Alliance for Public Wildlife

Living Legacy White Paper

The Challenge of CWD: Insidious and Dire

Only immediate action will avoid catastrophic outcomes

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Executive Summary

We have a problem. A big problem. Chronic Wasting Disease (CWD), a sister to BSE or 'mad cow,' is threatening our deer and elk. Unfortunately, CWD has broad implications. Without immediate action, we are heading for worst cases outcomes that include severe population impacts, extinctions, crashing economies, and, although unlikely, potential transfers of CWD to people.

Chronic Wasting Disease is an incurable, always fatal degeneration of the brain. Technically, it's a Transmissible Spongiform Encephalopathy (TSE), but there are a number of quite different versions, depending on species. They include in humans kuru and fatal familial insomnia, as well as some with even more unpronounceable names, such as the dreadful human Creutzfeldt-Jakob Disease (CJD) and Gerstmann–Sträussler–Scheinker Disease (GSS). The largest TSE epidemics have been in domestic or captive animals: such as Scrapie in domestic sheep, Bovine Spongiform Encephalopathy (BSE), or so-called 'mad cow' disease, Transmissible Mink Encephalopathy (TME) on mink farms, and CWD in captive deer and elk.

CWD emerged as a particular nasty variant, because it can be transmitted by body fluids of infected animals (urine, feces, and saliva). Unlike BSE, CWD is highly contagious and can spread to and through wild ungulate herds. The infective agents are mis-folded proteins called prions; they are virtually indestructible, can persist in the environment, and tiny quantities can transmit the disease. Prion diseases have repeatedly jumped species barriers—most alarmingly in the United Kingdom, when BSE-infected beef killed 229 people.

As CWD spread, naturally and through trade, the U.S. in 2001 officially declared a "State of Emergency." Every factor has since gotten worse. It has now been confirmed in 24 US states, 3 Canadian provinces, South Korea, and recently in Norway. Field studies are confirming potentially severe impacts on wildlife populations. So far no transmission to humans has been documented, but the risk is not zero. Non-human primates and transgenic (humanized) mice have been infected. In many jurisdictions, a lack of awareness and availability of free, rapid, and convenient testing of harvested deer has led to significant level of human exposure. Estimates show 7,000 to 15,000 CWD-infected animals are being consumed by hunter families every year, and this number continuing to rise by as much as 20% per year.

The combination of threats is sobering. CWD has been shown to persist and remain infectious in the environment, including in clay-based soils that can dramatically increase infectivity (up to 680 times). Decomposing carcasses create contaminated "super-sites." Prions are extremely resilient, known to resist disinfectants, alcohol, formaldehyde, detergents, protein enzymes, desiccation, radiation, freezing, and incineration >1100°F. Facilities infected with CWD have resisted all efforts at removing the infective agent. Canadian officials report that even on premises thought to be very low risk, restocking with healthy animals led to a 50% re-occurrence of CWD.

Transmission occurs animal to animal, soil to animal, mother-to-offspring, and from exposed plants or other surfaces including tools or surgical instruments (even autoclaving is ineffective). Now there is evidence the infective agent is taken up via the root systems of plants growing in contaminated soils, with transfer to stems and leaves. These were shown to be infective via inter-cerebral injection (oral tests are ongoing).

Left unchecked, the prospects for wildlife are bleak. CWD has clear population impacts; some models suggest extinction. Disproportionate impact on mature males carries implications for hunters and wildlife economies let alone populations. Still more bad news: Efforts for vaccines have failed, and evolutionary or adaptive salvation is unlikely and would be too late in any case. CWD is now deemed to be the largest-ever mass of infectious prions in global history, and experts sum up the threat (to wildlife, agriculture, our economies, and potentially to human health) in two words: "insidious and dire." Current policy and apathy toward the levels of CWD consumption by people has been described as "one of the most outrageous human susceptibility experiments in history."

The good news

There is, of course, much more—but we need to get to the good news: There is hope, beginning with the fact that CWD is relatively new—not a long-standing or indigenous disease of our wildlife. The vast majority of our herds are still disease-free. We have considerable expertise, leading-edge technologies, and the benefit of experience. We faced a crisis on this scale once before, almost exactly a century ago, when the very existence of wildlife on this continent was threatened by the severest of over-exploitation. Hunters and conservation organizations led the efforts to avert disaster. With the courage and foresight of presidents and prime ministers enlisting the best and ablest on both sides of the US/Canada border to enact science-based policies, they turned our greatest tragedy into a 'triumph of the commons.' Anchored in the public trust doctrine, and now recognized as the North American Model of Wildlife Conservation, it replenished an entire continent with wildlife.

We need, today, nothing less than a similar effort to manage the Chronic Wasting Disease crisis. We have the benefit of experience and principles for success. Following the Roosevelt Doctrine, the same concerned hunter and conservation organizations must once again be the standard-bearers of principled, science-and evidence-based leadership in wildlife conservation. We must be relentless in following the leading science and scholarship, tracking the evidence, and engaging in comprehensive analysis to foresee the implications. We understand how policies affect the spread of diseases, as documented in the scientific and historical record summarized below. This threat is dire, and immediate action is warranted.

While details and methods must be guided by science and evidence, there is significant agreement on critical needs; and we have assurances from leading experts and labs that we have the capacity to meet this challenge. We must secure mandate and funding to:

1. Contain the geographic spread of CWD by enacting and enforcing an immediate ban on the movement of all live cervids, all potentially CWD-infected carcasses, animal parts, products, exposed equipment, trailers, or other sources of infectious materials.

2. Mandate and implement for hunters, convenient, cost-free, rapid testing of all animals harvested from CWD-affected areas.

3. Ensure that no CWD-infected material reaches the food or feed chains, and that it is instead properly disposed of.

4. Establish and fund accountable research and science-based policy to protect public interest (health, wildlife and related industries, agriculture, our economies and communities).

The issues are numerous, serious, and complex, but complacency is not an option. The sooner we act, the greater the prospects to protect our greatest living legacy. Further details, discussion, citations, and scientific references follow.

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"The emergence of chronic wasting disease affecting mule deer, white-tailed deer, and elk is arguably the most important issue in the management of free-living cervids in North America."

Expert Scientific Panel, 2004

Chronic Wasting Disease

Facts, Evidence, Implications, Urgency, and Actions Needed

Fundamentals

Chronic Wasting Disease (CWD), a sister disease to Bovine Spongiform Encephalopathy (BSE), or 'mad cow' disease, is a misfolded protein or 'prion' disease[1] first observed and documented in captive mule deer in the late 1960s.[2] It is in the group of diseases known as Transmissible Spongiform Encephalopathy (TSE) and has now been confirmed in at least six species of deer.[3]

TSEs have repeatedly emerged and all of the largest epidemics have been documented in domestic or captive animals. These include scrapie in domestic sheep, Bovine Spongiform Encephalopathy (BSE) in domestic cattle, Transmissible Mink Encephalopathy (TME) on mink farms, and CWD in captive deer and elk. CWD seems unique in having established reservoirs and significant prevalence in wild species.

The origin of CWD is not definitively known, and may never be solved. It most likely is a conversion from the one prion disease known to have direct contact with deer and which it most closely resembles: scrapie —the similarly contagious version in domestic sheep.[4]

Leading experts Beth Williams, Tom Thorne, and Michael Miller postulated that: *"It is possible, though never proven, that deer came into contact with scrapie infected sheep either on shared pastures or in captivity somewhere along the front range of the Rocky Mountains, where high levels of sheep grazing occurred in the early 1900s. In addition, laboratory tests suggest that there is less of a species barrier to TSE transmission between deer, elk, and sheep, than between these and either cattle or humans."*[5] This is further supported by evidence that deer are susceptible to scrapie.[6]

"The epidemiology of CWD is most compatible with a single strain that originated in mule deer and then infected elk and white-tailed deer."[7] *"Spread (of CWD) has followed natural migration of deer and been (vastly) extended due to human intervention and trade."*[8].

Origin vs Novelty

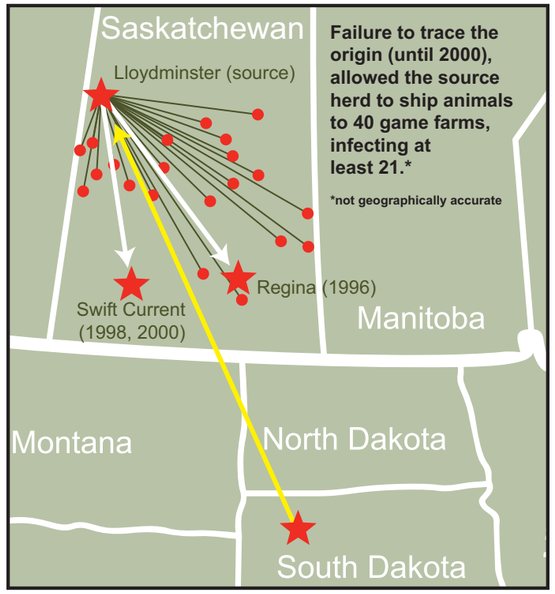
While we want to know the details of CWD's origin, a more important question is whether it is a new disease, or has been around longer. Ascertaining whether a disease is newly emerged, or has long been present is key to establishing epidemiologic characteristics, threat profiles and critical measures to protect public interest.[9] Diseases that have long been present in indigenous North American wildlife have typically been documented with evidence of scale, impacts, cycles, and relative risk patterns. On the other hand, newly emerged or introduced diseases—or new, significantly evolved versions of old pathogens—present uncertain risk to populations, to other species, to ecosystems, and to economies.

After CWD had been confirmed as a TSE in 1978, three generalized origin or novelty scenarios seemed plausible.[10] First, though considered highly improbable by even the early 1990s, was a possibility that CWD was an unrecognized, rare, but longstanding disease of North American wildlife, persisting at very low levels, without obvious or serious impacts. Second, that CWD recently and spontaneously emerged in deer, similar to sporadic variant Creutzfeldt-Jakob Disease (CJD) in people, where the cause or trigger is unknown. Third, that it may have been recently introduced from a non-indigenous prion disease like scrapie that, through unknown means transferred from domestic sheep or goats to establish as CWD in deer.[11]

By 2005, based on extensive documentation of presence (or absence), growth, spread, and persistence, it had become clear that CWD could not possibly be a longstanding disease of North American deer.[12] Nevertheless, given the profound role of this question in public policy, and given some lingering advocacy presuming the contrary,[13] further explanation is warranted.

