travelling from affected areas to the UK with contaminated equipment (e.g. boots, clothing, knives).

22. If CWD were to be present in the UK, as in Norway, there is a potential for many species of rodents and carnivores to contribute to the dissemination of CWD prions from a CWD-infected cervid carcass, these include, birds, squirrels, foxes and crows. Such animals could potentially feed on infected carcasses and also distribute prions. There has been one report to suggest that CWD prions may be found in very low concentrations in environmental water but this report needs to be confirmed (CFSH, 2016).

23. The DEFRA animal health assessment has estimated that overall, the probability of importing a TSE into the Great Britain deer herds from Norway and causing infection in British deer is uncertain but likely to be **no greater than very low** via movement of deer hunters, other tourists and British service personnel; **at most, low** via live animal imports or imported (non-ruminant) animal feed; **very low** for the use of urine lures specifically sourced in Norway and **negligible** for plant imports (DEFRA, 2017). However, if it was imported and (a) deer did become infected with CWD, the consequences would be severe as eradication of the disease is unfeasible, it is clinically indistinguishable from BSE infection in deer and populations of wild and farmed deer would be under threat (DEFRA,2017).

Transmission of CWD to livestock (cattle and sheep)

24. There is currently no evidence that CWD prions have infected any animals other than cervids in nature. CWD has not been reported in any cattle co-pastured with deer or elk in the USA or in surveys of cattle in endemic areas in the USA (CFSPH, 2016).

25. CWD appears to spread easily among cervids, with little or no species barriers, though the Norway data do show that strains infecting deer and moose are different . However, many studies have shown that cattle and sheep fail to develop CWD upon oral challenge and in the case of sheep, only after very long incubation periods following intracerebral inoculation. These data suggest that transmission of CWD to sheep and cattle seems very unlikely (VKM report, 2016).

26. It has also been reported that it is highly unlikely that prion disease in cattle and sheep are the origin of CWD in Norway. Given the endemic nature of sheep scrapie in continental Europe and the UK for centuries and the considerable overlap of habitat between sheep and a variety of cervid species, no CWD has been observed (VKM,2017). *In vitro* assessment and modelling studies of the species barrier argue against CWD originating in sheep or cattle as re-introduction of the prions to

the original host would be expected to occur more readily, regardless of adaptation in the new host (VKM, 2017). Nonetheless, areas where there is a high density of both cervids and sheep/cattle may be places to increase surveillance.

27. On this basis, it seems very unlikely that livestock such as cattle, sheep and other non-cervids need specific consideration in terms of exposure to CWD prions via meat consumption at this stage. The assessment will therefore focus on cervid meat only.

Transmission to humans through food

Cervid consumption in the UK

28. It is not known how susceptible humans are to CWD but given that CWD prions can be present in cervid muscle, it is likely that humans have been exposed to the agent via consumption of venison in various parts of the world (Sigurdson, 2008). Initial experimental studies suggest that human susceptibility to CWD is low and there may be a robust species barrier for CWD transmission to humans, this will be discussed further in the subsequent hazard characterisation sections.

29. In the UK, a notable amount of deer meat enters the food chain. Deer entering the food chain are divided into wild deer and farmed deer (see **Annex A** for details on each). Wild deer are shot by trained hunters and require a hunter's declaration and are processed largely in game handling establishments, which also process other wild game including wild birds, wild boar and less commonly, hunted sheep and goats. Scotland and England have the largest numbers of hunted/wild deer entering the food chain, but farmed deer are predominant in Wales and NI compared to wild deer**.** **Table 1** illustrates the UK deer slaughter position from 2011 to 2015. **Annex A** provides further details on definitions of wild and farmed deer.

Table 1: UK data on handling and processing of game (specifically for deer). Source: Food Standards Agency.

Country	Wild/hunted deer Processed at game handling establishments (Number of deer slaughtered)	Farmed deer Slaughtered at red meat slaughter lines (Number of deer slaughtered)	Total	Years
Scotland Wales England NI	67, 601 - 65,767 -	615 195 3,459 979	68,216 195 69,226 979	2011-2012
Scotland Wales England NI	74,084 - 63,932 102	602 250 3,226 716	74,686 250 67,158 818	2012-2013
Scotland Wales England NI	76,069 - 69,918 -	317 219 3,507 682	76,386 219 73,425 682	2013-2014
Scotland Wales England NI	84,704 8 72,228 369	307 228 3,080 217	85,011 236 75,308 686	2014-2015

30. Data from the last full deer stalking survey conducted in the UK in 2003 reveal deer culling figures for each UK country. In England, the main deer species culled were Roe and Fallow but all other UK species were culled in lesser amounts. In Scotland, the main deer culled were red and roe deer, with Sika and Fallow making up the remainder. In Wales, mainly fallow deer were culled, but smaller amounts of roe and red deer culling also occurred. For NI, roe, red and fallow deer made up the largest proportion of culled deer but other UK deer species were also culled to a lesser extent. These data were derived from cull returns from managed estates and returns from venison dealers (APHA, personal communication). The data provide an indication that all UK deer species enter the food chain and therefore could serve as a potential source of exposure to CWD prions if they were infected, possibly with the exception of fallow deer which appear not to be susceptible **(uncertainty).** It is not clear whether more recent data would be comparable **(uncertainty).**

<u>EU arrivals and imports of deer meat to the UK since 2012</u>

31. Since 2012, there has been a steady but varying amount of deer meat[1] arriving into the UK from the EU. In 2012, 50,692 kg arrived into the UK in total from Belgium, France, Germany and Spain, with France making up the largest amount. In 2013, 460,160 kg arrived into the UK from Belgium, France, Germany, Ireland, the Netherlands and Spain. Spain, the Netherlands and France made up the largest amount. In 2013, 116 kg of reindeer meat salted in brine, dried or smoked was also imported

[1] Fresh, chilled or frozen reindeer meat or edible offal thereof unless otherwise stated

from Norway. In 2014, 73,781 kg arrived in the UK from Finland (Nordic contribution was 29%), France and Spain, with Spain making up the largest amount. In 2015, 58,595 kg arrived into the UK from Finland (Nordic contribution made up 36%), France and Spain, with Spain and France making up the largest amounts. Data for 2016 show that deer meat arrivals to the UK came only from Spain (39,102 kg) (Source: Gail Adams, FSA Imports and Exports Branch). While it is unlikely that CWD- infected non-UK meat has entered the UK food chain, there is **uncertainty** on the CWD status of non-UK meat.

Road kill

32. A report from the British deer society in 2002 stated that that considerable numbers (hundreds, certainly but probably thousands) of poached or otherwise illegally obtained deer, e.g. road kills (there are an estimated 40,000 RTAs involving deer annually), are believed to enter the food chain annually. Many of these animals are, apparently, transported from Scotland to England or Wales. According to the report, there is a limited trade in deer carcasses in the opposite direction because of differences between Scottish and English legislation. In England although some animals can be legally killed out of season, the sale of venison from these animals is prohibited except between dealers. The venison can, however, be sold in Scotland. The deer society reports that it is easy to appreciate the opportunities for exploiting these differences. The report also states that, in practice, any illegal trade is probably limited since large scale out-of season shooting is usually carried out by those holding Game Dealer Licences. Cervid meat consumption from RTAs although less mainstream, provides additional **uncertainty** on the likelihood of exposure to CWD or atypical CWD prions via the oral route.

Venison consumption in the UK

33. Food consumption data focussing on venison consumption in UK adults showed a mean daily consumption value of 33.96 g (for all individuals that consume venison) and for high level consumers of venison (97.5th percentile) this increases to 69.53 g/day (Bates *et al*., 2014; Bates *et al*., 2015; Joe Shavila, Food Standards Agency).

