

Short Communication

Bovine Spongiform Encephalopathy and Aquaculture

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Abstract. Dietary consumption of fish is widely recommended because of the beneficial effects of omega-3 polyunsaturated fatty acids on the risks of cardiovascular and Alzheimer's diseases. The American Heart Association currently recommends eating at least two servings of fish per week. We are concerned that consumption of farmed fish may provide a means of transmission of infectious prions from cows with bovine spongiform encephalopathy to humans, causing variant Creutzfeldt Jakob disease.

Keywords: Bovine spongiform encephalopathy (BSE), fish, prion, transmission

It is now forbidden in much of the world to feed ruminant materials to ruminants because of the risk of transmission of bovine spongiform encephalopathy (BSE). An important consideration in regard to BSE, or atypical prion disease, is that it may develop in a cow via two mechanisms: either through transmission from a contaminated food source, or spontaneously, without any need of exposure to an infected animal (this is conjectural based on sporadic human disease, since proving the negative is not possible). Therefore, there is a theoretical risk of a prion disease developing in a cow even in the absence of feeding of material from other cows. There are no regulations in the USA concerning feeding of rendered material from cows to swine, poultry, pets, or fish (personal communication, L. A. Detwiler DVM, Sept. 23, 2008). Meat, as well as

bone meal from cows, is used in the US and elsewhere in aquaculture [1] (Personal correspondence, George Chamberlin, President, World Aquaculture Alliance, May 23, 2006). The risk of transmission of BSE to humans through ingestion of farmed fish would appear to be low because of the species barrier from homeotherm to poikilotherm. However, the history of prion diseases illustrates the danger of this assumption. The pattern of occurrence of kuru amongst the Fore in New Guinea did not suggest a transmissible disease until Hadlow [2] pointed out the similarity of the pathologies of kuru and scrapie in 1959. Subsequently, the agent, now known as a prion (PrP^{sc}), was not believed to be transmissible from primates to rodents, or from sheep to cows, or from cows to humans. Through the use of transgenic models these assumptions have been disproved.

As of June 2008, there were 163 deaths from probable or confirmed new variant Creutzfeldt Jakob disease (vCJD) in people in the United Kingdom, believed to be transmitted from cows to humans (Department of Health, UK). In 2008 there have been 16 cases of BSE (established by active or passive surveillance as

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of June 2008, UK Department for Environment, Food and Rural Affairs). BSE has not been limited to the UK. A ninth case of Canadian BSE was recently reported (Canadian Food Inspection Agency Report 3/26/07) and three cases of BSE have been found in the US.

Prion protein (PrP) homologues have been demonstrated in zebrafish, salmon, pufferfish, trout, and other fish species [3–6]. Although the sequence homology is low, fish PrP undergoes the same post-translational processing as its mammalian counterpart and would be expected to have the same cellular location. While the lack of significant sequence homology between mammals and fish may give rise to the expectation that fish would be unable to transmit the infectious material, previous reports on the ability of hay mites to harbor scrapie infectivity would argue against this false sense of security [7,8]. Thus, there are two underlying concerns: first, farmed fish eating material from a BSE-infected cow may undergo pathological transformation of the endogenous fish prion and subsequently transmit the agent to people. Secondly, a farmed fish eating material from a BSE-infected cow may act as a vehicle to transmit the agent to people without involvement of the fish prion, because the infectious agent of prion diseases is extraordinarily stable and resistant to inactivation by heat, chemical agents, or time [9]. Studies in rodents have demonstrated that the absence of apparent infection does not mean that transmission cannot occur through consumption of the carrier (as occurred with the BSE epidemic before 1986 [1]). The possibility of transmission of prion diseases via consumption of farmed fish through these two mechanisms has received little investigation [1]. Furthermore, it is currently believed that the BSE infection in cows was amplified by the feeding of material from cows to other cows, as mouse scrapie work shows that passage of infectious material through the same species results in augmentation of the infectious dose. Thus, if conversion of the endogenous fish prion protein occurred, although unlikely based on sequence differences, the feeding of fish remnants (such as fish bone meal), which is widely used in aquaculture worldwide, would lead to amplification.

A recent report by Ingrosso and colleagues [10] concluded that the risk of transmission of BSE to humans through fish was negligible. However, this study used the rodent-adapted scrapie strain, 139A, which produces the weakest proteinase K resistant PrP. The major goal of the study was to determine whether residual prions would remain after forced feeding. The majority of prions were cleared quickly; however, this experiment

does not directly test the effect of repeated exposure. In addition, even in transmission studies between different mouse strains, prions are not detected by bioassay during the latent phase. In terms of detecting propagation in the fish, it is highly likely that a significant species barrier exists between fish and any scrapie strain. In addition, these studies were limited to a maximum of 90 days due to the lifespan of the host. The typical incubation period for rodents infected intracerebrally with the 139A scrapie strain (i.e., in the absence of a species barrier) is approximately 135 days, with detection of replication about halfway through the incubation period. It is, therefore, unlikely to expect a shorter incubation period, or even detection of replication, in a scrapie strain-host strain combination where a species barrier does exist. In detection of propagation, the bioassays present another species barrier, which would limit the sensitivity of the assay. Thus, the article by Ingrosso and co-workers is inadequate to confer a sense of safety about the use of meat and bone meal additives to the feed of farmed fish since the experiments only ran for 90 days, much less than the typical incubation period of prion diseases and used a scrapie strain that produces weakly PK resistant prion protein. To more completely address the issue, a number of different experimental paradigms could be employed. First, it would be possible to attempt conversion of the fish prion protein either by traditional means or by using the more sensitive method of PMCA (protein misfolding cyclic amplification, a method of amplifying a protein conformation). Second, one could attempt to produce a fish adapted scrapie strain using fish cell culture. And finally, transgenic mice expressing the fish prion protein on a PrP knockout background could be tested for susceptibility.

There are several other reasons to be concerned about inadequate protection of the public from the risk of exposure to the BSE prion. Rendering facilities may process multiple species and despite proper labeling of product, it is not possible to adequately clean the facilities between species. Poultry may be fed ruminant materials and chicken litter may be fed to cattle. Furthermore, products are sold as supplements for human consumption containing “raw brain” of bovine origin for enhancement of vitality or cognition (Standard Process Inc, Palmyra, WI).

We suggest that current regulations should be revised to ban the feeding of rendered material from cows to fish, until further work establishes the safety of this practice. The observation that no cases of vCJD have yet been linked to the eating farmed fish should not provide any assurance of the safety of feeding ren-

dered material to fish, as the incubation period of prion diseases may last for decades and such an association would be difficult to establish. Even though the neuroscience of prion diseases is advancing rapidly, the prionopathies remain uniformly fatal, lacking effective therapies. Enhanced safeguards need to be put in place to protect the public from possible transmission of BSE through fish farming or other possibly hazardous practices. Importantly, the European Food Safety Authority Scientific Panel on Biological Hazards concluded that currently there is insufficient data to quantify the degree of BSE risk for animal or human health from feeding cattle blood products to farmed fish (January 2008) emphasizing the need for caution.

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