As detailed below, extensive evidence has shown CWD to be highly contagious and laterally transferable between living animals. CWD prions have been shown to persist and remain highly infectious in soils, on plants or other surfaces. Once established, CWD exhibited a consistent pattern of growth, spread, and persistence. By 2001,

consistent with the observed growth in prevalence and the invariably fatal nature of the disease, indications pointed to serious population impacts. Three of the leading CWD researchers stated: *"Modeled CWD epidemics failed to achieve a steady-state equilibrium in infected deer populations, suggesting that CWD may lead to local extinctions of infected deer populations if left unmanaged."*[14]



The Expert Scientific Panel traced Canada's CWD to game farm animals imported from South Dakota. It then spread to wildlife, including mule deer, white tailed deer, elk, and moose.

As of this writing (and further explained below), five separate field studies undertaken in multiple regions document significant population impacts in mule deer, white tailed deer, and elk. Meanwhile, there is neither evidence nor any published accounts of declining prevalence.[15]

Finally, and definitively, repeated instances of CWD testing of native populations have consistently failed to show any significant evidence of the disease outside of endemic areas. Wisconsin's published, state-wide analysis of more than 35,000 deer (500 from every county) in 2002—2003 is illustrative.[16] With large sample sizes and test sensitivity offering high confidence levels i.e., an 89—99% probability of detecting CWD even in prevalence as low as 1%, there was complete absence of positives in populations outside of the immediate infected area.

Similarly, in Alberta, a full decade of collection and analysis had tested 6,883 animals before finding a single positive in 2005,[17] near the Saskatchewan border (CWD had been spreading westward after spilling over to wild deer from infected Saskatchewan game farms).[18]

Let us assume that CWD is a longstanding, indigenous wildlife disease. Let us note that not a single epidemiological model shows declining prevalence. If we then accept the known evidence and observed pathology and epidemiology (including that from the eventual spread in Alberta), for this highly contagious, extremely resilient and persistent and always fatal disease, then testing for CWD should reveal positive results in one of every three Alberta deer.

Using that standard, the odds of Alberta testing 6,883 deer and finding only a single positive, are (in exponential notation), just less than 1 in 10^{1212}. These are not even odds of 1 in trillions, or even trillions of trillions.[19] Adding to Alberta and Wisconsin's data are Minnesota where more than 30,000 were tested to before finding a first wild positive,[20] and Iowa that tested more than 42,000 to find their first positive.[21]

Thus regardless of its origin, the question of novelty of CWD is not in doubt. There is neither evidence nor theory to support CWD as a longstanding, indigenous disease of North American wildlife. All known pathology and epidemiology, and all available evidence is consistent with CWD being newly emerged (or introduced) in or around the early 1960s.

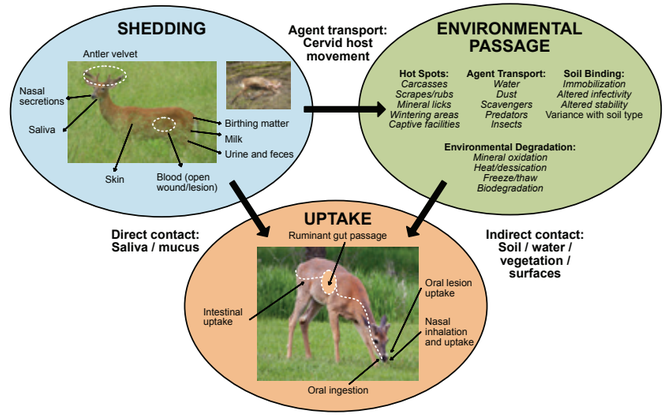
A resilient, persistent, contagious pathogen

The protein pathogens or 'prions' causing CWD are extremely resilient,[22] known to resist disinfectants, alcohol, formaldehyde, detergents, protein enzymes, desiccation, radiation, freezing, and virtual incineration >1100° F.[23, 24] That temperature, nearly the melting point of aluminum, was sufficient to completely 'ash' the tissue; weights were reduced by 98-99%. Yet *"when reconstituted with saline to their original weights, [prions] transmitted disease to 5 of 35 inoculated hamsters."*[25]

Normal sewage treatments do not degrade or inactivate prions: *"most would partition to activated sludge solids, survive mesophilic anaerobic digestion, and be present in treated biosolids."*[26]

"CWD is certainly the most contagious prion infection,"[27] with infected animals shedding prions from every orifice.[28, 29] It is *"characterized by very high prion replication in host tissues, which are readily shed in bodily fluids and excretions (saliva, blood, urine, feces)."*[30] *"CWD prions are shed by infected hosts throughout the disease course—minutes post-exposure to terminal-stage disease."*[31] Once clinical signs develop, CWD is invariably fatal[32].

CWD has been shown to persist and remain infectious in the environment.[33] CWD prions adhere to minerals such as montmorillonite (Mte) in clay-based soils that can dramatically increase infectivity, up to 680 times.[34] Interestingly, recent studies indicate that the high binding capacity of Mte could potentially be utilized to remove prions suspended in liquids, offering potential means of prevention, treatment, or decontamination.[35] Ultimate duration of CWD persistence has not been determined, but an epidemiological investigation of scrapie reoccurrence in Iceland *"established with near certitude that the disease had not been introduced from the outside and it is concluded that the agent may have persisted in the old sheep-house for at least 16 years."*[36]



Conceptual model of horizontal transmission of chronic wasting disease (CWD). Items in italics are poorly studied or unknown in cervid CWD. (Adapted from Bartz, et al, 2012.)

Experiments on species other than deer have shown how CWD can circumvent species barriers[37]. Many rodents, including the lab-favourite Syrian golden hamsters, effectively resist CWD. However, if CWD passes first though ferrets, it infects golden hamsters after all![38]

The fact that species barriers for prion diseases can sometimes be breeched via intermediate species shows the need for caution because of the risk of transfer to new species. And this includes potential risk to people. Studies of *"species that may act as reservoir … support a potential role for native rodents in the infection cycle."*[39]

"Studies have also demonstrated that prion diseases can be orally transmitted to many species: i.e., CWD to voles mice, and ferrets, scrapie to squirrel monkeys and hamsters, BSE to sheep, goats, cynomolgus macaques, and lemurs, and CJD and Kuru to squirrel monkeys, with some requiring prior in vivo or in vitro adaptation."[40] Further, *"once a prion strain has been adapted to a new host species, the prions from this new host species propagate more efficiently in a third host."*[41]

Health authorities advise precautionary measures

An absence of evidence of CWD having transferred to people is not proof that it cannot happen, which is why health authorities universally advise against consumption of any suspected prion material: *"Animals testing positive for any prion disease should not be consumed by humans or other animals."*[42] *"No tissues from infected cervids should be considered prion-free."*[43]

In addition to brain, spinal column, and various lymph tissues, infectious CWD prions have been confirmed in saliva, urine, feces, blood, velvet antler[44, 45] (potentially) milk[46] as well as in skeletal and cardiac muscle, and fat[47] *"demonstrating that humans consuming or handling meat from CWD-infected deer are at risk to prion exposure."*[48]

In any areas known to be positive for CWD, *"hunters are advised to avoid harvesting deer and elk that appear ill, to debone meat during processing, to wear latex or rubber gloves when dressing the carcass, and to avoid contact with brain, spinal cord, and lymphoid tissues."*[49] To prevent geographic transfer, hunters are advised against moving remains of harvested animals from areas with CWD, and to ensure appropriate disposal of all materials known to be positive.[50, 51]

"You'll have to be aggressive; remove all sources and all potential movement. Cut wider and deeper than you ever think necessary. The deer will come back; but you'll get one chance. If CWD gets widely established, you'll have it for a very long time."

Dr. Elizabeth S. Williams, 1996
Following confirmation of CWD on a Saskatchewan game farm, asked what Canada should do if it spills over into public wildlife.

Transfer

Transmission of CWD has been shown to occur: animal to animal, soil to animal,[52] plants to animal,[53] soil to plants to animal[54] (IC, oral tests ongoing),[55] and mother-to-offspring.[56] In addition, human caused (iatrogenic) *"transmission of the CJD agent has been reported in over 250 patients worldwide"*[57] including via surgical instruments that cannot be sterilized. And this has implications regarding any tissues, products, or tools infected with CWD.[58, 59]

Density and stress in the 'captive wildlife' industry (game farms) have been shown to exacerbate CWD risks.[60, 61] *"In*

one infected research facility, more than 90% of mule deer resident for >2 years died or were euthanized while suffering from CWD."[62]

As with other biological agents capable of exponential growth and spread, risk of transfer and introduction can be dire. The *Expert Scientific Panel* traced all of Canada's CWD to imports of game farm animals from South Dakota—perhaps even in a single animal. The disease repeatedly spilled beyond game farm fences, to public wildlife.[63]

A State of Emergency

CWD was declared a "State of Emergency" by the U.S. Secretary of Agriculture Anne Veneman in 2001.[64] Since that declaration, every factor (growth, spread, persistence, adaptation, exposure) of CWD has only increased and threat profiles continue to rise.[65]

To date CWD has been confirmed in some 24 states, 3 provinces (including retrospective finding in a mule deer in the Toronto Zoo in 1971), in South Korea (from Saskatchewan), and recently in reindeer and European moose in Norway.[66] The majority (but not all), cases have conceivable connections tracing to the original emergence in Wyoming and Colorado.

CWD is now the largest bio-mass of infectious prions in global history;[67] and unlike BSE, everywhere CWD has established itself, it grows, spreads, persists, while it evolves and adapts.[68]

Environmental reservoirs

In addition to readily transferring between live animals, *"mule deer were infected by contact with skeletal remains of CWD-affected deer and surrounding ground and vegetation."*[69]

On the landscape, CWD-infected carcasses can funnel the prions from decomposing brain into soil, where it will adhere to various minerals, creating a contaminated 'super-site.'[70, 71]

Carcasses provide easy, nutritious food sources for a spectrum of animals; and decomposition releases nutrients into the surrounding soils, stimulating a substantial flush of plant growth that persists for several years.[72] In studies of infectious anthrax, these carcasses are deemed 'fatal attraction sites'.[73] The documented effects in soil and forage ecology are significant and of direct relevance regarding reservoirs of persistent pathogens, and back-to-host as well as potential interspecies transfers.[74, 75]

Studies of CWD infected deer carcass confirm the widespread visitation, contact, and (varying) consumption by all manner of wild and domestic animals, including *"14 species of scavenging mammals and 14 species*

Deer carcass studies confirm widespread visitation, contact, and consumption by all manner of wild and domestic species. (Photo: Wisconsin DNR)

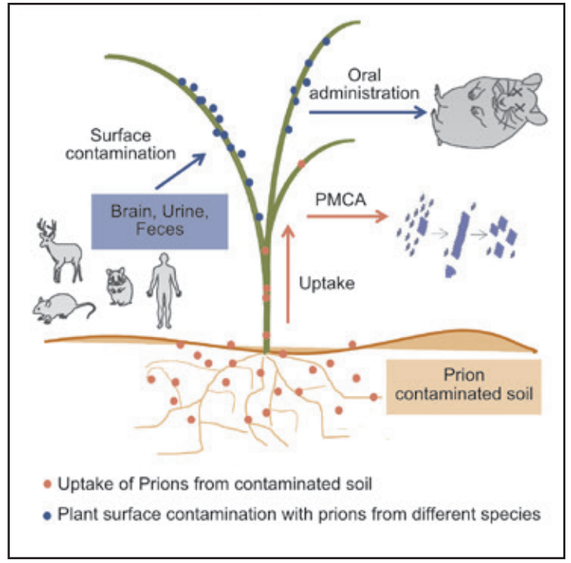
of scavenging birds. Prominent scavengers included American crows, raccoon, and Virginia opossums."[76]

Visitation (but not consumption) by deer was observed, while *"domestic dogs, cats, and cows either scavenged or visited carcass sites. This could lead to human exposure to CWD."*[77] The well documented pulse of nutrients and subsequent prominent flush of forage in carcass sites raises concerns of (probable) prion contamination and potential infectivity of plants growing in heavily contaminated CWD super-sites.