Distribution of CWD prions and atypical CWD prions in infected cervids

34. Distribution and concentration of CWD prions in cervids will be dependent on species and stage of infection, therefore it is not possible to accurately determine the level of exposure to CWD prions from infected cervid meat **(uncertainty).** CWD prions are present almost ubiquitously throughout diseased cervid hosts, including in muscle, fat, various glands, organs, antler velvet, peripheral and CNS tissue and are excreted in many bodily fluids and faeces of infected cervids

(Waddell *et al*., 2017). Edible tissues such as heart, liver, kidney, tongue, pancreas and adipose tissue and blood will likely be infected by the time clinical disease develops. (EFSA, 2017).Therefore, there is potential for human exposure to CWD by handling and consumption of infectious cervid material and this is likely to increase with increased disease prevalence (Saunders *et al*., 2012). CWD has not been reported in the UK cervid population or UK zoo cervid population to date.

35. Angers *et al*., 2006 showed that skeletal muscle in addition to CNS tissue of deer with CWD contains infectious prions. The authors inoculated transgenic mice expressing cervid prion protein intracerebrally with extracts prepared from semitendinosus/semimembranosus muscle of CWD-affected mule deer or from CWD-negative deer. The availability of CNS materials also meant that comparisons of prion infectivity in skeletal muscle and brain could be made. All skeletal muscle extracts from CWD-affected deer induced progressive neurological dysfunction in the (positive) inoculated mice. Mean incubation times ranged from 360-490 days, whereas the incubation times of prions from the CNS ranged from 230 to 280 days. The authors suggested that the differences in incubation periods between muscle and CNS tissue inoculations indicated higher prion titres in CNS tissue in addition to demonstrating variable titres in muscle tissue. In contrast, skeletal muscle and brain material from CWD-negative deer failed to induce disease in the transgenic mice expressing cervid prion protein. Although the muscle tissue from CWD positive cervids appeared to induce neurological dysfunction in this study, the authors reported that previous studies failed to detect misfolded prion protein by immunohistochemical analysis of skeletal muscle from deer with natural or experimental CWD. While this work demonstrates that cervid muscle tissue can contain infectious CWD prions, there is considerable uncertainty relating to prion distribution in tissues of cervids through disease progression **(uncertainty).**

36. Daus *et al*., 2011, demonstrated the presence of misfolded prion protein in skeletal muscle from white-tailed deer with CWD using Western blot analysis. Using the protein misfolding cyclic amplification assay (PMCA), the levels of misfolded prion protein in skeletal muscle were shown to be 2000-10 000 fold lower than in brain tissue.

37. Selariu *et al.* (2015) found that although only three out of nineteen clinically normal female elk were CWD prion positive in the retropharyngeal lymph nodes (and two of these three also in the brain stem at the level of the obex), fifteen of these animals were positive in several tissues when examined with the highly sensitive serial PMCA method. It is interesting to highlight that, five of these positive animals did not have detectable levels of CWD prion in the obex or lymphoid tissues (spleen, retropharyngeal lymph node, or rectal mucosa-associated lymphoid tissue), which indicates that in some animals CWD prions might replicate in peripheral tissues without reaching the

brain and causing clinical disease. This could be of relevance for food chain associated exposure from asymptomatic animals **(uncertainty).**

38. Despite the apparent widespread distribution of CWD prions in diseased cervids, in the absence of knowledge relating to whether or not there is a human infectious dose, there remains **uncertainty** relating to whether exposure to CWD prions has any impact on food borne transmission of CWD to humans.

39. Although deer with CWD in the advanced stages of the disease could be identified by the hunter and/or the carcass may be rejected due to emaciation at the official post-mortem inspection, the likelihood of identifying suspicion of disease in less advanced cases of wild deer may be weak, including for asymptomatic infected deer. Such infected wild deer may be more vulnerable to predators and therefore missed or undetected. The condition of wild deer carcasses can be very variable and the reliability of the hunter's declaration may be limited **(uncertainty)** (Angel Miguelez, FSA personal communication). For farmed deer, the situation may be simpler. It is likely that the animals are better monitored over their lives; therefore there is a greater likelihood of identifying abnormal behaviour and/or abnormal loss of body condition. Additionally, farmed deer are subject to official *ante-mortem* inspection by a vet with higher chances of identifying abnormal behaviour (Angel Miguelez, personal communication).

40. Therefore, it is reasonable to assume that asymptomatic or borderline cervids (wild or farmed) would be more likely to enter the food chain if CWD were present in the UK, than animals showing clinical signs (though detection of clinical signs is dependent on a reliable hunter's declaration for wild deer and this in itself may be associated with a degree of **uncertainty)**. Therefore to reduce the uncertainty around level of exposure to CWD prions via consumption of asymptomatic deer, data relating to CWD prion distribution and concentrations in different species of asymptomatic deer present in the UK would be extremely useful.

41. In terms of atypical CWD prion identified in Norwegian moose, the other hazard being considered in this assessment, distribution seems to be restricted to CNS-associated tissue (Helen Roberts, APHA personal communication) however, there are even more uncertainties associated with the behaviour of these prions. The Norwegian moose species *Alces alces* is not present in the UK outside of animal collections in a zoo or managed setting but it is not clear whether this atypical CWD strain can infect typical UK cervids if it were to enter the UK **(uncertainty).**

Exposure pathway

Deer inspection procedures in the UK

42. Both wild and farmed deer undergo a number of processing steps from farm to fork which are important to consider when assessing any exposure related to food borne transmission of CWD prions to humans. **Annex A** provides more detailed explanations of criteria used to determine whether deer are wild or farmed.

43. The general process pathway for wild deer carcasses from farm to fork in the UK is as follows *(*Ana Quintanilla and Enrique Vega, FSA veterinary advisors, personal communication*):*

- Deer are stalked by trained hunters (normal behaviour is assessed by the hunter prior to shooting)

- Gralloching: evisceration of the carcass (removal of green offal) normally in the same place where the animal is shot. The offal can be buried or left on site.

- Transport to a larder where the red offal and head are detached from the carcass and inspection takes place by trained hunter.

- Examination of the body and of any viscera removed must be carried out by a trained person, to identify any characteristics which may indicate that the meat presents a health risk. The examination must take place as soon as possible after killing. Following the examination referred to above, large wild game carcases eviscerated in the field require a declaration from a trained person. The declaration must contain information relating to the date, time and place of killing and carry an assurance that, based on an examination of the carcase and viscera:
  - there is no suspicion of environmental contamination
  - no abnormal behaviour was observed before killing
  - no abnormal characteristics were found during the examination

- Where the trained hunter's declaration is provided stating that no abnormalities were found, the head and the viscera need not accompany the body, except in the case of species susceptible to trichinosis, where the head (except for tusks) and diaphragm must accompany the body. Carcases not accompanied by the head and viscera must be the subject of a declaration signed by a trained hunter. In the absence of a signed declaration, such carcasses are not accepted in Approved Game Handling Establishments (AGHE), and are not eligible for human consumption. Where a carcass is accompanied by a hunter's declaration stating that abnormalities were found, then the offal must accompany the carcase and must be

correlated to it. In the event that the trained person is unexpectedly unavailable, carcases accompanied by the head and all the viscera (with the exception of the stomach and intestines) may be accepted into an AGHE without the declaration from a trained person.

- Transport to AGHE or non-FSA approved premises registered with a local authority. If carcasses go to non-FSA approved premises such as a butcher's shop, they will not undergo post-mortem examination and will not be health marked as have not been produced in an FSA-approved game handling establishment and can only be sold locally to customers. There is likely to be more **uncertainty** for this type of scenario. At the AGHE most carcases will be presented for inspection with no head or offal and with a trained hunter's declaration.