Potential role of plants

Excerpts from Dr. Christopher Johnson, USGS:

"Vegetation is ubiquitous in CWD-contaminated environments and plants are known to absorb a variety of substances from soil, ranging from nutrients to contaminants. The uptake of proteins from soil into plants has been documented for many years and we have been investigating the uptake of prions into plants in vitro. Using laser scanning confocal microscopy, we observed root uptake of fluorescently-tagged, abnormal prion protein in the model plant Arabidopsis thaliana, as well as the crop plants alfalfa (Medicago sativa), barley (Hordeum vulgare) and tomato (Solanum lycopersicum)."[78] With micrographic evidence of root uptake, transfer to stems and leaves of those plants as well as corn was confirmed using PMCA. The work further confirmed that: *"Both stems and leaves of A. thaliana grown in culture media containing prions are infectious when injected into mice, and oral bioassays are underway for A. thaliana and other plants. Our results suggest that prions are taken up by plants and that contaminated plants may represent a previously unrecognized risk of human, domestic species and wildlife exposure to CWD and scrapie agents."*[79]



CWD contamination on plants via urine, feces, or saliva, or root uptake of plants growing in CWD-infected soils present risk of spreading the diease. (Adapted from Pritzkow, et al, Cell Reports, 2015.)

Similar work at the University of Texas Medical Center by Dr. Claudio Soto also confirmed root uptake and the presence of CWD prions in wheat grasses.[80] Combining the studies, it is noteworthy that of the six plant species confirming prion uptake (every species tested), at least five have direct implications for agriculture. Given the prolific shedding of prions from infected animals (in urine, feces, and saliva), Dr. Soto's team also addressed the question of prion contamination on plants.

Wheat grasses exposed to urine and feces from infected deer were then aggressively washed (five times) in an attempt to remove the prions, but lab animals were consistently infected via oral exposure (just from eating it).[81] Research is ongoing to assess environmental contamination *"beyond plants to include soil and minerals, instruments, equipment, natural environmental surfaces such as stones, pieces of wood and small animals that live in contact with the soil and environment (e.g., earthworms)."*[82]

The amplifying role of captivity

While CWD contamination varies widely across natural areas, and can be observed spreading slowly after its emergence[83], and while it is affected by local population densities, prevalence, conditions and co-factors[84]—by far the highest levels of CWD infections, persistence,[85] and geographic transfer[86, 87] have been found in commercial game farms.[88] In such premises CWD was found to have extreme prevalence, persistence, transfer/geographic spread, and potentially irreversible contamination:[89] *"Healthy cervids can become infected solely from environmental exposure. No environmental decontamination procedures currently exist for application to prion-contaminated premises."*[90] In Saskatchewan, *"on premises with no evidence of environmental contamination, after the quarantine was lifted, of those that chose to re-stock…that is, to continue cervid farming, there was an alarming 50% re-occurrence rate of CWD."*[91]

While not yet undertaken for CWD, an analysis of *"the effectiveness of recommended scrapie farm decontamination regimens was evaluated by a sheep bioassay using buildings naturally contaminated with scrapie."*[92] Four separated pens were assessed by cumulatively adding (+) decontamination measures: from a control where only gross debris was brushed out; (+) pressure washing; (+) treatment with sodium hypochlorite solution containing 20,000 ppm free chlorine for one hour; (+) removal and replacement of metalwork (or treated by re-galvanization), and painting every item of immovable steel (gate posts), the floor, and wall (up to a height of 1.35 m) with hard wearing floor paint. *"A bioassay was then carried out by introducing (and carefully monitoring) scrapie susceptible lambs."* All efforts to decontaminate failed. *"Remarkably, despite the pen D decontamination regimen consisting of a complete repaint of every surface and replacement or re-galvanization of all metalwork, all five sheep were also scrapie positive by 18 months of age."*[93]

In captivity, high density, stress, squalor, artificial feeding and transportation fosters and spreads all manner of diseases. (Photo: Pat Davison)

The presence of dust may explain such persisting contamination and re-infection. Gough et al demonstrated *"airborne movement of scrapie containing material within a contaminated farm environment."* Airborne seeding was shown on various fomite surfaces beyond the reach of animals (vertical and horizontal), to sterile petri dishes, and to pasture 30 meters away from the scrapie contaminated buildings. That PrPsc (scrapie prions) were not detected 60 m away suggests *"that the chance of contamination decreases with distance."*[94] As the authors note, *"scrapie containing dusts could possibly infect animals during feeding and drinking, and respiratory and conjunctival routes may also be involved. It has been demonstrated that scrapie can be efficiently transmitted via the nasal route in sheep,"*[95] as is also the case for CWD in both murine models and in white tailed deer.[96, 97]

Additionally, *"naive deer exposed to water, feed buckets, and bedding used by CWD-infected deer contracted the disease."*[98] Given these and other findings of potential CWD contamination of facilities, tools, equipment, and various surfaces, and the potential infectivity in or on plants,[99] the protection of public wildlife demands closely enforced restrictions of any materials moving from contaminated sites, and to restrict wildlife's access to such.

As had been repeatedly warned by scientists,[100,101 102] the direct relevance and risks of commercial game farming to public interest have been documented repeatedly, in both the U.S. and Canada. These include substantial costs, demonstrated disease transfer, persisting threat of CWD transfer to public wildlife, with corresponding harm to economies, and risks to agriculture and human health. In April 2011, because of extreme, ~80% CWD prevalence and probable site and facility contamination, the Wisconsin Department of Natural Resources was compelled to purchase, double fence, and monitor the highly-infected premises known as the Buckhorn Flats Deer Farm in Portage County, WI.[103] In Canada, the Canadian Food Inspection Agency (CFIA) *"maintains any imposed declaration of infected place and associated quarantine for premises wherein there is evidence of environmental transmission."* Twenty such premises remain under indefinite quarantine in Saskatchewan,[104] *"requiring the CFIA to ensure full maintenance of perimeter fencing for the exclusion of wild cervids."*[105]

Wisconsin deer farm with severe (80%) prevalence of CWD. The DNR purchased and double fenced it to prevent wild deer access. 20 such CWD farms in Canada are under permanent quarantine at taxpayer expense.

Direct exposure of public wildlife to CWD-infected premises, erosion, carcasses and 'super-sites' provide substantial, high-concentration opportunities not just for interspecies transfer, but also for 'quiet carriers' and long distance transport.[106, 107] Resistance notwithstanding, prion passage through predator and scavenger species, including crows and coyotes have been studied, showing that CWD prions remain infectious in the feces.[108, 109]

Fences do not protect wildlife

History confirms that it is challenging to keep deer (let alone diseases) from crossing into or out of fenced facilities: *"Game ranches form a bridge for the transmission of livestock diseases between captive and wild populations."*[110] *"A CWD-positive elk pen in Minnesota, USA, was found to have >20 breaches within the fence and wild white-tailed deer were observed within the facility."*[111] Furthermore, given the persistence in soil, water and plants, natural erosion and vector passage present formidable containment challenges.

Indeed, as had long been predicted by scientists, the inevitability of disease transfer, emergence, and spillover from commercial game farms, and the corresponding costs and threats to public wildlife have been well documented.[112, 113, 114, 115] This highlights pivotal role of governance and public policy in wildlife conservation—and in protecting the resources and the rights, privileges, opportunities, and benefits they sustain. Public trust requires our representatives to consider carefully all aspects of our interactions, impacts, and endeavours, whether direct or indirect, immediate or long term, and to protect public interest above all else.

Analyses accurately predicted severe threats to wildlife

The Wyoming Analysis cited above[112] is revealing. In the late 1980s, John Dorrance III applied to establish a large commercial game farm in Wyoming. The facility was to import and contain many exotic as well as domestic species. Widespread concerns expressed by wildlife scientists, hunters, ranchers, and the general public led the state government commission a thorough examination of the proposal and its implications. Released in 1990, the Wyoming Analysis stands today as the most comprehensive investigation of game farming ever undertaken by a government. The state declined Mr. Dorrance's application.[116] The issues, science, evidence, and views of experts outlined in Wyoming's Analysis subsequently withstood repeated court challenges. This notably included time-tested testimony after the 2000 election when Montana voters passed ballot initiative i143. In a written affidavit, after observing ten years of repeated epidemics and myriad problems with game farms across the continent, the following quote summarized Wyoming Game and Fish Department's view of their analysis and decision:

> *"[T]he issues raised in our report are as valid today as they were in 1990. The issues of game farmed animals escaping into the wild, the spread of disease via escapes or movement of animals across jurisdictional boundaries in commerce, competition between native and exotic wildlife, the potential for hybridization and genetic pollution, the possibility of theft of public wildlife and an increase in poaching activity as a result of putting a monetary value on dead wildlife, and the damage penned shoots would have on the public's perception of sport hunting as a legitimate tool of wildlife management were issues that we thought made game farming an unacceptable risk to Wyoming's wildlife treasure. Events since 1990 have confirmed that the issues we raised in 1990 were real and reaffirmed the wisdom of the Commission's decision to completely deny the applications."*
>
> *"I declare under penalty of perjury that the foregoing statements are true and correct to the best of my knowledge."*
>
> *Robert P. Lanka,*
> *Wildlife Management Coordinator,*
> *Wyoming Game and Fish Department*
> *June 28, 2001*

Indeed, as part of the original CWD enzootic zone, Wyoming faced significant challenges that could only have been exacerbated by widespread commercial exploitation. The forewarnings detailed in their analysis emerged repeatedly. For example, just prior to and coincident with the acceleration of North America's CWD epidemic in 1996, an epidemic of tuberculosis on North American game farms in the early 1990s spread to cattle, bison, pigs, and people.[117] Investigation revealed that inadequate testing and false presumptions of safety enabled repeated outbreaks. Evidence suggests that Tb and CWD may have been transported into Canada simultaneously, in the same animals.[118, 119]

In 1989, Eileen Welsome, Pulitzer Prize-winning journalist for The Albuquerque Tribune, authored a six-part series on game ranching documenting serious problems and warnings from scientists.