- AGHE carcasses are chilled

- AGHE Carcasses are skinned and contamination/ shot damage removed and inspected by FSA meat inspectors or vet

- Carcass is deboned

- Meat is packaged or further processed (minced or diced)

44. The general process pathway for farmed deer carcasses from farm to fork in the UK is as follows (Ana Quintanilla, Angel Miguelez, FSA, personal communication) :

    - An official veterinarian carries out *ante-mortem* inspection
    - Deer are shot on farm or stunned and killed in a slaughterhouse. The latter scenario normally happens when the farm is co-located with the slaughter house. It is very difficult to transport live deer to the slaughter house therefore on farm slaughter is acceptable.
    - Once the animal is dead the head is removed and inspected by an FSA inspector or operational vet.
    - Carcasses are skinned
    - Carcasses are eviscerated (red and green offal are removed) and inspected by an FSA inspector or operational vet
    - Carcases can either be split in half or not, there is no legal requirement for this but it might happen. If splitting has occurred, the spinal cord remains attached and bone dust is rinsed off.
    - The carcase is deboned and meat is packaged or further processed (minced or diced).

Processing, preparation and handling of deer carcasses and meat

45. Carcasses for entry to the food chain are prepared into haunches, back legs, saddles, loins and breast and shoulder, which is boned for dicing and mincemeat. Loins are the most valuable parts of the carcasses. Other parts can also be added to pies, sausages etc.

46. It is possible that the spinal cord could accompany the carcass for human consumption because unlike the spinal cord in the case of cattle, sheep or goats, it is not regarded as specified risk material (SRM)[2] for deer. It is also possible that the spinal cord could be directed to category 2 or category 3 waste, depending whether it is rejected meat/unfit or destined for pet food. As there is no requirement for removal, the fate of the spinal cord will likely depend on individual plants **(uncertainty).** It is likely that the spinal cord and CNS tissue contains the highest concentrations of CWD prions in infected deer though no tissues can be considered CWD-free. Red offal from farmed deer is usually harvested and could enter the food chain. In the case of wild deer, this is less likely as there may be more damage, or contamination but it could be possible for this offal to be harvested subject to passing the official *post-mortem* inspection.

47. In terms of wild/hunted deer, disposal of green offal (which is often buried or left at the site of shooting by hunters) and animal heads may warrant highlighting if CWD were to be present in UK, as these practises provide the potential for CWD-prion contamination of the environment, infection of surrounding cervids and maintenance of infection. The fate of green offal and animal heads of wild deer remain an **uncertainty.**

48. Prions are resistant to most treatments that inactivate conventional pathogens including heat, so cooking venison and its products thoroughly will not provide an effective means of reducing exposure to CWD prions. Brown and Abee, 2005 investigated the efficacy of various chemical and physical agents to TSEs. Alcohol, ammonia, phenolics, hydrochloric acid, detergents, boiling, microwave and UV radiation were reported to be ineffective disinfectants for TSEs. 6-8 M urea, glutaraldehyde, steam heat (121 degrees Celsius), dry heat (300 degrees Celsius) were reported to be partially effective. Sodium hydroxide (1-2N), hypochlorite (1-5%), formic acid (100%), steam heat (134 degrees Celsius) and dry heat (>600 degrees Celsius) were reported to be effective disinfectants for TSEs. The reason why prions display this resistance remains largely unknown but is likely related to the conformation of the abnormally folded proteins and inaccessibility of residues to inactivating agents.

49. Additionally, processes such as freezing are unlikely to be effective in inactivating prions in infected meat in the context of a domestic or catering setting. Properzi *et al*., 2016 investigated the resistance of a mouse-adapted scrapie prion strain to freeze-thaw procedures by snap freezing brain homogenate containing these prions in liquid nitrogen for 5 mins and then allowing room temperature thawing (1, 5, 10 and 15

[2] SRM - Those parts of cattle, sheep and goats that are most likely to pose a risk of infectivity if the animal from which it comes from was infected with a transmissible spongiform encephalopathy (TSE) disease. It is essential, therefore, that it is removed from both the human and animal food chains and destroyed.

times). Only after repeated rounds of freeze-thawing (10 and 15 cycles) was there a reduction in infectivity titre by about 1 log TCIU (tissue culture infectious unit) suggesting that a denaturing process had become apparent. While these studies were carried out using scrapie prions and brain homogenate, they do provide an indication that it is reasonable to assume that prion titres in infected meat frozen in a domestic freezer (-20 degrees Celsius) and defrosted only once will not be affected to any appreciable level.

50. It is likely that processes such as curing or drying will not be sufficient to reduce exposure to prions in infected meat. The processes of drying or curing with salts and fermenting will likely reduce water activity of the treated meat and literature sources imply that dry environments can enhance prion resistance. Loss of water during drying could also effectively lead to a concentration of prions in the final product. During curing and fermenting, there are likely to be a multitude of interactions such as between microbial enzymes meat components and nitrates/nitrites, and new chemical compounds will be generated; there is uncertainty relating to the effects of these interactions or generated chemical compounds on prion proteins in infected meat (uncertainty). The impact of these processes/products on prion proteins if meat is cured or dried whole or chopped/minced/comminuted such as in sausage production is also uncertain **(uncertainty).**

51. Therefore, if CWD infected cervid meat enters the food chain, conventional food processing methods are likely to have no impact in reducing risk of exposure to CWD prions assuming that these behave in a similar way to other TSE agents **(uncertainty**).

52. Prions are very resistant to most disinfectants and can tightly bind to surfaces such as stainless steel and plastic without losing infectivity (CFSPH, 2016). Therefore, decontamination of areas within abattoirs, butchers' shops, and kitchen surfaces used for food preparation will be extremely difficult if exposure to CWD-infected meat has occurred. Surfaces and utensils used to prepare any infected meat could potentially serve to facilitate cross-contamination either directly or via person to person contact. The possibility of sub-cutaneous infection via handling of infected meat or via aerosols either during processing in abattoirs and butchers shops for example, or in the home or restaurant settings can also not be ruled out (**uncertainty**).

53. Most epidemiologic studies and experimental work have suggested that the potential for CWD transmission to humans is low, and such transmission has not been documented through ongoing surveillance (Saunders *et al.,* 2012).

Hazard Characterisation

<u>Prion diseases</u>

54. Transmissible Spongiform Encephalopathies (TSEs), or prion diseases including CWD, are a class of fatal and progressive neurodegenerative disorders affecting humans and animals, characterised by long incubation periods, spongiform changes associated with neuronal loss, and a failure to induce inflammatory response (CDC, 2015).

55. The causative agents of TSEs are believed to be prions. The term "prions" refers to abnormal, pathogenic agents that are transmissible and are able to induce abnormal folding of specific normal cellular proteins called prion proteins that are found most abundantly in the brain. Prions are free from nucleic acid content. The functions of these normal prion proteins are still not completely understood. The abnormal folding of the prion proteins leads to brain damage and the characteristic signs and symptoms of the disease. Prion diseases are usually rapidly progressive and always fatal (CDC, 2015). Prion diseases in addition to CWD include, kuru, Creutzfeldt-Jakob disease (CJD) and variant CJD. Humans and animals can potentially acquire TSEs by consuming prion-contaminated food.

56. Prion diseases are mostly but not fully controlled by a single gene that encodes the normal prion protein, PrP which is present in many tissues and at high levels in brain tissue. There is a substantial amount of research investigating the function of PrP (VKM, 2017). In prion disease, protein aggregates form which contain multimeric abnormal, misfolded PrP (PrP^{Sc}) The three-dimensional structure of PrP^{Sc} is significantly different to normal prion protein despite the same primary structure (VKM, 2017). Brandner *et al.,* 1996 demonstrated that transgenic mice which had the gene encoding prion protein (*Prnp*) inactivated, were resistant to prion disease, showing that endogenous *Prnp* is essential for disease development and progression in mice (VKM, 217).