Canadian officials found that the epidemiological tracing of both diseases in captive animals was compromised, because farm records were often in error. Irregularities and illegal transport were widespread.[120] Additionally, *"over 120 elk from Tb infected game ranches in Alberta and Montana alone were known to have escaped or were inadvertently released into the wild."*[121] CWD status of those animals remains unknown.

Further, as New Zealand's National Tb Advisor had warned, cervids can become grossly infected and infectious with bovine Tb,[122] explaining the unusual finding in Alberta where some 42 people (game farmers, veterinary technicians, and abattoir and rendering plant workers handling elk carcasses) tested (newly) positive for Tb.[123] Large numbers of animals were missing from infected and quarantined farms, causing *"Alberta's Director of Wildlife to issue an official warning to Alberta hunters that if they happen to shoot an animal with an ear tag, don't even touch it."*[124] *"The (game farm Tb) outbreak not only cost tax payers tens of millions (for indemnification, staff, and administration), it cost all of Canada Tb-free status, valued by Agriculture Canada at $1 Billion."*[125]

Principles and opportunities ignored

Early in Canada's Tb epidemic on game farms, there were opportunities to test for CWD in depopulated Tb infected herds. This led to formal requests to secure such tests, as such were not possible prior to importation of large numbers of captive animals from the U.S. The Tb epidemic provided authorities' with vital access to *"animals already under the control of Agriculture Canada, they were already dead, already paid for, and there had been many suspicious or inexplicable deaths on game farms. Although the request was directed to Agriculture Canada, the Alberta government dismissed the need, and declined the request."*[126] The possibility of finding CWD early would almost certainly have prevented the massive spread of CWD in Canada, and may well have had similar benefits for the U.S. (outside of the CWD-endemic area).[127]

The disease epidemics highlight the role of the precautionary principle, and of comprehensive analysis in forming public policy. Without such consideration, public wildlife, public interest, and traditional agriculture are jeopardized. Yet despite its unique and direct threat, the 'captive wildlife' industry has been all but immune from any accountability, or the 'polluter pay' principle.

Unfortunately, the modelled predictions about CWD impacting wildlife populations are now being borne out in the field. In the last two years, a series of published and ongoing studies have confirmed significant and potentially severe population impacts for deer,[128, 129, 130] which carry significant implications for hunting and North America's multi $billion wildlife economies.[131]

Impacts and threats by species

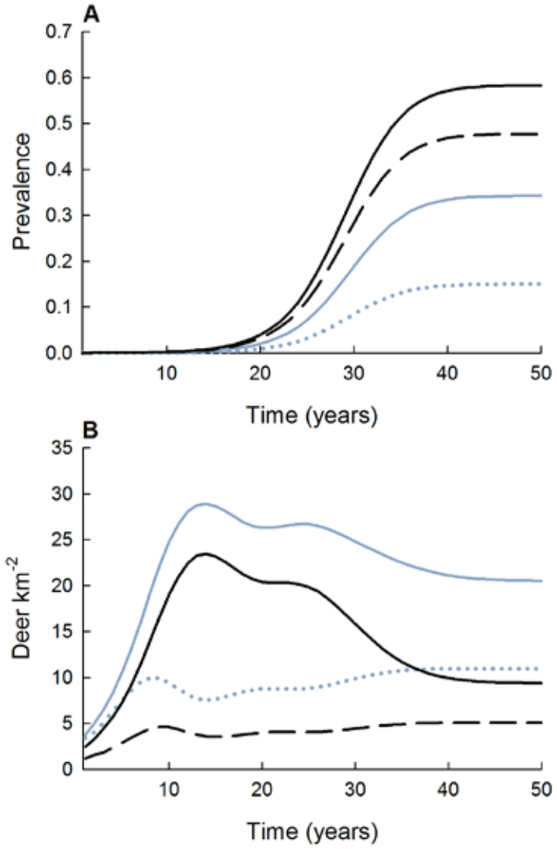
ELK: Study of an endemic elk herd (prevalence 12.9%), in Rocky Mountain National Park showed that *"CWD alone is capable of causing large declines in elk populations."*[132] *"CWD-caused mortality can exceed natural rates of mortality, reduce survival of adult females, and decrease population growth of elk herds." "Preventative efforts to minimize the risk of CWD into new geographic areas remains the most effective approach to minimizing long-term population limiting effects of CWD."*[133]

MULE DEER: Using advance testing and radio-collar monitoring, a study of 143 mule deer in the LaPrele Reservoir in southern Converse County, Wyoming showed *"an annual population decline of 19%,"* contrasted with *"a stable population growth rate under CWD-free conditions."*[134] The results suggest potential extinction of that mule deer population within 41 years.[135]

WHITE-TAILED DEER: A study of WT deer in east-central Wyoming showed that *"CWD has the potential to be population-limiting and the strong population-level effects of CWD suggest affected populations are not sustainable at high disease prevalence under current harvest levels.*[136]

"CWD-positive deer were 4.5 times more likely to die annually than CWD-negative deer. These results support concerns of wildlife managers, wildlife disease experts, and conservationists that this endemic (chronic) disease can diminish the sustainability of deer population at high disease prevalence."[137]

Analysis in Wisconsin and Illinois *"found that adult male deer have > 3 fold higher risk of CWD infection than female deer. Males also had higher disease mortality than female deer. As a result CWD prevalence was 2 fold higher in adult males than females."*[138]



Predicted CWD prevalence (A) and deer density (B) for fawns (dotted), male yearlings (dashed), female adults (solid blue), and male adults (solid black) using transmission estimates from the best supported sex-specific frequency- dependent model. This scenario represents a no-harvest strategy, initiating CWD in a deer population with initial density of <9 deer km22 with density-dependent fecundity as a population regulation mecha- nism (K<77 deer km22). doi:10.1371/journal.pone.0091043.g006

Activity analysis of deer in the Wyoming white-tailed deer study *"suggested CWD-positive bucks did not participate in the rut at the same level as CWD-negative bucks,"* and that *"CWD-positive bucks were less aware of the rut and the hunting season and were more susceptible to being shot by a hunter."*[139] Further, *"[o]ver-representation of CWD-positive deer in the hunter harvest suggests behavior is altered by CWD prior to clinically recognizable CWD infection. Rather than thinking of CWD as a strictly pre-clinical disease followed by a short, obvious clinical stage of disease, we believe CWD infection should be envisioned as a slow, progressive decline in health and alteration of normal behavior, which ends with clinically recognizable disease."*[140]

Potential for natural adaptation

Evolutionary adaptation based on genotypic resistant alleles remains questionable, and would likely be too late in any case. *"Wild cervid populations are unlikely to evolve quickly enough for selection to influence disease management."*[141] Even if hunting were stopped to accelerate the selection process through higher CWD prevalence—a prospect implying serious risks on many fronts— achieving the hypothetical resistance could take some 50 years.[142] Moreover, this assumes resistant genotypes have similar fitness as susceptible genotypes. In the interim, deer populations are likely to experience substantial population declines.[143] Where hunting or significant predation lowers prevalence, this timeline is extended beyond 200 years. But the health and suitability prospects remain suspect.

CWD resistant genotypes are weakly conserved, and attempts to breed deer with the resistant genotype have been unsuccessful. At a 2016 CWD symposium Dr. Michael Miller said: *"We actually tried breeding, for research purposes, 225 FF mule deer, tried for quite a few years, and there was something really wrong with them. It wasn't that they didn't look like mule deer, but they just weren't quite right."*[144] Dr. Tracy Nichols added: *"…mother nature doesn't like them. Ok, so in the wild, there aren't very many, and there's probably a very good reason for that. Are they immune-compromised, are they more susceptible to, perhaps, certain parasites or certain infectious diseases?"*[145]

Prospects for vaccines

Potential development of vaccines for prion diseases are extremely difficult for a number of reasons, beginning with the challenge of initiating an immune response. Also, vaccinations are not without safety concerns, potential side effects, issues in other species, prospects of amplifying virulence, and, in wildlife, significant delivery and monitoring challenges. The good news is that there have been some positive indications of an induced immune response to prion proteins. In a direct approach that targeted epitopes exposed by misfolding, a protective antibody response was shown *in vitro*. The group of authors note, however, that caution is advised on several fronts:

> *"PrPc-reactive antibodies could have pathological consequences in otherwise healthy animals." … "While any vaccine with a therapeutic benefit is undoubtedly a scientific success, the use of a prion vaccine in wildlife populations will likely need to consider the mechanisms of protection, in particular as they relate to safety." "Such concerns take on even greater priority for wildlife vaccines where there is less opportunity to oversee, monitor, and regulate vaccinations."* [146]

A partial therapeutic protective response to CWD was demonstrated for the first time *in vivo* in a *Salmonella*-delivered mucosal vaccine in white-tailed deer, including in a genotype with full sensitivity to CWD.[147] One may note that this approach may allow oral delivery of the vaccine using food pellets, or some slow-release preparations to stimulate the entire gastrointestinal tract.

Additional challenges and concerns regarding vaccines remain on many fronts, in both targeted and additional species. Unfortunately, while not on the scale of evolving resistance shown with antibiotics, evidence shows that neither bacterial nor viral vaccines are evolution-proof. *"Vaccine-driven pathogen evolution has been seen in several infectious diseases."*[148] There is no obvious reason to expect that protein-targeted vaccines could not be vulnerable to similar effects. But neither that, nor the unfortunate result in a recent CWD vaccine trial in Wyoming that caused 7 times more disease, with faster onset,[149] represents the greatest risk. The greatest risks are further delays in reassessing fundamental public policy. This also raises questions regarding the purpose and the benefactors of CWD vaccines. Even best case scenarios suggest that breakthrough disease management tools for wildlife would be decades away.

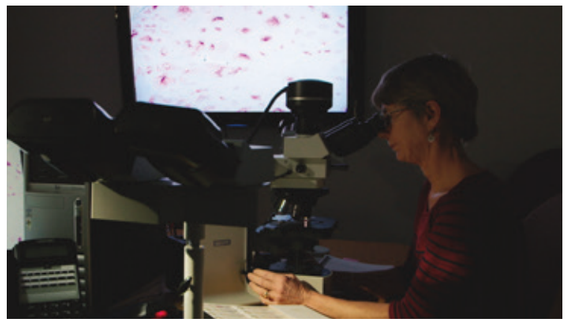
To be clear, given the importance and scale of the experimental opportunity, and potential zoonotic risk, CWD vaccine research should continue—but only (and cautiously) for potential application for human health, to assist in CWD control in wildlife (reducing prevalence and spread), or in restoring wild populations in areas with potential environmental contamination.

Potential Risk of Transfer to People

There are few considerations which require greater foundational context than questions of zoonotic risk of infectious diseases. Combining public policy and science is very much a matter of addressing uncertain risks that are dynamic, evolving, and with complex, even profound consequences.

The reality is that most (~70%) emerging zoonotic diseases have come from animals.[150, 151] Each presented

uncertain risks, and in every instance there was a point in history where the animal to human transfer of that particular pathogen had not yet occurred. Such absence of evidence or 'proof' can often elicit false inferences that dismiss or underestimate the risk. The UK example of BSE (unexpectedly) transferring to people as vCJD, is but one recent example.[152] The impacts were complex, extending far beyond immediate victims, bringing serious and prolonged socioeconomic and health consequences that included suicides tied to the severe economic impacts of BSE on the agricultural economy.[153] There are persisting uncertain zoonotic risks related to the BSE that remain to this day. For example, findings in lymphoreticular tissue (archived through appendix samples) indicate that 1 in 2,000 of the UK population are asymptomatic carriers infected with abnormal PrP.[154] The long term implications are unknown.



Dr. Delwyn Keene at the Wisconsin Veterinary Diagnostic Laboratory examines deer samples. Pink areas signal CWD. Testing is vital to avoid infected deer from being consumed.

Zoonotic risks are neither static nor merely historic phenomena: *"it is estimated that approximately 75 per cent of 'new' human pathogens reported in the past 25 years have originated in animals and the risk of zoonoses is predicted to continue to increase."*[155] As status quo matters of public policy they require consideration of known and potential consequences. *"The Global Burden of Disease Study estimates that, in the year 2000, infectious diseases were responsible for 22% of all deaths and 27% of disability-adjusted life years worldwide."*[156]

Such risk profiles can only be considered as snapshots in dynamic, evolving landscapes, where observation and evidence of variability—indicating change or evolution—is a vital consideration. This underscores the very essence of the precautionary principle, and nowhere is it more requisite than with respect to infectious pathogens. Inadequate policy or regulatory failures can result in pandemics that kill thousands or even millions of people or other animals, causing enormous damage on economies and ecosystems.

The Public Trust Doctrine

That government's primary responsibility is to assess such risk is the essence of the Public Trust Doctrine, the contractual relationship at the core of all governance. It embodies the components, relationships, and legal obligations of a classic fiduciary trust. Components include:

- Trustees (governing representatives in various levels and branches: elected, executive, and the courts)
- Beneficiaries (constituents and future generations)
- Public interest related to property (tangible and intangible) and wellbeing (life and liberty)

Trustees accept and bear a burden of responsibility to protect and defend the interests of their constituents, and those of future generations. Where so-called hard sciences probe the vital questions of 'what is' and 'what was,' governance, or political science, must build from that foundation to confront the equally challenging questions of 'what if.'

While often hidden by retail politics, the weight of this responsibility is profound. Fortunately, guidance has been further established in precautionary, accountability, and polluter-pay principles that have saved untold billions of lives and immeasurable costs.

The Precautionary Principle

Where there is a potential for severe or irreversible harm, especially to public wellbeing and interest, an absence of scientific consensus or proof of harm cannot be used to allow or maintain policies or actions underlying the risk. In such cases, the burden to 'prove safety' falls on those advocating the potentially harmful policy or action.[157]

The standard of "severe or irreversible harm" is a very high bar; yet one CWD has long surpassed regarding public wildlife. It is only against that backdrop that the potential transference of CWD to people can be reasonably considered. We must consider risk, consequences, and even worst case scenarios. The fact is that prion diseases are described by physicians and victim's families as aggressive, horrific, and dreadful.

Faced, in his medical practice, with the reality of human prion and neurodegenerative diseases, a leading scientists like Dr. Neil Cashman, (former) Scientific Director, PrioNet Canada, have long warned that CWD is *"an emergency in slow motion."* At the "On The Horizon" PrioNet Research Conference Dr. Cashman summarized the background and urgency as follows:

> *"CWD is spreading like wildfire. From a few foci in Saskatchewan, it has now come to involve deer and elk in Alberta and Saskatchewan and there are no geographical barriers. It will spread until it infects the entire continent. It also spreads across species. ...It can persist in water; it can persist in soil. It's spreading without check. It's arguably the most contagious prion disease, and the human health impact is unknown. We just frankly do not know if humans are susceptible to chronic wasting disease. It's an emergency in slow motion."*[158]

This combination of growth, spread, changing risk, and extreme consequence explains the near unanimity of caution in available zoonotic analyses: *"Although the zoonotic potential of CWD is considered low, identification of multiple CWD strains and the potential for agent evolution upon serial passage hinders a definitive conclusion."*[159]

Assessing zoonotic risk of new, emerging, and especially fatal diseases, is challenged by the inability to experimentally test susceptibility in people. Indeed, the ethical challenges are formidable enough regarding potential treatments. Yet questions of susceptibility require new approaches combining epidemiological and laboratory analyses (both *in vitro* and *in vivo*), as well as considerations of known and probable human exposure. Questions of appropriate policy and regulatory responses must be weighed against all implied consequences (biological, social, and economic), and the entire range of outcomes. This must include potential worst case scenarios even if they are thought extremely unlikely, not just because of evolving risk, but because market, media, and societal responses are often based more on perception than on science or reality.

Epidemiological analyses

Epidemiologic research regarding potential transfer of CWD to people has examined potential emergence as indicated by suspicious deaths, meta data and medical records, and unusual epidemiological patterns or clusters (especially in endemic areas).[160] We expect over the next few years, surveys of human appendix samples from endemic CWD areas for evidence of abnormal PrP.[161]

The precise levels of human exposure to CWD in endemic areas are not known with any certainty. There is, however, no doubt that what were probably minimal levels in the 1980s have been increasing steadily ever since (the studies of human appendixes may offer insights in this regard). While not definitive, the absence of any apparent evidence or abnormal patterns offer some comfort of a significant species barrier:

> *"The lack of evidence of a link between CWD transmission and unusual cases of CJD [i.e., vCJD], despite several epidemiologic investigations, and the absence of an increase in CJD incidence in Colorado and Wyoming suggest that the risk, if any, of transmission of CWD to humans is low."*[162]

Still, the authors advise caution based on other indicators and limited exposure:

> *"Hunters should avoid eating meat from deer and elk that look sick or test positive for CWD. They should wear gloves when field-dressing carcasses, bone-out the meat from the animal, and minimize handling of brain and spinal cord tissues."*[163]

More recent analyses suggest this remains prudent advice. Additional analyses and evidence indicate that the risk profile is changing. Many individual co-factors and potential side doors, as well as combinations—of intermediate species of susceptible mammals, interaction with fungi, plants, various stressors, etc.—remain unexplored. Meanwhile, as the baseline laboratory evidence continues to change, the once limited human exposure cited has increased.

In vitro laboratory analyses

While no longer in its infancy, the science of prion, or protein-only pathogenicity, is still relatively new. Indeed, many considered it all but heretical, long after Prusiner, an American doctor who was awarded the Nobel Prize in 1997 for the theory of 'prion,' or self-replicating, protein-only etiology. Against the backdrop that protein folding, and the multitude of complex biophysical interactions (covalent / hydrophobic effects), it stands among the great remaining challenges in biology.

Prions multiply by protein fold-conversion—re-templating natively folded PrP^c (cellular protein) to amyloid forming, protease-resistant PrP^d (disease prion). While analytical approaches differ from the genetic replication and synthesis typical of bacterial/viral/fungal pathogens, prion self-propagation offers the unique opportunity for cell-free analyses. These studies offer valuable insights into the possibility and potential rates of cellular prion PrP^c

Chronic stress compromises immunity; animals contract diseases more easily and are less able to mount immune responses. (Photo: Pat Davison)

conversion, and for comparisons of various kinds and strains of PrP^d.

Known factors include genetic backbone sequence similarity, 'natural state' molecular conformations (that may offer or block access), and, as revealed in a recent study, the identification of side chain interaction segments. These can present either complementary matches for disease-causing aggregations in 'steric zipper assemblies,' or, alternatively, mismatches leading to steric clashes and cavities that prevent conversion and help explain apparent species barriers.[164]

All protein folding and prion conversion processes have been shown to be influenced by variations in physiological conditions and stressors such as temperature, oxidative, salts and pH, as well as, within organisms, the presence of protective or denaturing osmolytes, chaperones (HSPs) and endoplasmic reticulum and other cellular mechanisms.[165] Few are well understood.

Early cell-free conversion experiments showed that CWD converts normal human PrP^c at low levels i.e., inefficiently, but at about the same rate as BSE.[166] The inefficiency was at least partially explained when recent *in vitro* analysis revealed that *"the CWD-human species barrier is largely maintained by the human-specific amino acids within the β2-α2 loop. Within the loop, human residues E168 and S170 are significant inhibitors of CWD conversion, as evidenced by in vitro conversion experiments. Human residues S143 and H155 likely also contribute to the CWD barrier. Collectively, these results help define the structural barriers that limit CWD transmission to humans."*[167]

Questions remain, however, as even more recent in vitro research (yet to be published) suggest potential for significant CWD adaptation and thus greater risk. This work showed that *"CWD adapts to a new host more readily than BSE and that human PrP was unexpectedly prone to misfolding by CWD prions."* The analysis further determined that *"human protein has a region that confers unusual susceptibility to conversion by CWD prions."* Most concerning, where *"BSE prions are essentially unaltered on passage to a new species, CWD adapts to the new species."*[168] Such adaptation alters how readily the disease will transfer, from the challenges of species barriers, to a transfer between cohorts.