57. Misfolding of normal PrP is directed by prions with molecular precision and in this way, misfolding can be spread within the host. When disease-causing prion templates are introduced into a healthy host, the process of misfolding can begin and there is potential to cause deadly prion disease (VKM, 2017). During TSE pathogenesis, the soluble, protease sensitive form of PrP is refolded and converted into an insoluble protease-resistant form. The latter has the same primary sequence as the normal protein but a different secondary structure. The protease sensitive normal form is higher in α-helical content and the protease resistant form is higher in β-sheet content (Moore *et al*., 2009).

58. Outbreaks of prion disease include an epidemic of kuru among the cannibalistic Fore tribe of the New Guinea highlands and an epizootic of BSE in the UK, caused by feeding protein supplements derived from prion-infected cattle offal to cattle. Food-based prion transmission between species also occurs, although a phenomenon known as the "species barrier" decreases transmission efficiency. *In vitro* studies

indicate that this natural barrier reduces human susceptibility to animal prion diseases, including CWD. Several epidemiologic studies provide evidence that, to date, CWD has not been transmitted to humans (CDC, 2015) Further details will be discussed in the below sections.

Clinical signs of CWD in cervids and contamination of edible tissues

59. The clinical signs of CWD in affected adult cervids are weight loss and behavioural changes spanning weeks or months. Additional signs could include excessive salivation, behavioural alterations including a fixed stare and changes in interaction with other animals in the herd and an altered stance (DEFRA, 2017, Williams, 2005). These signs are not distinguishable from cervids experimentally infected with BSE; therefore if CWD was to be introduced to the UK, infected deer populations would require testing to differentiate if they were infected with BSE or CWD to minimise the risk of BSE entering the food-chain through infected venison (DEFRA, 2017).

60. Clinical disease duration in cervids is very variable and death can occur within four weeks of onset though some infected animals can survive up to a year. Incubation periods range from a minimum of 16 months but are more likely to be between 2 and 4 years. Animals remain infectious during the pre-clinical period (DEFRA, 2017). This may be of particular relevance if there are opportunities for infected asymptomatic animals to enter the food chain as discussed in paragraph 32.

61. The CWD agent or prion protein (which can also be referred to as PrP^{CWD}) is first distributed in the gut associated lymphoid tissues, digestive tract for example tonsils, Peyer's patches, mesenteric lymph nodes and then in the brain and spinal cord as disease progresses (DEFRA, 2017, Sigurdson *et al*., 2008).

62. Given that CWD prions can be distributed almost ubiquitously throughout infected cervids, if CWD were present in the UK, it is possible that all edible cervid tissue from infected animals could contain CWD prions. Given that the evidence in the literature indicates that there is a strong species barrier to CWD prions causing infectivity for humans (discussed in more detail below), it is reasonable at this stage to assume that the disease will not be easily transmitted to humans, though some of the uncertainties around this will be further discussed below. As the disease has been found in Norway and USA, these populations would be sentinels for human disease, ahead of the UK.

63. The atypical CWD prion strain may be more localised to the brain and CNS tissue but it is uncertain whether this strain is capable of infecting UK cervid species.

Transmission of CWD to non-cervids, the species barrier effect and implications for human transmission

64. Prions are generally species-specific pathogens and have limited ability to move between different species under normal, non-experimental conditions. However, prions do display some structural plasticity and may adapt during propagation in a new host, such as reindeer or moose (VKM, 2017).

65. CWD has been experimentally transmitted via the intracerebral route to a large number of different mammals including sheep, goats, cattle, N. American non-laboratory rodents, cat, ferret and the non-human primate squirrel monkey (VKM, 2016). Following the initial transmission of CWD to squirrel monkey (*Saimiri sciureus*), a broader study was conducted comparing oral and intracerebral inoculation and also involving cynomolgus macaques (*Macaca fasicularis*) which are related more closely to humans. This study confirmed the susceptibility of squirrel monkey to CWD after intracerebral inoculation (80% of the animals developed clinical signs) whereas after oral exposure, 15% of squirrel monkeys developed the disease. Regardless of inoculation route, none of the macaques developed disease and even after 70 months post-inoculation remained healthy (VKM, 2016). Oral transmission to the mammalian squirrel monkey may be worthy of note.

66. A systematic review on the transmissibility of CWD prions to humans was carried out by Waddell *et al*., 2017. These authors screened 800 citations from the literature and evaluated seventy eight full papers before including twenty-three studies for consideration. Five epidemiological studies, two studies on cynomolgus macaques and seven studies on humanised transgenic mice (mice expressing human prion protein were challenged with a CWD prion source) provided no evidence to support the possibility of transmission of CWD prions to humans and evidence that the transmission barrier associated with the interaction of human PrP and CWD prions is fairly strong. The review also highlighted that ongoing surveillance in the United States and Canada has not documented CWD transmission to humans. However, two studies on squirrel monkeys provided evidence that transmission of CWD prions resulting in prion disease is possible in these monkeys under experimental conditions and seven *in vitro* experiments provided evidence that CWD prions can convert human prion protein to a misfolded state, although less efficiently than other prions and in some cases only after some protein modification by denaturation. Therefore, the authors concluded that future discovery of CWD transmission to humans cannot be entirely excluded on the basis of current studies, especially because it is possible that the incubation period for humans could be decades **(uncertainty).**

67. An important factor to consider in terms of disease transmission is human susceptibility. Polymorphisms at codon 129 of the human prion protein gene appear to be important (Gale *et al*., 1998), though there is **uncertainty** whether this is the case for CWD transmission to humans. Wild-type human PrP has two common allelic forms that encode either methionine (hu-M) or valine (hu-V) at codon 129. This human codon (No. 129) corresponds to a polymorphic codon (No. 132) of elk (Raymond *et al*., 2000). Gale *et al.,* 1997 reported that, evidence suggests that humans homozygous for huPrP-met are the most sensitive genotype to BSE prions. Raymond *et al*. (1997) have shown *in vitro*, that huPrP-met is converted by BSE prions PrP^{BSE}, into abnormal PrP approximately threefold more efficiently than huPrP-val.

68. One of the *in vitro* studies mentioned in paragraph 62 above, conducted by Raymond *et al.,* 2000 demonstrated that the abnormal CWD PrP of cervids readily induces the conversion of recombinant cervid PrP-sensitive molecules to the protease-resistant misfolded state and this is in line with the known transmissibility of CWD between cervids. In contrast, PrP^{CWD}-induced conversions of human and bovine PrP-sensitive protein were much less efficient. The efficiencies of the human PrP-sensitive conversions were >14-fold lower than the inter-cervid conversion reactions and >5-fold weaker than the homologous conversion reactions induced by human PrP-res from the brains of CJD patients homozygous for hu-M or hu-V PrP. These results according to the authors provide evidence for very weak compatibility between PrP^{CWD} and human PrP-sensitive molecules in conversion reactions. The authors concluded that the results demonstrate a barrier at the molecular level that should limit the susceptibility of these non-cervid species to CWD.

69. Kurt *et al*., 2015 investigated PrP sequence determinants that affect CWD transmission to humans. The authors reported that it appears that a strong species barrier for humans to CWD prions exists, and the β2-α2 loop sequence of human normal PrP appears to offer a major barrier to PrP conversion by CWD prions. Although the amino acid residues of the prion protein (PrP) that prevent or permit human CWD infection are unknown, the authors stated that NMR-based structural studies suggest that the β2-α2 loop (residues 165–175) may have an impact on the species barrier. The authors reported that engineered transgenic mice expressing human PrP with four amino acid substitutions that result in expression of PrP that exactly match that of elk PrP in the β2-α2 loop (residues 165–175) compared with transgenic mice expressing unaltered human PrP were highly susceptible to elk and deer CWD prions but were at the same time, less susceptible to CJD prions. Testing other human-cervid residue differences *in vitro* revealed that only two residues 143 and 155 had a further impact on human PrP conversion by CWD (Kurt *et al*., 2015).

70. CWD transmission to humans has not been documented through ongoing surveillance and most experimental work suggests that the

potential for transmission of CWD to humans is low. Interspecies transmission of prion diseases often shows a species barrier effect where transmission is less efficient compared with intraspecies transmission which manifests in lower attack rates and extended incubation periods. The species barrier effect is associated with minor differences in normal PrP sequence and structure between the host and target species. Prion strain and route of inoculation also affect the species barrier; for example, interspecies transmission via intracerebral inoculation is often possible but oral challenge is ineffective (Saunders *et. al*., 2012). In general, this so-called 'species barrier' is removed after a few subpassages (usually 2–3) of the prion in a new host, reflecting prion adaptation to its new host (Beringue *et al*., 2008).

71. Although at present there is little evidence that CWD prions could be transmitted to humans and cause disease, some researchers hypothesise that a CWD prion more readily transmissible to humans could emerge over time given sufficiently extensive human exposure (Waddell *et al.,* 2017). Given that it is possible that some prion diseases have an incubation period of decades (approx. 50 years for Kuru for example) there is **uncertainty** about the significance of lack of reported human transmission at present.

72. One study conducted by Czub *et al*., 2017 at the Canadian food inspection agency was presented at the May Prion 2017 conference in Edinburgh (Abstract available) and may highlight that there could be some uncertainty around the human species barrier effect. The study challenged Cynomolgus macques with characterised CWD-infected deer or elk material from naturally infected animals by intracerebral, oral (gavage) and skin exposure routes. Although incomplete, the study showed that disease transmission could occur via the oral (gavage) administration route. While previous studies have reported that macaques were unable to be infected with CWD, this work provides evidence to suggest that under appropriate conditions infection can result. Macaques are more closely related to humans genetically than other primates such as squirrel monkeys and the study is an important advance in potentially demonstrating that the human species barrier to CWD prions could be breached under the appropriate conditions **(uncertainty)** and that consumption of meat from cervids can induce CWD**.** The study is work in progress and it is possible that very high doses of prion were experimentally administered and how these might compare with levels ingested by humans under more natural conditions from eating infected meat is not clear **(uncertainty).** What may be important is that the administration route by-passed tonsils and contact with mucosal membranes which would possibly facilitate oral transmission and nonetheless resulted in oral transmission. The full publication of this paper and more details relating to the experiment will help to address the uncertainty on the significance of this finding.

73. While an infectious dose of CWD prions (if any) for humans via any transmission route has not been established given a lack of evidence

for human transmission, it may be useful to consider human oral infectious doses for other prions. The oral/intragastric route of infection is less efficient than the intracerebral and intraperitoneal routes (Gale *et al*., 1998). The oral route is approximately 100 000 fold less efficient for transmission of BSE to mice for example (Gale *et al*., 1998). Gale *et al*., 1998 while investigating water-borne transmission of BSE to humans, calculated the human oral ID_{50}[3] to be 10^{13} PrP^{BSE} molecules and reported that 1 g of brain from a confirmed bovine would contain approximately 10^{13} BSE prions. Compared with conventional water-borne pathogens (which were the scope of the authors' work), BSE transmission to humans requires a large number of particles. For comparison, the ID_{50} for calf *Cryptosporidium parvum* in humans is about 150 oocysts and for *Giardia lamblia*, the ID_{50} is about 35 cysts. Food matrices may also impact on exposure.

74. However, Gale *et al.,* 1998 using low dose extrapolation, calculated the risks of BSE infection from ingestion of fractions of an oral ID_{50}. The authors calculated that the risk to human health from lower doses are very small and a minute but finite risk is associated with a dose of a single PrP^{BSE} molecule. However, given the uncertainty relating to CWD prion distribution and titres in cervids through disease progression, or any literature around infectious dose for humans via ingestion, there is considerable **uncertainty** whether the infectious dose of CWD prions via ingestion would be similar to BSE prions and **uncertainty** relating to incubation period (if any) for humans. The authors calculated the overall risk of BSE infection from drinking water to be remote but factors specific to an aquatic environment such as environmental dispersion and dilution of prions were considered in this estimation.

75. As CWD has not been reported in humans yet, there is **uncertainty** relating to the fate of ingested CWD prions in humans or their ability to cause disease. Prion distribution in humans can vary depending on the TSE. For variant CJD and other human TSEs, brain, spinal cord, retina, spinal ganglia, pituitary gland attain a high titre of infectivity in the later stages. For other tissues which can be considered as lower infectivity tissues, distribution is more variable. For variant CJD, PRP^{TSE} can be detected in lymph, tonsils, jejunum, ileum, large intestine, lymph nodes and blood while this is not the case for other human TSEs (Brown and Abee, 2005).

<u>Current evidence investigating CWD prion exposure and development of a prion disease in humans</u>

76. Five observational studies conducted in the USA between 1979 and 2011 examined the association between CWD exposure and human disease. Waddell *et al*., 2017 reported that none of these studies found

[3] ID_{50} - The infective dose that will cause 50% of exposed individuals to become ill.

an association between exposure to CWD and development of a prion disease.

77. One of the studies mentioned above was conducted by Olszowy *et al.,* 2014. This was a six year follow up study on eighty one individuals exposed to CWD positive venison served at a sportsman's feast in the USA in 2005. No CJD or related diseases were reported in this group of hunters. This incident remains the only known large-scale point-source exposure to a CWD infected deer according to the authors. The authors reported that prion diseases can incubate for multiple decades before the manifestation of clinical symptoms; therefore, continued surveillance of this exposed study population represents a unique opportunity to assess the risk of CWD transmission to humans.

78. Another of the above studies was reported by Belay *et al*., 2001 and investigated reports of three unusually young patients with CJD who regularly consumed deer or elk meat which prompted the authors to examine the possible transmission of CWD to humans. Medical records were examined, family members and state wildlife and agriculture officials were interviewed. Brain tissue samples were tested using histopathologic, immunohistochemical, immunoblot, or prion protein gene analyses. The authors reported that although the occurrence of three unusually young patients with CJD who consumed venison suggested a possible relationship with CWD, the follow-up investigation found no strong evidence for a causal link.

79. The Centres for Disease Control and Prevention in collaboration with Wyoming Dept. of Health, Colorado Dept. of Public Health and Environment and Wisconsin Dept. of Health Services assessed CJD incidence in deer and elk hunters by cross-checking information about these hunters with mortality data. Belay *et al*., 2015 presented this work at the Prion 2015 conference. In Colorado, about 1.2 million hunters were represented between 1995 and 2011, in Wyoming, between 1996 and 2013 about 0.6 million hunters were represented. During this time, eleven Colorado hunters and four Wyoming hunters were identified to have died from CJD. In Wisconsin, four hundred hunters who had consumed venison from CWD positive cervids have been enrolled for a follow-up. The group concluded that the study showed that CJD incidence among hunters in Colorado and Wyoming is not higher than expected and these data together with the data from hunters who had consumed CWD-positive venison are valuable for monitoring CWD transmission to humans (Prion 2015 conference abstract).