In vivo (animal) experiments

Results of CWD laboratory challenges of non-human primates are mixed. CWD transferred readily to squirrel monkeys orally (92%), but macaques, which are genetically closer to humans than squirrel monkeys, have demonstrated significant resistance, even to direct intracerebral injection.[169] It should be noted, however, that recently macaques were shown to be susceptible to scrapie, but only after an extended, silent incubation of ten years.[170]

Squirrel monkeys, susceptible to CWD

Macaques, robust species barrier

In repeated studies, transgenic mice expressing human prion protein seemed to resist CWD infection. However, *"a recent bioassay with a natural elk CWD isolate in a new humanized transgenic mouse line led to clinical prion infection in 2 out of 5 mice (3 out of 5 if an infected animal that died is included)." "These results indicate that CWD prion has the potential to infect human CNS or peripheral lymphoid tissues and that there might be asymptomatic human carriers of CWD infection."*[171]

This follows the 2014 research demonstrating transmission of scrapie to transgenic humanized mice: *"The serial transmission of different scrapie isolates in these mice led to the propagation of prions that are phenotypically identical to those causing sporadic CJD (sCJD) in humans. These results demonstrate that scrapie prions have a zoonotic potential and raise new questions about the possible link between animal and human prions."*[172]

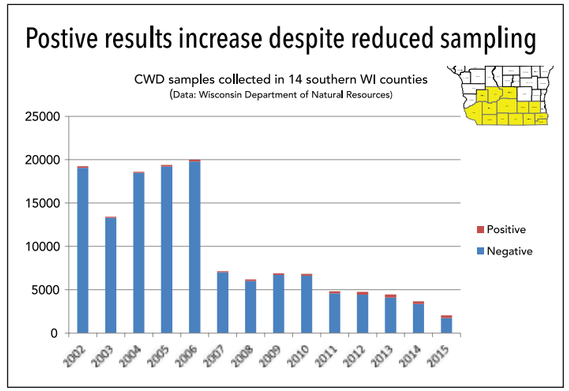
Human CWD exposure, prion load, and threshold dose

Despite universal warnings from health authorities advising against consumption of any infected prion products, levels of human CWD exposure have been steadily increasing. In Saskatchewan, Canada's most severely infected province, policy requiring that hunters pay for their own tests was recently reversed, yet only a minuscule proportion of hunter-harvested cervids (i.e., a fraction of 1%) are being tested.[173] A cooperative initiative to increase testing is underway, but funding is inadequate to meet the needs.[174]

The Wisconsin DNR posts the CDC advisory, that *"… people not consume meat from deer, elk, or moose which test positive for CWD;"* and that *"In keeping with this recommendation, the Wisconsin Division of Public Health recommends that venison from deer harvested in CWD affected areas not be consumed or distributed to others until CWD test results on the source deer are known to be negative."*[175] Despite these advisories and documentation of CWD growing and spreading, the state's testing and funding have been dramatically reduced.[176] Further, even as the number of tests in Wisconsin has declined, the number of positives has increased. Where 20,000 tests in 2006 showed 205 positives, that number was surpassed (219 positives) in 2010 with only 6,853 tests. By 2014, only 3,665 tests were conducted, but showed 327 positives.[177]

As the prevalence rate for CWD increases, the number of undetected CWD positive deer carcasses entering the food chain is growing exponentially. By one estimate, in Wisconsin alone, this number was over 4000 such carcasses for 2015 alone.[178] At the current rate of increase, the number of undetected carcasses being consumed will double every three years. Yet testing continues to decline.[179]

While cutbacks in testing have compromised accuracy, North America wide, some 7,000—15,000 CWD-infected animals are now being consumed by hunter families and friends every year.[180]



Experts weigh in

Given their own and the risk analyses of others, leading scientists are expressing concern:

> *"The increasing levels of CWD exposure are highly concerning." "As a matter of policy, I believe all animals taken from CWD-infected areas should be tested before consumption and people should definitely not be consuming any infected material."*[181]
>
> *Qingzhong Kong, PhD,*
> *Case Western Reserve University*

> *"The CWD situation and increasing levels of CWD exposure is a concern for cervid and human public health." "CWD-testing should be conducted on animals harvested from CWD-infected areas prior to consumption."*[182]
>
> *Candace Mathiason, PhD,*
> *Colorado State University*

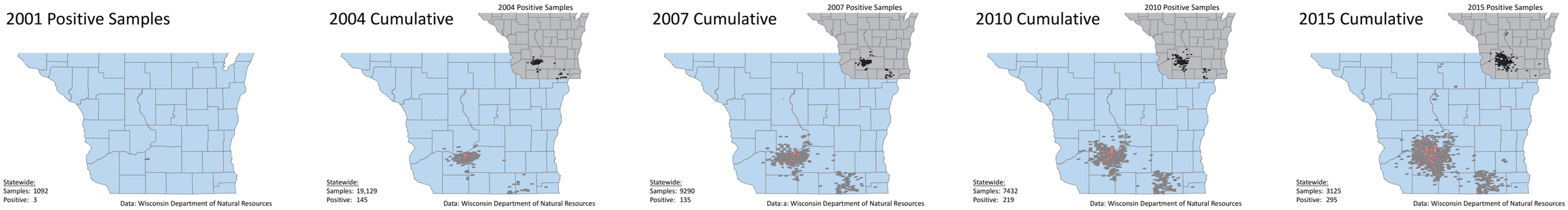
> *" … The more opportunity to expose humans to this stuff, the more we're potentially playing with fire, in terms of these strain adaptations. It wouldn't take very many cases of human prion disease that were linked back to chronic wasting disease, to where this whole conversation could change, fairly dramatically, and pretty much overnight. So I think while we have the opportunity, to get out in front of this … where we can as best we can, we should probably take advantage of that."*[183]
>
> *Michael Miller, PhD,*
> *CO Division of Wildlife*

The full spectrum

The scope of human exposure to CWD is broader than is generally appreciated. It includes some direct exposures that have been largely ignored, lessons from history notwithstanding. When early suspicions of BSE being spread through consumption of blood, bone, and nerve tissues were confirmed in 1988,[184] it led to bans on feeding meat and bone meal (MBM) supplements.[185] Yet the potential risk of CWD in velvet antlers (i.e., blood, bone, and nerve tissue) sold for human consumption continued to be ignored long after both the confirmation of BSE being transferred to people as vCJD,[186] and the repeated findings of CWD on game farms.[187]

A Risk Assessment of TSE products (dated June 2000) undertaken for Health Canada identified *"pharmaceutical products containing high risk tissues and elk antler velvet food supplement"* as the highest ranking risks.[188] Under public pressure the Canadian Food Inspection Agency pledged in October 2000 to destroy velvet antler from CWD-infected animals. However, no recalls nor warnings to potential consumers have ever been issued.[189] The difficulty of recalling product widely distributed throughout

In 2009, the University of Kentucky proved that CWD can be passed through velvet antler. (Photo: Pat Davison)



Asia is accepted; but it also illustrates the challenge and the consequences of failing to detecting potential zoonotic transfer. Furthermore, this passive approach regarding velvet antler continues even after confirmation of PrP^{d} in velvet antler in 2009.[190]

Why worry?

As evident from challenges in achieving a CWD vaccine for cervids, there is little hope that breakthrough treatments would soon emerge. CWD has been in the shadows; but the toll of other protein misfolding diseases in people (Alzheimer's, Parkinson's, Huntington's, ALS, Creutzfeldt-Jakob, etc.) affects tens of millions of Americans and cost hundreds of $billions per year. Yet the scale of complexity and level of difficulty is such, that, even after decades of research, there are no cures, and few effective treatments for any of them.[191] Moreover, and as with any disease, containing and managing risk of CWD will demand an understanding and acceptance of the relentless capacity of this disease, as it continues to grow, spread, persist, and evolve. *"Prions are distinguished from other amyloid diseases both by their infectious character and the observed exponential growth of infectious material."*[192]

With its growth and spread, human exposure from all sources has been increasing exponentially, and we would do well to consider the implications of both known and unknown factors. For example, prion load has been shown to be relevant, but note the title of McLean and Fryer's 2011 work *"There is No Safe Dose of Prions."* Analysis of 4,338 mice showed *"that infection is possible at the very low dose of a 1000-fold dilution of the dose that infects half the challenged animals (ID50)."* [193]

After pointing out that bank voles (which are circumpolar) are described as the 'universal acceptor for prions,' Sigurdson asks if the sequence in the human β2-α2 loop creates a permissive host PrP^{C} sequence that is converted by prions from other species, despite sequence mismatches.[194] With multiple avenues of direct and indirect human exposure, potential bioaccumulation, the potential role of co-factors, stressors, and potentially consequential passage to or through intermediate species, caution remains prudent. Moreover, it's becoming clear that our understanding will be well served by looking beyond mammals. Quite apart from the work documenting mammalian prions taken up or adhering to plants, Susan Lindquist's team has recently shown the *"first protein from the plant kingdom with bona fide prion attributes."*[195]

Science, our greatest ally

These analyses outline more than risk: they offer hope. Lindquist has long been at the front of breakthrough prion research with yeast, and has not only documented many collaborative interactions, but key evolutionary and epigenetic analyses to help explain the phenotypic benefits that have conserved prion existence for 800 million years. These and other insights [196] into prion function may well open opportunities to prevent, limit, or potentially even reverse prion disease.[197]

However hopeful those breakthroughs might be, they are distant, and the levels of human exposure to CWD are already into the UK's range of 1,000—10,000 BSE-infected carcasses sufficient to result in BSE transferring to a person.[198] North American hunter families are consuming some 7,000—15,000 CWD-infected animals per year, and the number is growing exponentially.[199] Though deer are much smaller in mass than cattle, this is more than offset by the fact that CWD prions are spread far more broadly than BSE prions in tissues most likely to be consumed.[200] Prion load per animal may thus be higher in deer, despite the difference in mass. And while retail markets for beef reach more genetically susceptible consumers, that is less comforting when considering that the entire deer is often consumed by one hunter family.

Overall, the zoonotic risk profile of CWD is complex, uncertain and evolving. Without exception, dozens of experts consulted for this work concur with the current Director, Prion Diseases Program for the Public Health Agency of Canada, Dr. Michael Coulthart, who describes the risk of CWD transferring to people as *"far from negligible."*[201]

Implications are broad, deep, and longterm

What is clear to policy analysts is that even a single transfer of CWD to a person will carry catastrophic implications in reactions of the public, in markets, and in public policy and international trade, regardless of how the disease manifests. And we cannot ignore the reality that CWD is highly contagious in deer.[202] It is not inconceivable that a possible transfer to people could result in similar prion shedding in urine, feces, and saliva. Such an occurrence is beyond any known, practical means of containment or treatment, or avenues to curtail the economic fallout.