80. There is also **uncertainty** around whether transmission of CWD to humans would be detected adequately if it occurred. For example, clinical and pathological signs may/may not appear to differ to different forms of CJD, testing methodology is not distinguished enough at present to address these questions except for laborious and costly

transgenic mouse studies. Additionally, as with BSE, zoonotic transmission of CWD may be detected more easily when a cluster of unusual cases such as young individuals showing symptoms, unusual brain tissue pathology are presented. (E. Belay, CDC, personal communication).

Ongoing human surveillance in the USA

81. In Wisconsin USA, there is an ongoing programme gathering data on hunters. Hunters are encouraged to submit heads from hunted cervids for testing with a view to consuming the animals only after CWD negative results are obtained. However, it has been evident that some hunters do consume the animals without confirmation of negative results. If this scenario occurs and subsequent results are confirmed CWD positive, the information is added to a database; approximately 500 hunters and families that fall within this scenario have been added to the database to date. Data are still being collected and could provide some invaluable information in a decade or more. (E. Belay, CDC, Personal communication). Additionally, with hunters, it may be difficult to separate direct occupational/hobby exposures from foodborne ones.

Genetic susceptibility of cervids to CWD, prion strains and prion disinfection

82. The main principle of prion protein propagation is that misfolding of normal cellular PrP (the substrate) results in accurate copying of the incoming aggregated PrP structures that constitute the prion agent, named the prion template (VKM, 2017). If the PrP structure fits readily into the abnormal PrP structure the misfolding process occurs efficiently and disease progresses rapidly. If the substrate does not fit well into the aggregated template, the process is inefficient and disease development is blocked or slower.

83. A one amino acid residue difference between substrate PrP and template prion can be sufficient to influence the prion replication. Mammalian prion protein genes are conserved amongst mammals but there is some genetic variation between species and within species. For example, there is a slight difference in the human PrP gene compared to the sheep PrP gene and reindeer PrP differs to that of sheep etc. There is a high degree of normal genetic variation in the PrP gene in some mammals such as humans and sheep, leading to several polymorphisms while for cattle there is limited genetic variation. Some of the PrP polymorphisms in cervids are capable of modulating disease susceptibility, though there are no truly resistant phenotypes and this observation relates more to length of incubation period and rate of progression of disease (VKM, 2017).

84. Variation in *Prnp* sequence in deer is limited and has not been observed in roe deer and fallow deer. In elk or red deer (*Cervus elaphus*) amino acid variations at codon 132 appear to play a role in terms of incubation period. Hamir *et al*., 2006 investigated the genetic susceptibility of elk (*Cervus elaphus* nelsoni) with various alleles of the *Prnp* gene, which encodes the normal cellular prion protein, to CWD. The authors dosed eight 8-month old elk calves of 3 genotypes (2 132MM, 2 132LM, and 4 132LL) orally with CWD-infected brain material from elk. Twenty three months after inoculation, both 132MM elk had lost appetite, developed clinical signs of weight loss and central nervous system (CNS) dysfunction, and were euthanised. Two other elk (both 132LM) developed similar clinical signs of disease and were euthanised during month post-inoculation month forty. All four affected elk had microscopic lesions of spongiform encephalopathy and the disease-associated form of the prion protein, was detected in their CNS and lymphoid tissues. The authors concluded that elk with MM and LM at codon 132 are susceptible to orally inoculated CWD prions. All four LL elk were reported to be alive at year four post-inoculation and were clinically normal. The authors suggest that 132LL elk may have reduced susceptibility to oral infection with CWD-infected material or may have prolonged incubation time.

85. There is little known about *Prnp* variants in the UK deer species (uncertainty) though ongoing studies will yield more information. Prion replication occurs with high fidelity but several PrP aggregates can be formed and some can differ slightly from the bulk of protein conformers. In subsequent serial passages of the prion in the same host, the dominant structural conformer will be propagated which will also usually be when transmission to a new host occurs. If by chance however, a minor structural component of the prion isolate propagates more efficiently in a new host, this structural conformer would then emerge as the new dominant prion form after passage into the new host. This appears to be the basis of strain mutation in prion diseases, providing a way in which prions may adapt to new hosts and give rise to new strains (VKM, 2017).

86. Current data suggest that there are two different strains of CWD in Norway, the strain that affects moose appears unusual and may be a novel CWD strain while the reindeer strain appears very similar if not identical to that previously recognised in N. America (VKM, 2017).

87. At present there is no evidence that the N. American and Norwegian CWD strain has infected humans. However, indirect experimental work (*in vitro* conversion studies and a recent feeding study with macaques) could imply the species barrier for humans could be breached under certain conditions and that there is uncertainty relating to the incubation period (if any) required for CWD to manifest in humans following exposure to infected cervid meat or products via ingestion or handling of meat but also possibly via inhalation of aerosolised meat during processing. The distribution of the atypical CWD strain is likely to be

more localised to CNS tissue but there is even less information on behavioural characteristics of this strain **(uncertainty)** and a lack of data relating to prevalence in cervids and human surveillance **(uncertainty).**

Prion disinfection

88. As previously discussed, prions are resistant to most conventional treatments that inactivate pathogenic microorganisms, including heat. Prions are also resistant to disinfectants including alcohol and formalin and to UV radiation, microwave irradiation and ionising radiation (CFSPH, 2016). Prion resistance is even more apparent when prions are protected in organic material or when titres are high. Autoclaving at higher temperatures and pressure (134°C at 3 atm pressure for 1 h) and chlorine (> 1 ppm) and sodium hydroxide (> 1N) solutions and other chemical agents with strong protein denaturing properties will give significant inactivation of prions (VKM, 2016)

89. Cervids are exposed to infectious prions via saliva, urine, fomites such as soil particles. Johnson *et al*., 2007 showed that oral transmissibility of prion disease is enhanced by binding to soil particles. Food matrices may also be protective for prions.

Risk Characterisation

90. *The following factors have been considered in evaluating the risk of developing chronic wasting disease from eating (and handling) cervid meat infected with CWD prions and atypical CWD prions:*

- Exposure to CWD prions via food could potentially occur through consuming meat, meat products such as sausages, offal, pies or tissues from infected deer or via handling of infected deer and parts during processing. However, the extent of exposure via more unusual pathways such as ingesting antler velvet or powdered deer horn which are not legally permitted in the EU is difficult to determine **(uncertainty).**

- Robust information relating to susceptibility of certain UK deer species to CWD is lacking for example for Roe deer and Chinese water deer **(uncertainty)** so on the basis of current scientific understanding, it is likely that given exposure to an infectious dose of CWD, most UK deer species apart from Fallow deer could become infected **(uncertainty).**

- While CWD has not been reported to occur in Europe outside Norway, improved surveillance may provide more information. The extent of CWD in the cervid population of Norway and other EU countries remains uncertain **(uncertainty).** In December 2016, at the request of the EU Commission, EFSA proposed a three year

surveillance system differing for farmed and wild or semidomesticated cervids, with two stages of sampling (random sampling of cervids and sampling targeting high risk animals). The surveillance is proposed for Estonia, Finland, Iceland, Latvia, Lithuania, Norway, Poland and Sweden and will consider seven wild, semidomesticated and farmed cervid species (Eurasian tundra reindeer, Finnish (Eurasian) forest reindeer, moose, roe deer, white-tailed deer, red deer and fallow deer) (EFSA, 2016).

- The likelihood of importing a TSE into the UK deer herds from Norway via all possible pathways and causing infection in British deer is **uncertain** but likely to be no greater than very low.

- CWD is readily transmitted amongst cervids with little or no barriers between species (though in Norway, the reindeer and elk (moose) cases were some distance away and the hazards appear different) however, evidence suggests that transmission of CWD to other food producing animals such as sheep or cattle is very unlikely.

- It is unclear at this stage whether the atypical CWD strain identified in Norwegian moose is capable of infecting UK cervids **(uncertainty).** The Norwegian moose species infected by this strain is not present in the UK except as part of animal collections in a zoo environment or managed collections for example.