If less dramatic, the risk profile is broad, complex, and with potentially dire outcomes at every turn. As to one

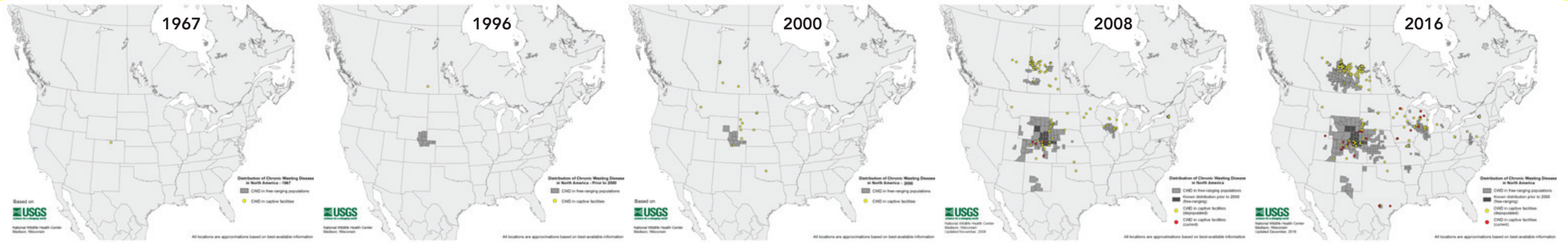
CWD emerges in captive mule deer at a research facility in Ft. Collins, CO

CWD detected in game farm elk in SK; confirmed in wildlife in CO, WY

CWD detected on game farms in MT, OK, SD, NE, SK; spillover to wildlife confirmed in SK

CWD on game farms in KS, MN, WI, NY, MI, AB; in wildlife in NE, SD, WI, IL, NM, UT, NY, WV, KS, AB

CWD now in 24 states and 2 provinces; continues to grow, spread, persist, and evolve

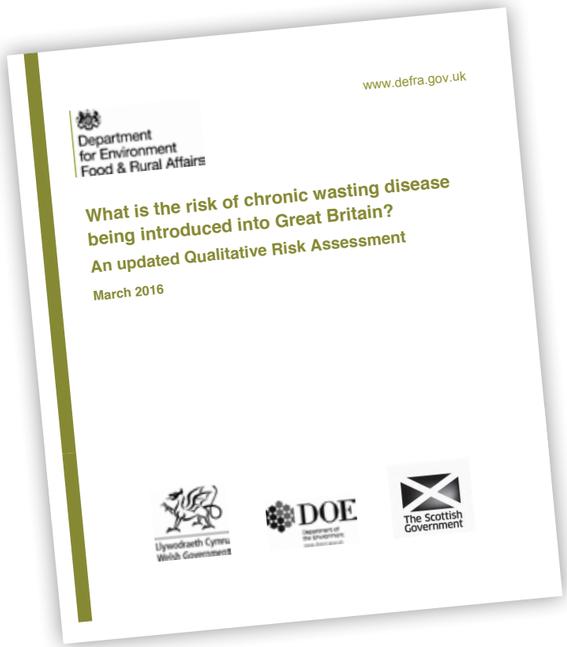


minor example: consider the risk of CWD transfer through pet food. That was included in the UK's updated, March 2016 Qualitative Risk Assessment regarding chronic wasting disease being introduced into Great Britain.[203] The assessment asks: What is the risk of CWD being introduced into Great Britain (GB) from North America and causing infection in deer?

The analysis focuses on three routes of potential CWD introduction:

1. importation of animal feed
2. importation of deer urine lures
3. importation of CWD prion on contaminated equipment and clothing/footwear of hunters or other tourists and British servicemen

The assessment cites the European Union Trade Control and Expert System (TRACES), which confirmed that *"in November and December 2015, for example, GB imported 13.6112 tonnes of processed cat and dog food (including dog chews) containing products of ungulate origin from Canada and USA."*



The UK Assessment points out that while the U.S. Food and Drug Administration (FDA) recommends that CWD positive deer or elk, or even such considered at risk, may not enter the animal feed system, it is only a recommendation. They therefore conclude that CWD risk material *"may constitute a small percentage of the very low tonnage of non-fish origin processed animal proteins imported from the U.S. into GB."* therefore considers

Articles from the UK, warning of the risk of CWD to their wildlife and landscapes.

that *"there is a* **greater than negligible** *risk that (non-ruminant) animal feed and pet food containing deer and/or elk protein is imported into GB."* (Emphasis in the original.)

As more information becomes known, and major market players get involved, that status quo is unlikely to stay. Pet food regularly includes a variety of rendered animals and animal parts, including road kills. Sept. 15, 2003 the FDA issued guidance that *"Material from CWD positive deer and elk may not be used in any animal feed."* That may have seemed a solid precautionary measure, however, Dr. Dave Clausen (from the CWD positive state of Wisconsin) explained that the results soon turned perverse: *"Since results of CWD tests would typically take a few days or weeks, renderers in the CWD areas cite this section as the reason to* **not** *accept any deer carcasses that* **have** *been tested for CWD. Fear was that a positive test would compromise their interest and/or shut down operation. Thus renderers will take untested carcasses just not tested ones."*[204]

Then, with CWD continuing to extend its range to 24 states and 2 provinces, the FDA recently took further steps, adding a section to cover: *"deer and elk considered at high risk for CWD"*[205] But as the UK Assessment pointed out, this is mere guidance, and does not establish legally enforceable responsibilities.[206] Moreover, FDA rules and guidelines for ensuring composition requirements, compliance, monitoring and enforcement are weak, and interstate and international transport of pet foods is widespread and poorly regulated.[207]

Given their experience with BSE, the UK assessment of risk via pet food is somewhat surprising. Their experience included the world's first documented instance of interspecies transfer of prion diseases in 1990, when a house cat developed scrapie-like skin irritation so fierce he licked himself bare. Dubbed "Mad Max" by the British press, the cat died from Feline Spongiform Encephalopathy (FSE), a toll eventually reaching 89 domestic cats in UK, one in Northern Ireland, one in Norway, one in Switzerland, and one in Liechtenstein.

Virtually all species of large cats in zoos were similarly infected, including: five cheetahs, three pumas, three ocelots, three tigers, five lions, and one Asian Leopard Cat.[208] All were instances of simple oral ingestion of BSE-contaminated feed. The news of transfer across species barriers immediately rocked public confidence and affected markets, which were damaged further with the subsequent admission that people were dying of vCJD from consuming infected beef.[209]

The UK assessment outlines a similarly *"***greater than negligible***"* risk of importation of CWD prion on contaminated equipment and clothing/footwear of hunters, and that *"the annual risk of at least one infection of deer in the UK with CWD from deer urine lures imported from the USA is medium."* But whereas official assessments of CWD threats to European wildlife have been measured, largely unseen, and potentially understated, concerns raised by NGOs and the media have been blunt, as in an article in *The Times* headlined: *"Disease from the U.S. could wipe out all the deer in Britain."*[210]

Deer dead from CWD. Excessive salivation and thirst drives diseased animals to riparian areas. Prions persist in soil and water, presenting risk of further transfer. (Photo: Wisconsin DNR)

No known 'off switch'

Any news of international transfer of CWD by any means, to any species whether deer, rodents, pets, or livestock (such as domestic sheep), would almost certainly have severe consequences. The economic implications would be felt most acutely in North American CWD affected areas.

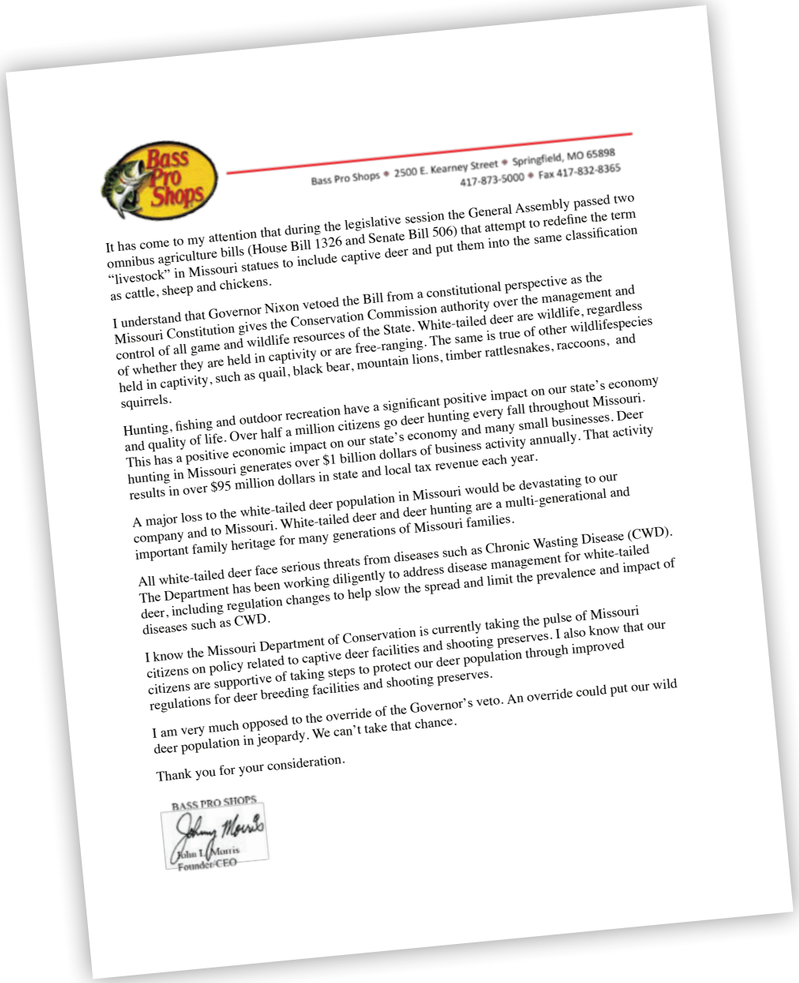
The UK experience with vCJD is instructive, but key differences are noteworthy. Despite recent confirmation of PrPd in saliva of BSE cattle,[211] the absence of (efficient) lateral transfer of BSE between living animals limited growth and spread of the disease,[212] and it allowed the ruminant feed ban to eventually halt both the epidemic and the subsequent trade embargo. This underscores a contrast of some significance: CWD with its prolific prion shedding in saliva, feces and urine, is a highly contagious, extremely persistent disease, which has established unprecedented reservoirs in public wildlife and the environment. Compared to BSE, CWD offers no apparent 'off switch.'

Lessons from BSE

From a public policy perspective, the experience with BSE offers vital lessons—from the foundational frame to the conclusions and recommendations by the official inquiry (paraphrased for brevity):

- *"At the heart of the BSE story lie questions of how to handle hazard — a known hazard to cattle and an unknown hazard to humans."*
- *"BSE developed into an epidemic as a consequence of intensive farming practice(s) … unchallenged over decades, (that) proved a recipe for disaster."*
- *"Government was preoccupied with preventing an alarmist over-reaction … (they) believed that the risk was remote. It is now clear that this campaign of reassurance was a mistake."*
- *"Public was repeatedly reassured that it was safe to eat beef."* [213]
- *"Repeated statements that 'there is no evidence that BSE is transmissible to humans' does not explain that such evidence would take many years to emerge."*[214]
- *"Even when risk to humans seems remote, all reasonable precautions must be taken."*
- *"There should be more checks on possible pathways of transmission, and on occupational risks."*[215]
- *"Where there is uncertainty, government must not shrink from saying "we are not sure."*[216]

The analyses and recommendations of the UK experience with BSE are founded on failures of governments to



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It has come to my attention that during the legislative session the General Assembly passed two omnibus agriculture bills (House Bill 1326 and Senate Bill 506) that attempt to redefine the term "livestock" in Missouri statues to include captive deer and put them into the same classification as cattle, sheep and chickens.

I understand that Governor Nixon vetoed the Bill from a constitutional perspective as the Missouri Constitution gives the Conservation Commission authority over the management and control of all game and wildlife resources of the State. White-tailed deer are wildlife, regardless of whether they are held in captivity or are free-ranging. The same is true of other wildlifespecies held in captivity, such as quail, black bear, mountain lions, timber rattlesnakes, raccoons, and squirrels.

Hunting, fishing and outdoor recreation have a significant positive impact on our state's economy and quality of life. Over half a million citizens go deer hunting every fall throughout Missouri. This has a positive economic impact on our state's economy and many small businesses. Deer hunting in Missouri generates over $1 billion dollars of business activity annually. That activity results in over $95 million dollars in state and local tax revenue each year.

A major loss to the white-tailed deer population in Missouri would be devastating to our company and to Missouri. White-tailed deer and deer hunting are a multi-generational and important family heritage for many generations of Missouri families.

All white-tailed deer face serious threats from diseases such as Chronic Wasting Disease (CWD). The Department has been working diligently to address disease management for white-tailed deer, including regulation changes to help slow the spread and limit the prevalence and impact of diseases such as CWD.

I know the Missouri Department of Conservation is currently taking the pulse of Missouri citizens on policy related to captive deer facilities and shooting preserves. I also know that our citizens are supportive of taking steps to protect our deer population through improved regulations for deer breeding facilities and shooting preserves.

I am very much opposed to the override of the Governor's veto. An override could put our wild deer population in jeopardy. We can't take that chance.

Thank you for your consideration.

BASS PRO SHOPS
John L. Morris
Founder/CEO

Letter of concern regarding CWD from Johnny Morris, Founder/CEO, Bass Pro Shops.

uphold public trust and the precautionary principle. The lessons are directly applicable to CWD: Without immediate, science-based intervention by North American governments to contain and limit the spread, growth, evolution, and exposure of CWD, the likelihood of 'worst-case' outcomes will continue to increase, and wildlife is in the cross hairs in every scenario.

Impacts on wildlife economies

The evidence regarding the presence, growth, spread, persistence, evolution/adaptation, and impacts of CWD on wildlife are overwhelming. The full extent of the ecological harm will not be known for decades, but it will have direct impacts on human-wildlife interactions. While CWD impacts may vary across areas, ecosystems, species, and people, the experiences and impacts documented in Wisconsin are worth noting.

"In early 2002, CWD was discovered in three wild white tailed deer in Wisconsin. Nine months later, hunting license sales had declined by over 90,000, revenue to the Wisconsin Department of Natural Resources (WDNR) had dropped by over $3,000,000 (Heberlein, 2004), and the economic loss was estimated at over $50,000,000 (Bishop, 2004)."[217] To assess potential impacts against perceived risk, Vaske and Lyon *"presented hunters with six scenarios depicting hypothetical CWD prevalence levels and human health risks from the disease (e.g., death), and asked if they would continue or stop hunting deer in the state."* Responses followed risk, culminating in 64% of respondents saying they would quit hunting under conditions of proven risk to people.[218]

Market-based threats

While less obvious, CWD presents a threat to North America's $trillion agriculture and agri-food economy,[219] of which exports represent about $150 billion per year.[220] Where our previous descriptions focused on science in the transfer of the disease, regulatory responses and economic drivers operate on substantially different criteria. Markets are often affected as much by perceptions as by science. The growth capacity of infectious diseases looms both real and persuasive. As a result, international trade is routinely restricted as a precaution against potential transfer that may harm people, industry, markets or public interest. One needs to note that this includes threats to wildlife or the environment, and that reactive trade restrictions based on perceived threats can be initiated in a matter of days or even hours.[221]

Prion diseases are comparatively rare, but the uncertainty (lack of adequate or live testing), coupled with extreme resilience of prions and the invariably fatal outcome of TSEs have led to widespread trade restrictions for both animals and products. By 1998, two years after the UK's admission of human deaths from vCJD, the BBC reported that BSE control and trade restrictions had cost UK taxpayers more than £4 billion.[222] The global ban on all UK beef and beef products would last a decade (1996 to 2006). It had devastating impacts on agricultural communities.

Canada's May 2003 confirmation of a single case of BSE in Alberta initiated an immediate ban on exports of Canadian beef. *"By the end of 2004, financial losses for Canadian beef producers as a result of BSE reached $5.3 billion."*[223] As the world's largest exporter of beef, U.S. producers initially benefited from the restrictions on Canadian beef. Then BSE was confirmed in a cow in Washington State in December of 2003. Leading importing countries banned U.S. beef within days; the 2008 International Trade Commission Report estimated lost revenues of $11 billion.[224]

In addition to the direct costs to producers, agriculture and agri-food industries are directly tied to securities, commodities and futures markets that are inherently speculative. Science, evidence, and regulatory changes matter, but, by definition, market investments and trades are based largely in perception of implied and probable effects on price. Companies can be held to certain standards and guidelines, but investors and pundits are free to speculate about how markets will move, allowing potential net gain. They can trade, lobby, and pontificate at will, often with little evidence or proof, impacting individual share prices, competing or related companies and sectors, consumers, and, as with the recent 'housing crash,' not just markets, but entire economies.

Markets continue to be affected by prion diseases. For example, BSE was found in a single cow in California in April, 2012. Officials expressed confidence, reassuring the public that it did not go to the food or feed chains. But as the multi-media, investor services group Motley Fool reported: *"Markets felt otherwise. Pilgrim's Pride (NYSE: PPC), the world's second-largest poultry company, saw its stock price climb 7.22% on the possibility consumers will (at least temporarily) switch up their meat consumption." "Tyson Foods (NYSE: TSN) rose 1.53%. Cattle futures dropped the most in 11 months in Chicago (via Bloomberg), and "the world's largest beef producer, Brazil's JBS SA (JBSS3), fell by as much as 5.2% before closing 0.3% lower in Sao Paulo."*[225]

Legal basis of perception over science

The substantial role of perception in both markets and public policy has been well documented in issues such as GMO food labeling.[226] Specific to TSEs, the interaction of science, markets, perception, and policy was examined in law in Creekstone Premium Beef v. U.S. Department of Agriculture.[227] After the finding of BSE in the U.S. in 2003, trade bans in the company's key markets of Japan and Korea were costing Creekstone $200,000 per day. In order to protect their customers and restore access to valuable international markets, the company built a testing lab and trained their staff so they could test all their animals for BSE. The USDA rejected Creekstone's request to perform BSE testing, refused to sell them the test kits, and intervened to stop Creekstone from purchasing (the same) test kits internationally. In their June 4, 2004 letter USDA reasoned that *"allowing a company to use a BSE test in a private marketing program is inconsistent with USDA's mandate to ensure effective, scientifically sound testing for significant animal diseases and maintain domestic and international confidence in U.S. cattle and beef products."*[228]

Citing continued revenue losses even after the bans were lifted, to address persisting consumer fears about BSE, (i.e., customer perceptions about the safety of their products), the company demanded the right to test all their animals, and brought suit on March 23, 2006. On appeal the case centered on the USDA authority under the Virus-Serum-Toxin Act (VSTA), but of relevance here is that **the substance, intent, and justification argued by both parties centered around the vital role, impact, and interaction of science, evidence, and perceptions when confronting uncertain risk.**[229] Whether or not consumers know the science, their fears are based on perceptions that Creekstone sought to address through more testing; they wanted only to increase, not replace USDA testing. Similarly, the issues argued by the USDA regarding potential false inferences because of the limitations of science, or inaccurate or invalid testing, and the questions of authority under VSTA are all, necessarily, questions of perceptions versus reality. Facts *and* perceptions are both relevant, as is their interaction in science, in policy and

The necessity of depopulation of CWD-infected farms by state agencies becomes a taxpayer burden, and is only one part of containment.

law, and in markets. All are at play and have been deemed applicable throughout vast areas of law, regulatory structures and protocol, and in international treaties and agreements. There is neither evidence nor a plausible theory to suggest this would exclude CWD.

As science and the UK Assessment points out, CWD is a proven threat to red deer, reindeer, sika deer, muntjac deer, European moose, and several species of circumpolar rodents. Merely raising the alarm about the threat of global transfer through CWD-contaminated plants or agricultural products, may catch the attention of foreign wildlife advocates as well as non-North American, highly motivated (multi $billion) competitive agricultural producers. This presents a substantial risk regarding the potential for trade restrictions on North American agriculture products.[230]

Should that happen, the effects of wildlife being condemned by agricultural interests as 'infected vermin, shedding prions into landscapes and into agricultural lands and crops' will be devastating. Even without media attention, the effect of prion contamination on property values has already been demonstrated as severe. The dozens of game farms cited earlier that remain under permanent CWD quarantine represent a greater than total loss of value, as fences have to be maintained to prevent disease transfers off the property. This will only increase as information regarding plant contamination becomes better known.

Unfortunately, our experience confirms that reactions to potential threats to agriculture from wildlife are real. Regardless of agriculture's role or responsibility in causing the problem, wildlife will be routinely targeted. For example, elk and bison contracted bovine tuberculosis and bovine brucellosis from cattle.[231] By the mid-20th century, concern over the possibility transmissions to cattle, and threats to valuable disease-free trade status, led to repeated culling of wildlife to protect agricultural interest. In Canada, even though bison lived in the far north Wood Buffalo National Park, and despite the value of the bison genome, the agriculture lobby demanded the complete elimination of bison to protect their interest.[232]

Consensus on urgency and vital actions

The preceding are but glimpses into the various disciplines, aspects, and complex factors involved in analyzing CWD, the existing impacts, and dynamic risks. It is abundantly clear, however, that the CWD crisis is, indeed "insidious and dire." While details and methods must be guided by science and evidence, there is significant agreement on critical needs; and we have assurances from leading experts that we have the labs and capacity to meet this challenge.

Immediate action is required to avoid worst-case outcomes. We require mandate and funding to:

1. Contain the geographic spread of CWD by enacting and enforcing an immediate ban on the movement of all live cervids, all potentially CWD-infected carcasses, animal parts, products, exposed equipment, trailers, or other sources of infectious materials.

2. Mandate and implement for hunters, convenient, cost-free, rapid testing of all animals harvested from CWD-affected areas.

3. Ensure that no CWD-infected material reaches the food or feed chains, and that it is instead properly disposed of.

4. Establish and fund accountable research and science-based policy to protect public interest (health, wildlife and related industries, agriculture, our economies and communities).

It is important to note that consensus regarding these needs extends to optimism regarding the efficacy, the practical efficiency, and cost-effectiveness of the actions. Comprehensive analysis with vital stakeholder engagement will foster understanding, re-connection, and genuine appreciation of interrelated systems on which we depend. While dire, we have a unique opportunity to realize enormous advantages of cooperative effort and precautionary approach.

Photo: Gordon Petersen

Policy matters.

Photo: Dan Reiland, Leader-Telegram

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