- In the UK, a significant amount of UK produced cervid meat enters the food chain, mainly wild deer but also farmed deer; all UK deer species can enter the food chain. A steady but varying amount of cervid meat also enters the UK from other EU countries and data since 2012 have been considered in the assessment. Approx. 116kg was imported from Norway in 2013. There is uncertainty relating to the amount of non-UK cervid meat consumed in the UK. Although there have been no reports of CWD in cervids in the EU, improved surveillance would provide further reassurance particularly for Nordic countries.

- Although deer with CWD in advanced stages could be identified by the hunter, the likelihood of identifying suspicion of disease in less advanced cases of wild deer may be weak, including for asymptomatic infected deer. The condition of wild deer carcasses may be variable and the reliability of the hunter's declaration may be limited **(uncertainty)**. For farmed deer, the situation may be simpler and the animals may be better monitored over their lives, improving the likelihood of identifying abnormal behaviour and/or abnormal loss of body condition and farmed deer are subject to official ante-mortem inspection by a vet improving the chances of identifying abnormal behaviour. Nonetheless, the possibility of infected asymptomatic cervids wild or farmed entering the food chain in the UK cannot be ruled out completely **(uncertainty).**

- If CWD were to be present in the UK, it is reasonable to assume that asymptomatic or borderline cervids are more likely to enter the food chain than animals showing clinical signs.

- It is not possible to accurately determine the level of exposure to CWD prions in infected cervid meat **(uncertainty)** and level of exposure will depend on the cervid species and the stage of infection. However, CWD prions have been documented to be present almost ubiquitously throughout diseased cervid hosts including in edible tissues such as muscle, fat, CNS tissue, heart, liver, kidney, tongue and blood. It might be expected that regular consumers or those consuming larger quantities of cervid meat would be most at risk. An infectious dose for cervids has not been established (**uncertainty**)

- While infectious CWD prions have been detected in muscle of infected cervids, there is a lack of information relating to prion titres and distribution in asymptomatic infected cervids which are more likely to enter the food chain than animals with advanced disease **(uncertainty)**. There is a lack of information relating to prion distribution in cervids through disease progression **(uncertainty).**

- The recent case in Norway, a clinically healthy, living reindeer, was detected using samples taking from gut associated lymphoid tissue. This is a new test and is not widely used, but it may point to infection present throughout carcases in healthy animals.

- In some animals CWD prions might replicate in peripheral tissues without reaching the brain and causing clinical disease. This could be of relevance for food chain associated exposure from asymptomatic animals but the extent of this is uncertain **(uncertainty).**

- It is likely that atypical CWD prions are more likely to be localised in and around CNS tissue and not be distributed as widely.

- Ordinary safety nets such as cooking that can reduce exposure to pathogenic micro-organisms for example will not have any effect in reducing exposure to CWD prions in contaminated cervid meat and meat products such as sausages, pies and offal. Processes such as curing and fermenting will also likely be ineffective but there is **uncertainty** on the effects of curing and fermenting on cuts of meat and ground meat. Cross-contamination of utensils and kitchen surfaces may also prove very difficult to prevent if CWD-prion infected meat were to enter the kitchen for preparation as prions are resistant to most disinfectants and can tightly bind to steel and plastic surfaces, possibly providing a reservoir for contamination of other foods and person to person transmission **(uncertainty)**.

Subcutaneous transmission via handling infected meat in a domestic kitchen or restaurant can also not be ruled out **(uncertainty).** Potential transmission via inhalation during meat processing also needs acknowledgement.

- If exposure to CWD-infected meat has occurred, decontamination of areas where handling and processing of the meat may occur is likely to be difficult, including abattoirs, butchers' shops and domestic and catering kitchens.

- The fate of various parts of slaughtered wild deer such as green offal which is often left at the site where the animal is shot and the head in terms of disposal remains **uncertain** and could provide an avenue for introduction of CWD infection into the environment if CWD were present in the UK . Hunters might choose to retain the head of the animal as a trophy for example; this handling and mode of disposal of body parts could facilitate transmission of CWD and environmental contamination if CWD were present in the UK.

- As there is no requirement for the removal of the spinal cord for deer, it is possible this could accompany the carcass for human consumption but this is likely to vary in different plants **(uncertainty).** Doses of prions are likely to be higher in CNS tissues.

- While CWD has been experimentally transmitted to a large number of different mammals, there is as yet no evidence to suggest that non-cervids can be naturally infected. CWD transmission to humans has not been documented through ongoing surveillance and most experimental work suggests that the potential for transmission to humans is **low.** This indicates the presence of a relatively strong species barrier.

- Five observational studies conducted in the USA between 1979 and 2011 examined the association between CWD exposure and human disease. None of these studies found an association between exposure to CWD and development of a prion disease. It is possible that further decades of surveillance will be needed to reduce the **uncertainty** associated with the incubation period (if any) for humans. There is ongoing surveillance in the USA that is likely to provide some very useful information in years to come.

- There is evidence to suggest that the human PrP sequence (particularly at residues 165-175) plays an important role in maintaining the species barrier for CWD to humans and allowing these residues to become more elk or deer like via expression experiments using transgenic mice, renders the transgenic mice more susceptible to PrP conversion by CWD prions.

- Some of the PrP polymorphisms in cervids can modulate disease susceptibility, though there are no truly resistant phenotypes and this observation relates more to length of incubation period and rate of progression of disease There is little known about *Prnp* (the PrP encoding gene) variants in UK deer species **(uncertainty)** though studies are ongoing and should yield more information. Therefore, on the basis of current scientific understanding, it is likely that given exposure to an infectious dose of CWD, most deer species in the UK (possibly minus fallow deer) could become infected with CWD **(uncertainty)**

- However, there is some uncertainty associated with the species barrier effect as highlighted by a recent unpublished study which demonstrated that CWD can be transmitted to Cynomolgus macaques by the oral route (gavage) by administering characterised CWD-infected cervid tissue. While it is likely that the doses administered here were high and it is not possible at present to determine how these doses compare with more natural doses as a result of consumption of infected deer meat, macaques are more closely related to humans genetically than other primates such as squirrel monkeys (which have also been shown to be infected experimentally). The study is an important advance in potentially demonstrating that the human species barrier to CWD prions could be breached under the appropriate conditions. As the study is unpublished it is difficult to know whether there were any design weaknesses and if the experiment is repeatable – peer review will be important **(uncertainty).**

- Seven different *in vitro* experiments provided evidence that CWD prions can convert human prion protein to a misfolded state, although less efficiently than other prions and in some cases only after some protein modification by denaturation. However, how this translates into a more real life scenario remains **uncertain.**

- While there is no direct evidence of transmission to humans at this stage despite ongoing surveillance in exposed populations, transmission of CWD to humans cannot be entirely excluded because it is possible that the incubation period for humans could be decades **(uncertainty).** There is also some uncertainty around whether transmission to humans could be adequately detected at this stage.

- It is not known how susceptible humans are to CWD and there have been no reports of human infection to date and as a result, absence of information relating to a human infectious dose (if any) **(Uncertainty).** While there is good evidence to indicate the presence of a strong species barrier, a small number of studies e.g. the recent study with macaques and various *in vi*tro experiments

indicate that that a negligible risk of transmission cannot assigned at this stage.

Overall risk

87. Taking into account the above components of this assessment and considering the uncertainties that have been flagged; the risk of developing CWD from eating (and handling) cervid meat and products infected with CWD prions is likely to be **very low with a high level of uncertainty**[4].Given the lack of information relating to atypical CWD prions at this stage, it has not been possible to assess the level of risk associated with this hazard, though it is likely that general aspects of prion behaviour might be exhibited such as heat resistance. Numerous key uncertainties have been identified in this assessment and are outlined in **Annex B**. The risk level classification system developed by the European Food Safety Authority (EFSA) has been used to estimate the risk level in this assessment further details can be found at **Annex C**:

Uncertainties
Key uncertainties associated with this assessment are outlined in Annex B.

Annex A
Wild and farmed deer guidance
See attached.

Annex B

Key Uncertainties

Key uncertainties have been identified and grouped together on the basis of themes. At present the uncertainties can be considered as high level.

- **Sources of exposure** - Exposure to CWD prions via food could potentially occur through consuming meat, meat products such as sausages, offal, pies or tissues from infected deer or via handling of infected deer and parts during processing. There is uncertainty relating to more unusual sources of oral exposure and the extent to which these may occur in the UK population such as consumption of unauthorised food supplements (**Exposure assessment**).

[4] The estimation of overall uncertainty is based on current evidence; if further information becomes available; this will be noted and may or may not result in a change to the level of overall risk and uncertainty.

- **Susceptibility of UK deer species** - Robust information relating to susceptibility of certain UK deer species to CWD is lacking for example for Roe deer and Chinese water deer, so it must be assumed that given exposure to an infectious dose of CWD prions, all UK deer species can be infected, though fallow deer appear not to be susceptible (**Exposure assessment**)

- **Presence and prevalence of CWD** - The extent of CWD in the cervid population of Norway remains uncertain though further EU surveillance as proposed by EFSA in 2016 will help to reduce this uncertainty. It is unlikely that CWD is present in the UK, but improved surveillance will reduce this uncertainty (**Exposure assessment**).

- **Introduction of a TSE into the UK cervid population** -The likelihood of importing a TSE into the UK deer herds from Norway and causing infection in British deer is uncertain but likely to be no greater than very low. There is also uncertainty on the likelihood of importing a TSE from other Nordic countries (**Exposure assessment**).

- **Characteristics of atypical CWD prions** - It is unclear at this stage whether the atypical CWD strain identified in Norwegian moose is capable of infecting UK cervids (uncertainty) and there are significant uncertainties relating to the behaviour of this atypical strain, prevalence in cervids and a lack of information relating to human surveillance. The Norwegian moose species infected by this strain, however, is not present in the UK except for example as part of animal collections in a zoo or managed environment (**Exposure assessment**).

- **Lack of robust surveillance** - Improved surveillance would help to reduce the uncertainty relating to the CWD-status of cervid meat in the UK , EU and Norway. While CWD has not been reported in the UK or EU, improved surveillance would provide increased reassurance. There is uncertainty around the amount of non-UK cervid meat consumed in the UK but it is likely to be small compared to UK production (**Exposure assessment**).

- **Reliable detection of infected cervids if CWD were to be present in the UK**- Although wild deer with CWD in advanced stages could be identified by the hunter, the likelihood of identifying disease in less advanced cases of wild deer may be weak, including for asymptomatic infected deer. The condition of wild deer carcasses may be variable and the reliability of the hunter's declaration may be limited. While the situation for farmed deer may provide more reassurance, the possibility that asymptomatic infected cervids (farmed or wild) could enter the food chain if CWD were to be present in the UK cannot be completely ruled out. Other less mainstream routes of exposure may also occur such as consumption of cervid meat from road kill and there is uncertainty whether infected cervids could enter the food chain via this route (**Exposure assessment**).

- **An infectious dose for cervids** or other animal species has not been established (**Hazard Characterisation**).

- **Exposure to CWD prions via infected meat from asymptomatic cervids** - At present, it is not possible to accurately determine the level of exposure to CWD prions in infected cervid meat and level of exposure will depend on the cervid species and the stage of infection. However, CWD prions have been documented to be present almost ubiquitously throughout diseased cervid hosts including in edible tissues such as as muscle, fat, CNS tissue, heart, liver, kidney, tongue and blood. While infectious CWD prions have been detected in muscle of infected cervids, there is a lack of information relating to prion titres and distribution in asymptomatic infected cervids which are more likely to enter the food chain than animals with advanced disease. There is a lack of information relating to prion distribution in cervids through disease progression. In some animals CWD prions might replicate in peripheral tissues without reaching the brain and causing clinical disease. This could be of relevance for food chain associated exposure from asymptomatic animals but the extent of this is uncertain (**Exposure assessment**).

- **Cervid CNS material entering the food chain**- As there is no requirement for the removal of the spinal cord for deer, it is possible this could accompany the carcass for human consumption but this is likely to vary in different plants. Doses of prions are likely to be higher in CNS tissues (**Exposure assessment**).

- **Cervid genetic susceptibility** - Some of the PrP polymorphisms in cervids can modulate disease susceptibility. There is little known about *Prnp* (the PrP encoding gene) variants in UK deer species though studies are ongoing and should yield more information (**Hazard characterisation**).

- **Potential for cross-contamination-** While conventional processes such as cooking, curing and fermenting (uncertainty on effects of prions during curing and fermenting for cuts of meat and ground meat), drying and freezing will have little or no effect on reducing exposure to CWD prions, there remains uncertainty about the potential for cross-contamination as a result of infected cervid meat entering the domestic and catering environments and in slaughterhouses. Cross-contamination of utensils and kitchen surfaces may prove very difficult to eliminate if CWD-prion infected meat were to enter the kitchen for preparation as prions are resistant to most disinfectants and can tightly bind to steel and plastic surfaces, possibly providing a reservoir for contamination of other foods and person to person transmission. Subcutaneous transmission via handling infected meat in a domestic kitchen or restaurant can also not be ruled out (**Exposure assessment**).

- **Potential for environmental contamination** - The fate of various parts of slaughtered wild deer such as green offal which is often left at the site where the animal is shot and the head in terms of disposal remains uncertain and could provide an avenue for introduction of CWD infection into the environment if CWD were present in the UK (**Exposure assessment**).

- **Transmission of CWD to non-cervids and humans** - While CWD has been experimentally transmitted to a large number of different mammals, there is as yet no evidence to suggest that non-cervids can be naturally infected. CWD transmission to humans has not been documented through ongoing surveillance and most experimental work suggests that the potential for transmission to humans is low, as such there is uncertainty relating to the infectious dose for humans (if any). This indicates the presence of a relatively strong species barrier. While there is no direct evidence of transmission to humans at this stage despite ongoing surveillance, transmission of CWD to humans cannot be entirely excluded because it is possible that the incubation period for humans could be decades. There is also uncertainty relating to human genetic susceptibility to CWD and the fate of ingested CWD prions in humans (**Hazard characterisation**).

- **Detection of CWD in humans**- There is also uncertainty around whether transmission of CWD to humans would be detected adequately if it occurred **(Hazard characterisation).**

- **Strength of the species barrier** - While there is good evidence to indicate the presence of a strong species barrier, a small number of studies e.g. the recent study with macaques and various *in vitro* experiments indicate that that a negligible risk of transmission cannot be assigned at this stage. Seven different *in vitro* experiments provided evidence that CWD prions can convert human prion protein to a misfolded state, although less efficiently than other prions and in some cases only after some protein modification by denaturation. However, how this translates into a more real life scenario remains uncertain**.** The recent unpublished macaques study also provides some evidence that the species barrier may be breached under certain conditions, though the full relevance of this study will become more apparent when full details are published (**Hazard characterisation**).

Annex C: Risk estimation

Risk Level Classification

Probability Category	Interpretation
Negligible	So rare that it does not merit to be considered
Very Low	Very rare but cannot be excluded
Low	Rare, but does occur
Medium	Occurs regularly
High	Occurs very often
Very High	Events occur almost certainly

Table from EFSA (2006) modified from OIE (2004)

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